SYNTHESIS OF DISPIRO COMPOUNDS AND DERIVATIVES
AS POTENTIAL MEDICINAL AGENTS

by

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ABSTRACT

The syntheses of 8-amino-16-azadispiro[6.1.6.2]heptadecan-16-one and its 8-chloroacetyl derivative are reported. The compounds were characterized by their infrared spectra and by elemental analysis of the latter compound. Data is presented for the attempted reaction of dimethylaminoacetic acid with 7-amino-14-azadispiro[5.1.5.2]pentadecan-15-one and 8-amino-16-azadispiro-[6.1.6.2]heptadecan-17-one using dicyclohexylcarbodiimide as the condensing reagent. The reduction of the product obtained from the latter reaction is described. The addition of the β-dimethylaminoethyl group to the 8-amino dispiro compound named above, in the presence of sodamide was also tried.

A β-dimethylaminoethyl derivative of 7,14-diazadispiro[5.1.5.2]penta-decane was synthesized by the lithium aluminum hydride reduction of the pentadecan-15-one analog. A correct elemental analysis was obtained for the unsaturated compound but the reduced derivative was identified only by its infrared spectrum. It was not determined whether substitution had occurred at the secondary or the lactam nitrogen. The reaction of chloroacetyl chloride with 7,14-diazadispiro[5.1.5.2]pentadecan-15-one using a variety of reaction conditions is described. Data is also presented for the attempted purification of the product obtained from the latter reaction; both thin layer and column chromatography were employed. The condensation reaction of 1-amino-cycloheptanecarbonitrile in the presence of sodium ethoxide and a trace of moisture does not yield the expected 8,16-diazadispiro[6.1.6.2]heptadecan-17-one.

Signature of Examiners

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ACKNOWLEDGEMENT

INTRODUCTION

The synthesis of derivatives of dispiro compounds was begun in order
to make them available for pharmacological testing. These compounds are
unique because they contain alicyclic saturated rings that are held perpen-
dicular to the side chain. Molecules of this type would provide a particu-
larly large blocking area at any receptor to which they might become attached.
Pharmacological data on these compounds will help to characterize the steric
and electronic requirements of the receptors with which they interact.

The side chains proposed for the dispiro compounds are the ones that
have been found to produce relatively strong antihistaminic, local anesthetic,
or antimuscarinic activity when attached to suitable parent molecules. For
good antihistaminic activity, a dimethylaminoethyl group is generally required.
Potent local anesthetics often contain a dimethylamino group linked to the
parent compound through an amide linkage, and many very active anticholinergics
contain the trimethylammonium function. These are the types of side chains
that have been proposed for the dispiro compounds. A brief outline of the
pharmacology and structure activity relationships of the antihistaminics,
local anesthetics, and antimuscarinics follows. Note is also made of the
pharmacological results obtained from some related spiro compounds.

A.   ANTIHISTAMINES

1. Pharmacology

Antihistamines may be defined as drugs which diminish or prevent some
of the effects of histamine by a mechanism other than the production of pharma-
cological responses diametrically opposed to those of histamine. Bronchiolar
and intestinal spasm, hypotension, increased capillary permeability, cutaneous

wheal and flare, release of epinephrine from the adrenal gland and salivation
(but not gastric secretion) are some of the effects of histamine that are
diminished by these drugs. Other effects of the antihistamines include, in
varying degrees, sedation, local anesthesia, an atropine-like effect that
accounts for the drying of mucous membranes, and anti-anaphylactic properties
when given in fairly large doses.

It is generally believed that an antihistamine exerts its action by
competing for the cell receptors of the tissue involved. By attaching itself
or covering the receptors in some way, it prevents histamine from exerting
its influence on the cell (1a).

The greatest beneficial effect of these drugs is in the symptomatic
treatment of allergic conditions, notably in mild pollinosis and in acute
urticaria. Angioneurotic edema, serum sickness and reactions from certain
drugs are usually relieved by the administration of the antihistamines. Atopic
dermatitis, contact dermatitis, pruritus ani and vulvae, generalized pruritus
and insect bites are some of the itching skin conditions ameliorated by the
administration of these drugs (2a). Antihistamines are effective drugs for
the prophylaxis of motion sickness (3), but this is probably not a consequence
of their antihistaminic activity.

Undesirable side effects which vary greatly in severity and incidence
with the individual drug are produced by all antihistamines. Considerable
variation also exists in the sensitivity of individual patients to the toxic
as well as the therapeutic actions of these compounds. Sedation ranging from
mild drowsiness to deep sleep, is the most common side effect of most of the
antihistamines. This effect in turn may give rise to dizziness and disturbed
coordination. Lassitude, muscular weakness, dryness of mouth, gastrointestinal

upset and anorexia are commonly seen (4).

2. Structure Activity Relationships

Most of the antihistaminic substances known can be related to the
following general formula:

$$R_1 — \underset{R_2}{\overset{}{X}} — R_3 — \underset{R_4}{\overset{}{N}} — R_4$$
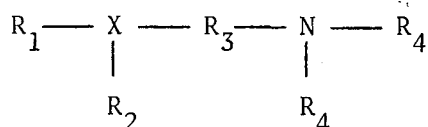
When R_3 is an ethylene linkage, the compounds can be classified into three
broad categories:

1. Ethanolamines, where X = oxygen.

2. Ethylenediamines, where X = nitrogen.

3. Propylamines, where X = carbon.

In general, active antihistamines are obtained if X is O, N. or C, and it may
be incorporated into a suitable heterocyclic ring. For maximum activity, the
N-terminal should be tertiary and in particularly, R_4 should be methyl groups,
or it may be part of a ring without serious loss in activity. R_1 and R_2 may
be aryl, arylmethyl, heterocyclic or heterocyclic methyl. Some representa-
tive antihistamines and their structural relation to histamine are shown in
Figure 1.

The groups present on the N-terminal should be small, symmetrical, and
planar. Secondary and primary amine groups in this position result in almost
inactive compounds. If a diethylamino or trimethylammonium function is pre-
sent, the antihistaminic activity is decreased and the antispasmodic activity
is increased (1a). The dialkyl amino group may be incorporated into certain
ring systems without significant loss in antihistaminic activity. The

following groups are in approximate order of decreasing utility:

dimethylamino $\gtrsim$ pyrrolidino = piperidino > morpholino = thiomorpholino > diethylamino > dibutylamino > secondary amine > primary amine.

The R_3 group confers the best activity to antihistamines when it is an ethylene function. Except in the phenothiazine series, lengthening or branching of the chain results in a sharp decrease of activity. The addition of an alpha methyl group to the N-terminal of one phenothiazine results in one of the more active antihistamines, promethazine. It is generally believed that the nucleus of these drugs should have at least two aromatic groups or their equivalent in a polycyclic system (1a). However, preliminary results obtained on a cyclohexyl analog of diphenhydramine synthesized in this laboratory, indicated that compounds with only one aryl group may still have considerable antihistaminic activity (5).

In the ethanolamine series, the most effective group attached to the O atom has been found to be the benzhydryl radical, but replacing one of the phenyl groups with 2-pyridyl or 2-furyl also produces effective compounds. Substitution of one of the aromatic rings with a para methyl, methoxy, or halogen is generally advantageous in the non-phenothiazine types of antihistamines.

Several different radicals may be used to produce active compounds in the ethylenediamine series. The groups are either isocyclic or heterocyclic aromatic ring systems, one of which may be separated from the nucleus N by a methylene group. Many of the active compounds contain a 2-pyridyl group and a benzyl, substituted benzyl, or one of the isosteres of the benzyl group (1a). Unlike the ethanolamines, fusing of the aromatic rings in the

Histamine
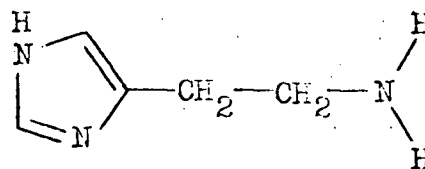
Diphenhydramine

(an ethanolamine)
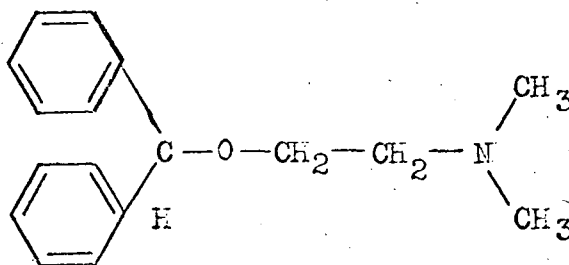
Pyrilamine

(an ethylenediamine)
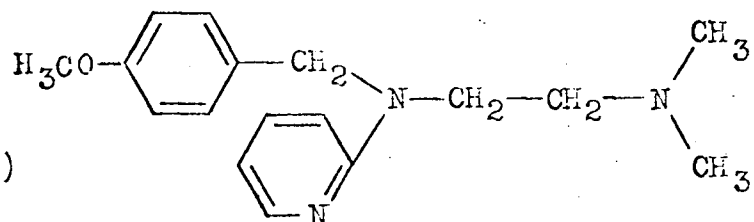
Chlorpheniramine

(a propylamine)
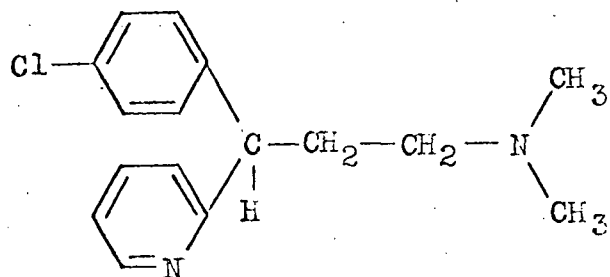
Chlorcyclizine

(a piperazine)
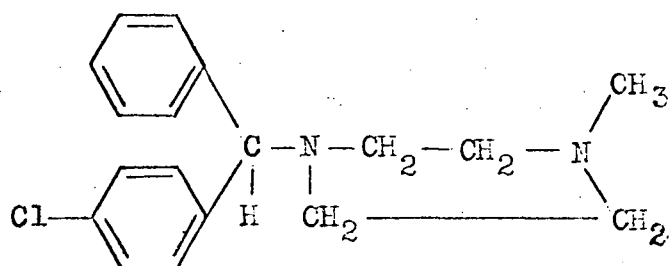
Promethazine

(a phenothiazine)
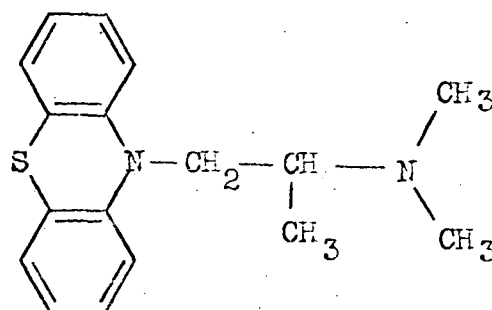
Figure 1. Histamine and Representative Antihistamines

ethylenediamine series produces phenothiazines that are active antihista-
mines. A third type of ethylenediamines is one in which the diamine is part
of a piperazine ring. Chlorcyclizine is the most active member of this series;
it is four times as active and one-half as toxic as diphenhydramine.

In antihistaminic agents that show optical or geometrical isomerism,
one isomer is invariably more active than the other. In optical active anti-
histamines, the activity generally resides in the dextrorotatory isomer.
This isomer specificity, as well as the fact that attempts to relate physical
properties such as ionization constants, solubilities, and relative surface
activities to antihistamine potency have failed, indicate that steric factors
are extremely important in determining activity in this group of drugs.
Further information regarding the structure activity relationships of the
antihistamines is found in references (1a), (6), (7), (8) and (9).

B. LOCAL ANESTHETICS

1. Pharmacology

Local anesthetics are drugs that block both the generation and con-
duction of nerve impulse when applied locally to nerve tissue. The effect of
injected local anesthetics varies, depending upon the particular nerve blocked
and the concentration of the drug used. The essential features, however, of
injection into nerves containing both sensory and motor fibres, are analgesia
and muscle relaxation. These drugs may be administered by infiltration of
the tissue to bathe fine nerve elements, by injection adjacent to nerves and
their branches, by injection into the epidural or subarachnoid spaces, or by
topical application.

Local anesthetics block conduction by interfering with the large transient increase in the permeability of the membrane to sodium ions that is produced by a slight depolarization of the membrane (2b). Shane suggests that local anesthetics increase the surface pressure of the lipid layer that constitutes the nerve membrane, thereby closing the pores through which the ions move (10). It is known that increasing the external calcium concentration raises the threshold for action potential production, and recently evidence has been obtained suggesting that these drugs compete with calcium for membrane sites (11). Further research will be required before the mechanism of action of these drugs is elucidated.

Local adverse reactions of these drugs include neurolysis, slough and edema. Systemic effects of local anesthetics are of little or no therapeutic value. The main serious manifestations of toxicity include depression of the central nervous system and cardiovascular depression. Anaphylactoid shock has occurred after intravenous injection of local anesthetics (12).

Lidocaine is of particular interest because it is an aminoacyl amide as are the azadispiro compounds, (the attempted syntheses of which are reported in this thesis). Lidocaine produces more prompt, more intense, longer lasting, and more extensive anesthesia than an equal concentration of procaine, which has been used as the standard of comparison for the local anesthetics (2b).

Overlapping pharmacological activities are seen in many classes of drugs, including local anesthetics, antihistamines, and antimuscarinics. For example, many local anesthetics, as classified by their chemical structure, possess also varying degrees of antihistaminic, anticholinergic, sedative, antitussive, and convulsive activities. Some examples of synthetic local

anesthetics are shown in Figure 2.

2. Structure Activity Relationships

The clinically useful local anesthetics may be classified into two groups, the ester and amino compounds, and the non-nitrogenous hydroxy compounds. The latter group are used largely for surface anesthesia and even then they are not as effective as the nitrogen containing compounds. Only the structure activity relationships of the nitrogenous compounds will be discussed here.

The useful local anesthetics consist of three parts: a lipophilic aromatic group, an intermediate group, and a hydrophilic residue. The general formula for local anesthetics can be stated:

Lipophile --- Intermediate Chain --- Hydrophile

For good activity, a balance between the lipophilic and hydrophilic portions of the molecule is essential (13). The drug must be water soluble enough to be transported through the extracellular fluid and lipid soluble enough to penetrate the cell membrane.

The lipid portion of the molecule is commonly derived from benzoic and para-aminobenzoic acids. In general, the carbonyl group must be conjugated with the aryl group for maximum activity; the introduction of a methylene function between them results in a considerable loss of activity. Substitution of a para-amino group on the benzoic acid residue results in an increase of activity; subsequent N-alkylation increases both anesthetic potency and toxicity. Para-alkoxy substitution also increases activity, and the anesthetic activity increases with the molecular weight of the alkyl group. The inter-
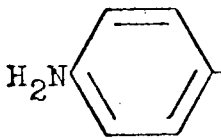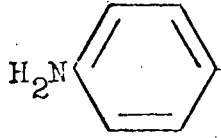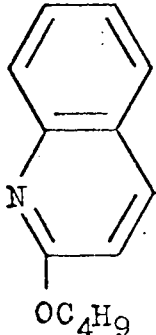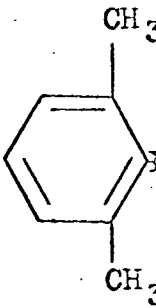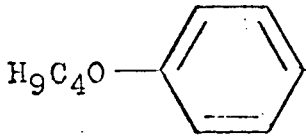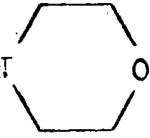
Figure 2. Examples of Synthetic Local Anesthetics

mediate chain frequently contains an ester linkage, but other groups such as substituted amides, substituted imides, urethanes and ethers are also seen. If the linkage present is stable to hydrolysis in the body, it will result in a compound with a longer duration of activity. Thus lidocaine (see Figure 2) has α-methyl groups on the phenyl ring that sterically hinder the hydrolysis of the amide bond. The propylene group, as seen in promoxine, appears to be the optinum length for the akyl portion of the intermediate chain, although the ethylene group joined to the ester residue is more commonly seen. The methylene group is reported to make the ester too irritant (1b).

The hydrophilic group is usually a secondary or tertiary amino group. Anesthetic potency increases with the size of the alkyl groups as does the toxicity; the maximum increase in activity occurs at C_3 to C_4. However the diethylamino group is the most commonly seen. No advantage has been observed when the groups on the nitrogen are the same. As was seen in the antihistamines, the nitrogen may be part of a suitable heterocyclic ring, such as piperidine (1b).

C.   ANTIMUSCARINICS

    1. Pharmacology

Antimuscarinics are drugs that inhibit the actions of acetylcholine on structures innervated by postganglionic cholinergic nerves, and on smooth muscle that repond to acetylcholine but lack cholinergic innervation. This class of drugs is also termed atropine-like, anti-cholinergic, antipara-sympathetic, and spasmolytic. In general, small doses of antimuscarinics depress salivary, bronchial, and sweat secretion; larger doses cause mydriasis,

cycloplegia, and increase heart rate. Still larger doses inhibit micturation and decrease the tone and motility of the gut. Gastric secretion is inhibited only if the dose is increased even more. Thus doses of antimuscarinics that are large enough to reduce the tone and motility of the stomach and the duodenum and depress gastric secretion, usually result in dryness of the mouth, blurred vision, photophobia, and tachycardia (2c). These are the most common side effects seen in the treatment of peptic ulcer with antimuscarinics. Anhydrosis, constipation, urinary retention, and impotence are also encountered. Besides their use in gastrointestinal disorders, these drugs are used in ophthalmology to produce mydriasis and cycloplegia. Some of the drugs in this series have central actions which are important in the treatment of Parkinson's disease, and the poisoning due to alkyl phosphate compounds and in the treatment of motion sickness (2c).

Two antimuscarinics of special interest here are dibutoline and dicyclomine. These compounds both lack aromatic functions that are usually seen in this group of drugs. The azadispiro compounds whose synthesis was attempted in this work also lack aromaticity. Dibutoline (see Figure 3) is used in ophthalmology because of its rapid, relatively brief action after topical application. Dicyclomine reduces the spasm of the gastrointestinal tract, biliary tract, ureter, and uterus without producing the characteristic atropinic side effects already mentioned (14). It has been suggested that dicyclomine does not act by competitive antagonism of acetylcholine as do the other anticholinergics, but rather by a local anesthetic action that interrupts local reflexes regulating tone and motility of these muscles (15).

2. Structure Activity Relationships

Antimuscarinics vary in chemical structure probably more than do the

members of any other single class of pharmacologically active drugs. The
relationship between chemical structure and the antimuscarinic activity is
enormously complex; consequently, it will be only briefly outlined here.

The general formula for antimuscarinic agents can be represented as:

$$R_2 - \underset{\underset{R_3}{|}}{\overset{\overset{R_1}{|}}{C}} - R_4 - \overset{|}{\underset{|}{N^+}} -$$
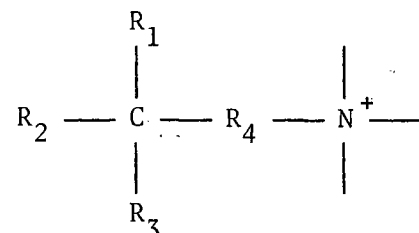
In this formula, R_1 is a planar ring, such as phenyl, R_2 is a secondary sub-
stitution, which may be alkyl, aryl, or hydrogen, and R_3 is a hydrogen bonding
group. The group linking the terminal C to the cationic head, R_4, is often
an ester. The cationic head is a quaternary ammonium group or a tertiary
amine with pKa such that a high percentage of the compound is protonated at
biological pH (1c).

The lipophilic portion of the molecule, R_1, may vary widely but certain
specific volume requirements are usually met. One of the substituents should
be a planar ring which is equal or less than a phenyl group in volume, such
as the thienyl group. Compounds containing substituted phenyl rings have
usually shown a decrease in anticholinergic activity. The phenyl group it-
self is not essential for activity (16); for example, high activity has been
reported for cyclopentyl-substituted acetic acids (17).

The secondary substitution (R_2) may be the same as R_1 and it may be
incorporated into rings with R_1, such as in phenothiazines. Or an alkyl
group up to normal hexyl or an alicyclic group can represent R_2. The assym-

metric quaternary carbon atom often increases activity (18). This probably

indicates a multipoint interaction with an optically active receptor.

The group linking the terminal carbon and the cationic head, R_4, may

be varied greatly without markedly altering the inhibitory action. The

interatomic distance can vary from 5-9 A. Although many highly active com-

pounds contain an ester linkage at R_4, many other linkages result in active

antimuscarinics. Musculotropic activity increases with the length of the

linkage.

The cationic head is the primary point of attachment of the molecule

to the cholinergic site. It is essential for highly active compounds (19),

but non-nitrogenous carbocholines have been synthesized that will effectively

compete with acetylcholine at the cholinergic receptor (20). Optimal activity

appears with substitutions larger than methyl, with isopropyl being the

largest useful group before a reduction in activity is seen. Heterocyclic

rings also may be used in this position to produce compounds with high anti-

muscarinic activity. The structure of acetylcholine and some antimuscarinics

are shown in Figure 3.

The azadispiro compounds whose syntheses are proposed in this thesis

differ most significantly, from the antihistamines, local anesthetics, and

antimuscarinics commonly used, in their lack of aromaticity and their steric

configuration. The dispiro compounds contain saturated rings that are per-

pendicular to the N-terminal side chain. Most of the clinically useful drugs

of all three of the groups mentioned contain aromatic rings that may assume

a planar conformation with the N-terminal group. Thus far, the requirement

for aromaticity in the antihistamines and the local anesthetics has been

Acetylcholine

$$CH_3COOCH_2CH_2 - \overset{\oplus}{\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{N}}} - CH_3$$

Atropine
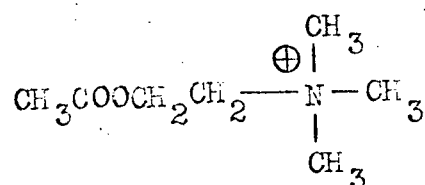
$$\text{(structure of atropine)}$$

Propantheline
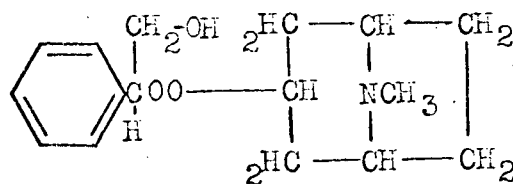
$$\text{(structure of propantheline)}$$

Dibutoline

$$(C_4H_9)_2NCOOCH_2CH_2 - \overset{\oplus}{\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{N}}} - C_2H_5$$
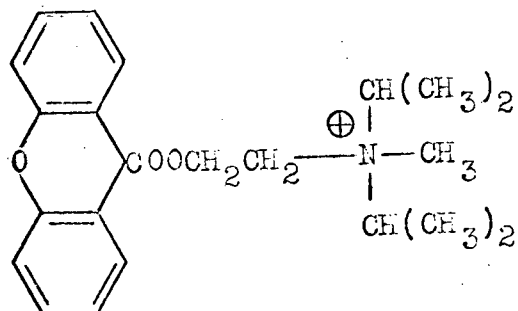
Dicyclomine
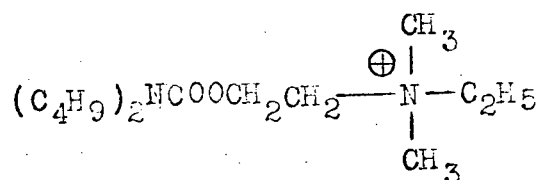
$$\text{(structure of dicyclomine)}$$
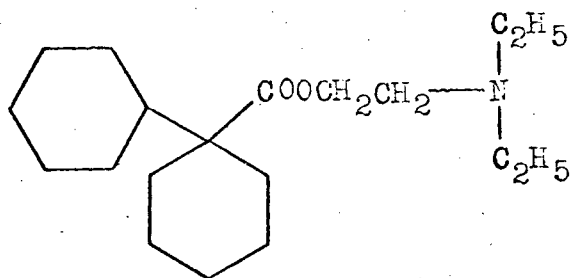
Figure 3. Acetylcholine and Some Antimuscarinics

found to be very strict. However some active antimuscarinics with no aromatic character are known, as was mentioned previously.

A proposal for future work on the azadispiro compounds is the synthesis of a series of esters. The second group of dispiro compounds used as starting material in this thesis, can easily be converted to their secondary alcohol derivatives (21). Thus a series of sterically hindered esters could be prepared. These compounds would contain alicylic rings that are perpendicular to the side chain as do the compounds proposed in this thesis, but would differ by the presence of an ester rather than an amide linkage. The ester group is more commonly seen in the local anesthetics and the anticholinergics than is the amide group.

D. PHARMACOLOGICAL ACTIONS OF SOME SPIRO COMPOUNDS

The syntheses of innumerable spiro compounds have been reported. These include compounds with nitrogen, oxygen, silicon and phosphorous incorporated into heterocyclic rings. Spiro compounds composed of three to eight rings, which may or may not be fused to aromatic or steroidal structures, are often seen in the literature. In most cases, only the chemistry of the compounds has been studied, and functional groups characteristic of pharmacological agents are not incorporated into their structures.

However, several series of spiro compounds have been synthesized in order to determine structure activity relationships and to provide better therapeutic agents. For example, Capps et al have recently synthesized a large number of triazaspiro compounds, some of which have shown strong anthelmintic activity (22). Certain sulfamylurea derivatives of 1-oxa-8-aza-dispiro[4.5]decane have been found to have hypoglycemic properties in both

animals and man (23). In order to further delineate the requirements for

psychopharmacological agents, spiro(4-piperidinomethyl-1,3-dioxolane)-2-1'-

cyclododecane and related compounds were prepared (24), but no significant

biological activity was found. Spirobarbituates were first synthesized as

early as 1921 (25). Recently, silicon-substituted derivatives have been pre-

pared (26), but these silaalkylspiro analogs did not result in more desirable

therapeutic effects. Numerous cycloalkanespiro-5'-hydantoins have been

tested for anticonvulsant activity (27), (28), (29), and (30). Analgesic and

antiinflammatory activity have been reported with certain cyclohexyl analogs

in this series (31). In another series of spirohydantoins, a series of

fluorenyl derivatives was synthesized and found to have antitumor activity

(32). A large group of spirodihydroperimidines was also tested for anti-

neoplastic properties, but only a few of these compounds exhibited any

appreciable activity (33).

Another series of cytotoxic agents containing spiro rings was prepared

as part of a very extensive study of spiro compounds by Rice, Grogan and

Geschickter (34). The general structure of the compounds studied by this

group is shown below. In the series of compounds prepared for cytotoxic
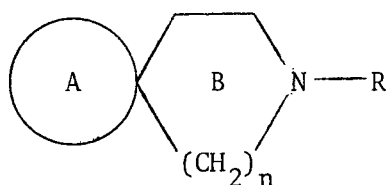
activity, ring A was varied from a simple alicyclic ring of five to eight

carbon atoms, to substituted carbocyclic rings, and to bicyclic rings such

as the tetralins (35), and to heterocyclic rings containing sulphur or oxygen

atoms. The value for n varied from one to two and R was a series of dialkyl-

aminoalkyl groups. Clinical studies of N-dimethylaminopropyl-9-t-butyl-3-azaspiro[5.5]undecane (see Figure 4) on patients with severe carcinomas and sarcomas were very promising (34). Recently Rice extended the A ring to form azatrispirans (36), but less active antitumor activity was seen. When R was substituents such as propargyl, hypnotic and tranquilization effects were seen, while certain allyl and dimethylamino derivatives showed CNS stimulation and local anesthetic activities, respectively (37). If para-fluoro-aroylalkyl substituents represent the R moiety, potent CNS depressant, hypotensive, and antiinflammatory activity were observed in screening tests, and certain of the compounds were clinically active as tranquilizers (38). A series of phenothiazines (39) and butyrophenones (40) linked to the spiro compounds through the endo nitrogen, yielded more compounds with CNS depressant activity. Rice and Grogan also studied permutations of the general formula shown previously, in which the nitrogen in ring B was exo. Pharmacological examinations found that aminospiranes in which the exo-nitrogen atom was substituted β or γ (but not α) to the spiro carbon atom, displayed potent analgesic, analeptic, and local anesthetic activities (41). A final example of spiro compounds that produced biological activity are the bisdialkylamides of 3,9-dicarboxy-2,4,8,10-tetraoxaspiro[5.5]undecane (42); sedation, muscle relaxation, and tranquilization were seen in the test animals.

Considering the structure activity relationships of the local anesthetics discussed previously, it is noteworthy that certain of the spiro compounds such as 3-dimethylamino-3-azaspiro[5.5]undecane-2,4-dione, exhibited local anesthetic activity, although they lack an aromatic function (37). This is consistent with the hypothesis that dicyclomine exerts its antispasmotic effect at least partly through the production of local anesthesia (15). Because of the similarities between the dispiro compounds proposed in this thesis, such

as 7-β-dimethylaminoethyl-7,14-diazadispiro[5.1.5.2]pentadecan-15-one
(shown in Figure 4 as A), and N-dimethylaminopropyl-9-t-butyl-3-azaspiro-
[5.5]undecane, mentioned earlier (34), (and shown in Figure 4 as B), pharmacol-
gical screening for anticancer activity on compounds such as A, its
dimethylaminopropyl derivative, and the corresponding reduced products,
could be profitable.

The spiro compounds whose pharmacological activities have just been
outlined above, contain N-substituents that can easily assume a planar
conformation with either of the spiro rings. These compounds are repre-
sented by B, the antitumor agent named in the previous paragraph. As seen
in Figure 4 the new dispiro compounds proposed in this thesis, represented
by A, differ from the above compounds in that the N-substituents are held
approximately at right angles to the terminal cycloalkyl rings, so that such
substituents can not assume a planar conformation with the terminal spiro
rings.
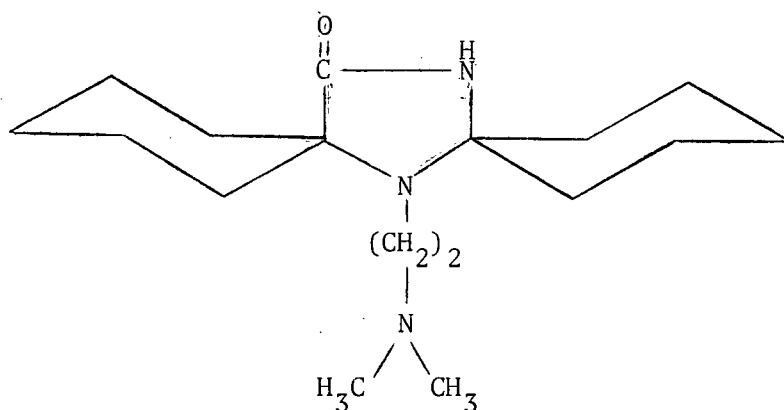
A

(7-β-Dimethylaminoethyl-7,14-diazadispiro[5.1.5.2]pentadecan-15-one)
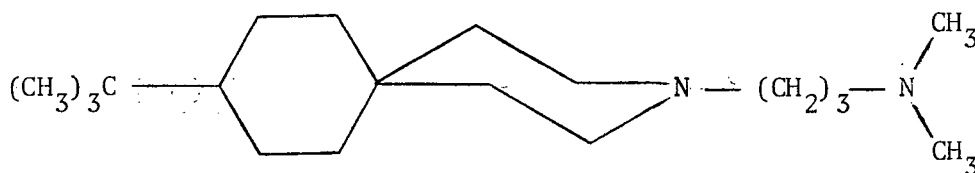
B

(N-Dimethylaminopropyl-9-t-butyl-3-azaspiro[5.5]undecane)

Figure 4. The Structural Relationship Between Spiro Pharmacological

Agents Previously Prepared and the Dispiro Derivatives Proposed

in this Thesis.

PART II

STATEMENT OF THE PROBLEM

The purpose of this investigation was to prepare derivatives of dispiro compounds which contain two cyclohexyl or cycloheptyl rings that are rigidly held perpendicular to the side chain. Molecules of this type would provide a particularly large blocking area at any receptor site to which they might become attached. Pharmacological data on these compounds would give information regarding the steric and electronic requirements of the receptors with which they interact.

The side chains proposed for the dispiro compounds are the ones that have been found to produce relatively strong antihistaminic, local anesthetic, and antimuscarinic activity when attached to suitable parent molecules. They are β-dimethylaminoethyl, dimethylaminoacetamido, and trimethylammoniumacetamido, respectively.

PART III

CHEMISTRY OF THE PARENT COMPOUNDS

A.   7,14-DIAZADISPIRO[5.1.5.2]PENTADECAN-15-ONE

The starting material for the first set of new reactions, 7,14-diazadi-
spiro[5.1.5.2]pentadecan-15-one (DDP), was first synthesized by Noland,
Sundberg and Michaelson (43) at the University of Minnesota. At that time
they were investigating potential synthetic routes to 14-hydroxy-14-azadispiro-
[5.1.5.2]pentadec-9-ene-7,14-dione 7-oxime (C-I), one of the starting
materials used in the second section of the Experimental. They first obtained
DDP in 8% yield in an attempted condensation of 1-aminocyclohexanecarbonitrile
with ethyl cyclohexanone-2-carboxylate, catalyzed by sodium ethoxide in
absolute ethanol. Repetition of the reaction in the absence of the carboxylate,
but in ethanol containing a little moisture, gave DDP in 94% yield. The
reaction sequence that they propose for the formation of this compound is
shown in Chart 1. They believe that the diamine LXVIII could readily
cyclize to give the iminoamide LXIX, and this could subsequently be hydrolyzed
to LXVII (DDP) by moisture present in the ethanol (43). No n.m.r. data
have been reported for DDP and the structure has not been proven unequivo-
cally.

B.   14-HYDROXY-14-AZADISPIRO[5.1.5.2]PENTADEC-9-ENE-7,15-DIONE
                    7-OXIME AND ANALOGS

Condensation reactions of aliphatic aldehydes with secondary nitro-
paraffins forming nitroalcohols, and of primary nitroparaffins forming nitro-
olefins, especially if the aldehyde is aromatic, are numerous. However there

Chart 1.

XXXIV

LXVIII

LXIX

LXVI

LXVII
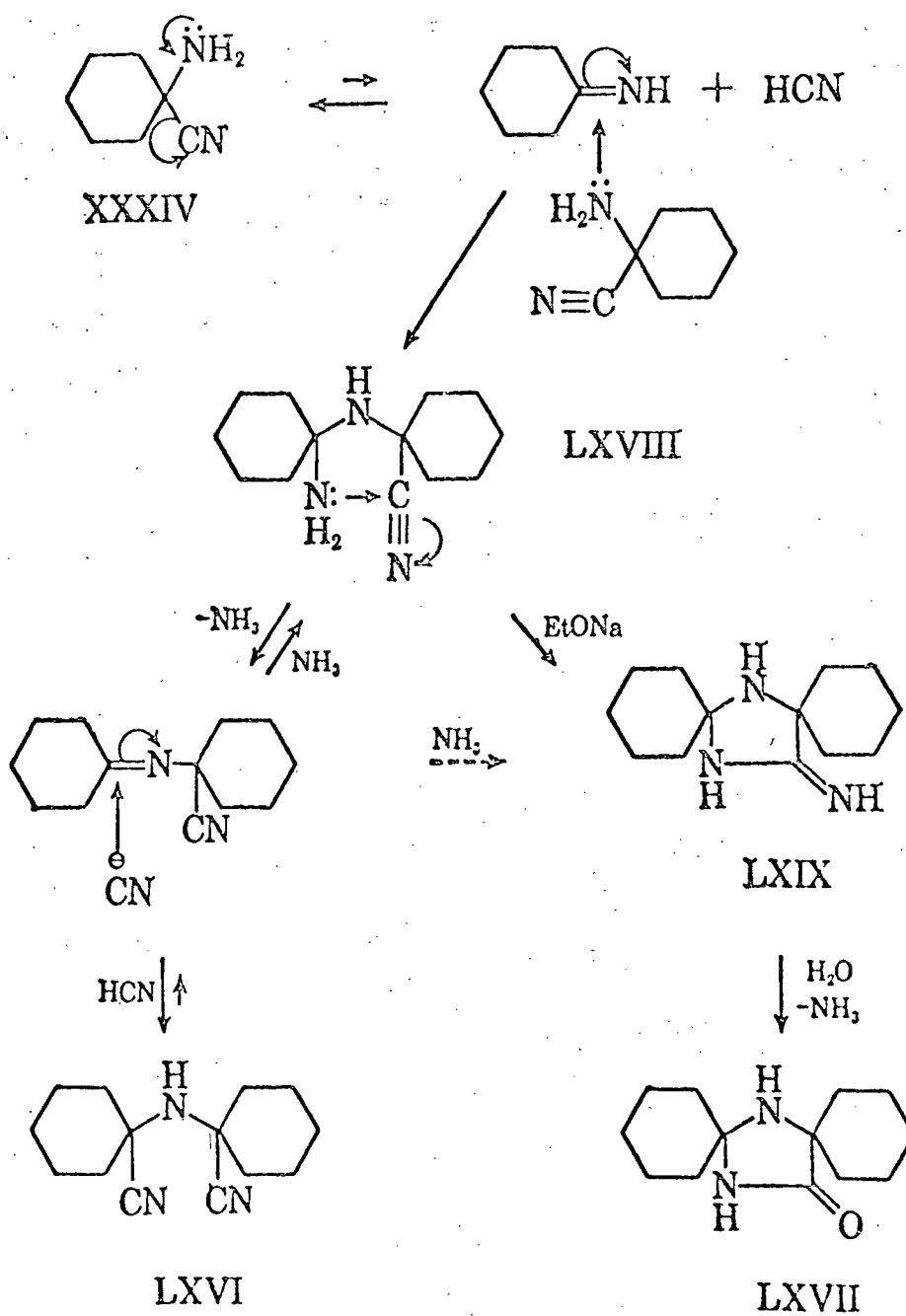
have been relatively few reports of similar condensation reactions with ketones. The first report of a condensation reaction between cyclohexanone and nitromethane was made in 1934 when Fraser and Kon prepared 1-nitromethyl-cyclohexanol using sodium ethoxide to catalyze the reaction, and mainly 1-nitromethylcyclohexene using piperidine as catalyst (44). They tried methylamine, ethylamine, concentrated ammonia and aqueous sodium and potassium hydroxide as catalysts, but smaller yields of the 1-nitromethyl compounds were obtained using these bases. The first solid to be isolated from this type of reaction turned out to be C-I. The structure of C-I and its reduced derivative, C-II, are shown in Figure 5.

As mentioned in Part III A., C-I was one of the starting materials used in the second section of the Experimental. This compound was first prepared in 1941 by F. B. Erickson in Nightingale's laboratory at the University of Missouri. Cyclohexanone and nitromethane were heated to 105° with piper-idine as the catalyst to yield 8.3 per cent of an unidentified solid with a melting point of $261-262^{\circ}$ (dec.) (45). The same solid was obtained if di-N-propylamine was used as a catalyst (46). Analogous solids were also obtained from 4-methylcyclohexanone and 3-methylcyclohexanone but not from 2-methyl-cyclohexanone (46). In 1947 Lambert and Lowe (47) isolated the same solid using diethylamine as a catalyst. They wrote the formula $C_{14}H_{20}N_2O_3$ on the basis of carbon, hydrogen, and nitrogen analyses and a molecular weight determination by X-ray methods. They also isolated 1-nitromethylcyclohexene, 1-nitromethylcyclohexanol and 1,1-bis(nitromethyl)-cyclohexane from the same reaction. Nightingale et al (46) obtained C-I in low yields from both 1-nitromethylcyclohexanol and 1-nitromethylcyclohexene in the presence of amine catalysts. Her groups also increased the yield of C-I to 14% by remov-ing the water as it formed by azeotropic distillation from benzene. They

C-I

(14-Hydroxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,14-dione 7-oxime)

Raney Ni,   30-60 p.s.i.,
Hydrogen   R.T.
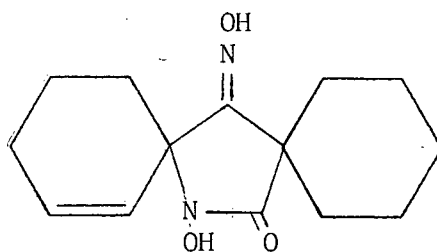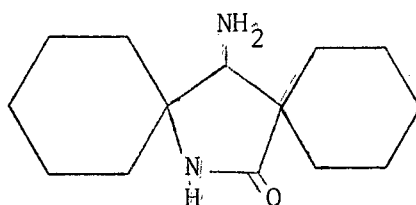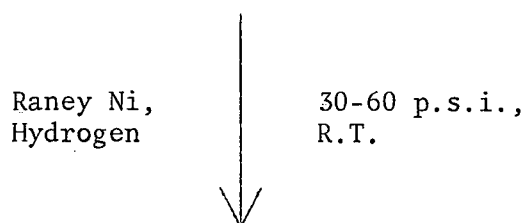
C-II

(7-Amino-14-azadispiro[5.1.5.2]pentadecan-15-one)

Figure 5. Hydrogenation of C-I to C-II

found that no solid was obtained if nitroethane,1-nitropropane or phenylnitro-methane replaced the nitromethane. And no solid was obtained from the reaction if sodium ethoxide was used as catalyst. An analogous solid was obtained using cyclopentanone (46).

The most thorough investigation into the reaction of alicyclic ketones with nitromethane with respect to the type and quantity of different amine catalyst needed to produce the best yields of solid compound, was carried out by Shozo Miki in 1961 at Nightingale's laboratory (48). At that time the structure of the solid material obtained was not known, but the functional groups present had been determined accurately. Table I summarizes the results of the better catalysts tried. Figure 6 indicates the structure and names of the different compounds. Included are the results from previous studies already referred to as well as subsequent ones (49), (21) and (50) by Nightingale's group. The yield of P-I was the most variable; the yields of two reactions using reagents from the same bottles varied from 12 to 24%. The ketone to catalyst ratio that gave the best yield of P-I was 14:1 and not 4:1 as indicated in Table I of reference (49). The maximum yield reported by Miki was 47.2% for C-I using piperazine as catalyst but a yield of 67.0% was later reported (49). Using piperidine as catalyst, Noland and Sundberg (51) obtained a yield of 29% by adding the amine occasionally during the reaction period and increasing the reflux time to 72 hours. The yield of H-I reported in (49) is 51.5% using piperazine but this result is based on the weight of the piperazine salt obtained, m.p. 208-209° (dec.) but was calculated for the H-I itself (48). All the compounds in the table melt with decomposition and some sublimation. The latter causes considerable variation in the melting points reported by different workers. The 3,11-dialkly analogs of C-I have two asymmetric carbons and two centres leading to geometric isomers, making

TABLE I

MAXIMUM YIELDS OF COMPOUNDS I WITH VARIOUS AMOUNTS OF CATALYSTS

I	Ketone moles	Catalyst	Moles	C_6H_6 ml.	Hours Reflux	Yield %	Ratio of Ketone to Catalyst	M.P. $^\circ$C
P-I[a]	0.87	piperidine	0.06	115	57	24.3	14:1	246-247
C-I	0.93	piperidine	0.13	115	100	23.7	7:1	262-263
C-I	0.55	morpholine	0.50	100	64	22.3	1:1	261-263
C-I	1.86	piperazine	1.86	290	30	67.0	1:1	273-274
M-I[b]	0.21	piperazine	0.10	35	64	40.5	1:1	272-274
E-1[c]	0.80	piperazine	0.79	150	19	37.0	1:1	272-276
n-Pr-1[c]	0.28	piperazine	0.15	75	23	29.0	1.8:1	270-271
i-Pr-1	0.20	piperazine	0.20	130	71	40.0	1:1	294-295
t-B-1	0.24	piperazine	0.12	80	63	33.7	2:1	320-321
s-B-1	0.16	piperazine	0.08	100	118	23.0	2:1	285-286
Ch-1	0.20	piperazine	0.10	100	87	20.3	2:1	303-304
H-1	0.10	piperidine	0.10	50	72	48.0	1:1	250-251
H-I	0.21	piperazine	0.10	50	80	51.1	2:1	250-251
0-I	0.24	piperazine	0.12	57	48	0.9	2:1	230-231

All data is from reference (49), except (a), from (48); (b), (50); and (c), (21).
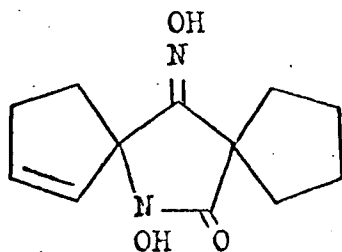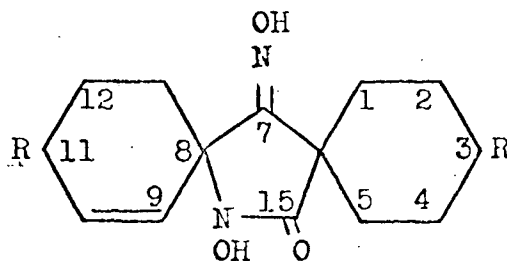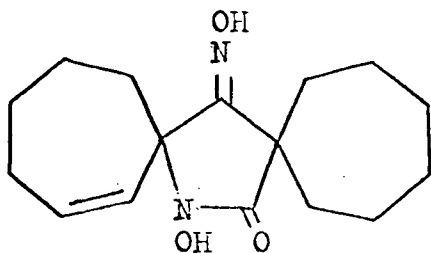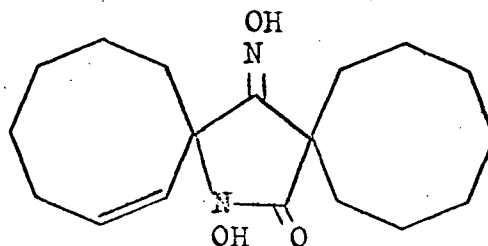
P-I 12-Hydroxy-12-azadispiro[4.1.4.2]tridec-8-ene-6,13-dione 6-oxime.

C-I 14-Hydroxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione 7-oxime.

M-I 3,11-Dimethyl- 14-hydroxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,
15-dione 7-oxime.

The other 3,11-dialkyl analogs of C-I are named in an analogous fashion.

C-I.	R = H
M-I.	R = CH_3
E-I.	R = C_2H_5
n-Pr-I.	R = n-C_3H_7
i-Pr-I.	R = i-C_3H_7
t-B-I.	R = t-C_4H_9
s-B-I.	R = s-C_4H_9
Ch-I.	R = C_6H_{10}

H-I 16-Hydroxy-16-azadispiro[6.1.6.2]heptadec-10-ene-8,17-dione 8-oxime.

O-I 18-Hydroxy-18-azadispiro[7.1.7.2]nonadec-11-ene-9,19-dione 9-oxime.

Figure 6.   Structure and Nomenclature of Azadispiro Compounds

eight possible racemates. No effort was made by Nightingale's group to deter-
mine whether or not these products are single racemates. One sample of t-B-I
obtained by Miki (48) had a m.p. of 284-285° and a correct elemental analysis,
but subsequent reactions yielded a solid that melted at 320-321° (49). In
the reaction of cyclohexanone catalyzed by morpholine, and in the reaction
of cycloheptanone catalyzed by piperidine, hexamethyleneimine and morpholine,
no solid separates from the reaction mixture until after acidification with
hydrochloric acid (49).

The structure of C-I was first elucidated in 1962 by Noland and Sund-
berg (51). Nightingale, Reich and Erickson (46) had previously reported an
extensive study of the reactions of C-I in 1958, and had proposed the partial
structure $C_{13}H_{18}NO-(C=O)NHOH$; they suggested that it contained a C=N group
and a -C=C- group, both of which are unconjugated. Noland and Sundberg sub-
sequently proved the atomic skeleton by functional group determination experi-
ments shown in Chart 2 (51). Acidic hydrolysis of the oximino group in I to
Form IV and failure of acid-catalyzed esterification of the latter indicated
that a hydroxamic acid group was not present in I as originally thought.
Hydrogenolysis of the acidic hydroxyl group of IV under mild conditions and
the position of the amide carbonyl band in the infrared spectrum of XV were
consistent with a five-membered ring N-hydroxylactam structure of IV and not
a carboxylic acid as would be obtained from a hydroxamic acid structure in I.
Conversion of the ketone IV to Ie, the syn or anti stereoisomer of I by oxima-
tion, and the subsequent hydrogenation of Ie to II as shown in Chart 3 (51)
proved that Ie and I have the same atomic skeleton. Application of Hofmann
degradation to IIe did not result in the formation of an olefinic elimination
product; this suggested that the carbon bearing the trimethylammonium group
in IIe is attached to carbons bearing no hydrogens. This is supported by the

Chart 2.*

I
C₆H₅SO₂Cl
pyridine

Ii + Ij

Ii, R = SO₂C₆H₅ (54%)
Ij, R = H (13%)

Ie
(*syn* or *anti* oxime
stereoisomer of I)

IV

Id

XV

If
(*syn* or *anti* oxime
stereoisomer of Id)

IVa

Chart 3.*

XVd

IIg

Ie
(*syn* or *anti* oxime
stereoisomer of I)

IId

IIe

I

IIf

V

XV

II

XIV

* From reference (51).

-fact that the n.m.r. spectrum of XV contains a single large peak at 8.31τ attributed to twenty essentially equivalent methylene protons of the two cyclohexane rings. Hofmann degradation was carried out on the trimethylammonium derivative of V to form an intramolecular displacement product, an epoxide; this reaction is characteristic of β-hydroxyamine methiodides. Thus the hydoxyl group in V and the amino group in II must be beta to the amine and amide nitrogens, respectively. This set of reactions confirmed the structure of II as shown in Chart 3 and the skeleton of I as an unsaturated five-membered ring ketoxime N-hydroxylactam. House and Magin (52) independently arrived at the same atomic skeleton by a different degradative route.

An independent synthesis of XV and II was performed as synthetic proof of the atomic skeleton of I (C-I). The scheme used by Noland and Sundberg (51) is shown in Chart 4. Acylation of 1-aminocyclohexanecarbonitrile with ethyl chloroformylacetate and subsequent cyclization with sodium ethoxide yielded XXXVI. After alkaline hydrolysis with accompanying decarboxylation and dialkylation with 1,5-dibromopentane, XV was produced. Since XV has been converted to II and the latter is derivable from I under conditions of low-pressure hydrogenation, it was assumed that the atomic skeleton proved to be present in II is also present in I.

The double bond was shown to be in the left-hand ring by acid cleavage of the β-ketolactam group with the action of strong alkali at 200° on IV, to yield cyclohexanecarboxylic. The n.m.r. spectrum of the 3,11-dimethyl homolog of IVa clearly showed that the double bond was not in the 10,11-position; the double bond in this position would give a spectrum with only one vinyl proton rather than the two seen to be present. This completed Noland and Sundberg's determination of C-I (51).

Chart 4.*

EtONa
68%

KOH
67%

Br$_2$
72%

Br(CH$_2$)$_4$Br
NaH
2-3%

H$_2$NOH·HCl
pyridine
78%

H$_2$
Ni·
61%

COCl
CH$_2$
COOEt
pyridine
42%

XXXIV

XXXV

XXXVI

XXXVIIa

XXXVII

XV

XVc

II

Chart 5.*

2

CH$_3$NO$_2$

1. −H$_2$O
2. CH$_3$NO$_2$

2CH$_3$NO$_2$
−H$_2$O

−H$_2$O

−H$_2$O

LXIX

LXXI

LXX

LXXVII

LXXII

LXXIII

LXXIV

LXXV

LXXVI

I
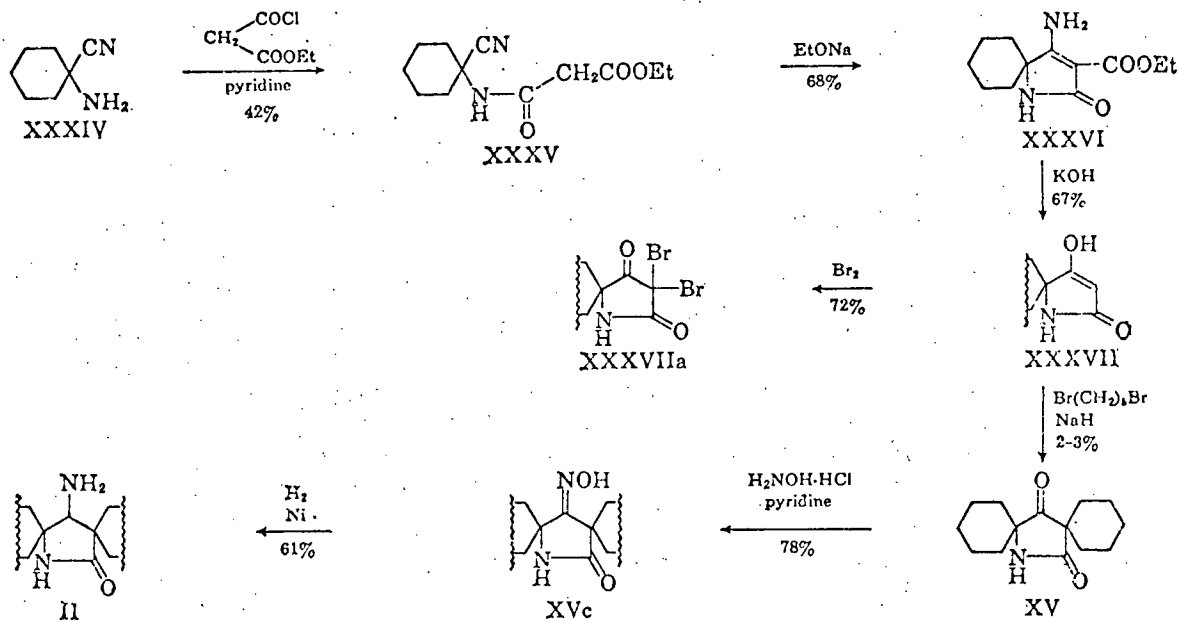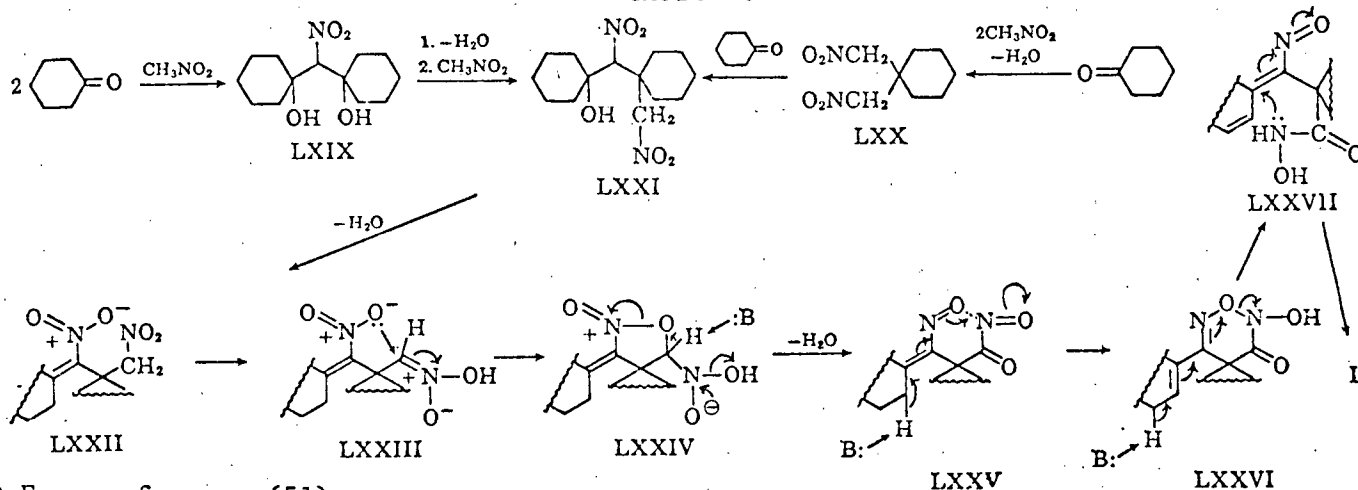
* From reference (51).

In Chart 5 is a mechanism for the formation of C-I suggested by Noland and Sundberg (51). They state that LXXI is the probable intermediate for the link between LXXVI which could readily cyclize to form C-I and the 2:1 condensation product LXXI (which has been isolated from the reaction in which C-I is formed), or the 1:2 adduct LXIX. From LXXI would follow a series of steps involving intramolecular oxygen transfer, dehydration, and oxidation-reduction, possibly proceeding in the order shown in the chart.

PART IV

DISCUSSION OF THE REACTION SEQUENCE

A.   SYNTHESIS OF DERIVATIVES AND ANALOGS OF 7,14-DIAZADISPIRO[5.1.5.2]-
PENTADECAN-15-ONE

The first dispiro compound chosen as starting material for the prepara-
tion of compounds with possible biological activity was 7,14-diazadispiro-
[5.1.5.2]pentadecan-15-one (DDP). This compound was prepared by the method
of Noland and Sundberg (51) from 1-aminocyclohexanecarbonitrile. The latter
compound was synthesized by reacting cyclohexanone with sodium bisulfite,
followed by potassium cyanide to form the cyanohydrin (66); this in turn was
treated with ammonia gas to form the aminocarbonitrile (51). The reaction
sequence to DDP is shown in Chart 6.

The overall yield of DDP from the ketone was 36%. The maximum yield
obtained for the final reaction was only 70% as compared with 94% obtained by
Noland and Sundberg (51). This may be due in part to residual benzene present
in the 1-aminocyclohexanecarbonitrile, since the yield obtained by them for
the latter compound was 61%, but the apparent yield obtained in this laboratory
for the same compound was 92%.

An attempt was made to form the cycloheptyl analog of DDP; exactly the
same procedure (51) was used except that the ketone was cycloheptanone. The
cyanohydrin and the 1-aminocycloheptanecarbonitrile were obtained in comparable
yields, 47% and 99% respectively. But when the latter compound was reacted
with sodium ethoxide, the only solid that separated from the reaction mixture
was sodium cyanide. Assuming that the dispiro compound forms by the mechanism
suggested by Noland and Sundberg (shown in Chart 1) there appears to be no
simple explanation for the lack of formation of at least some 8,16-diazadi-

Chart 6.

DDP
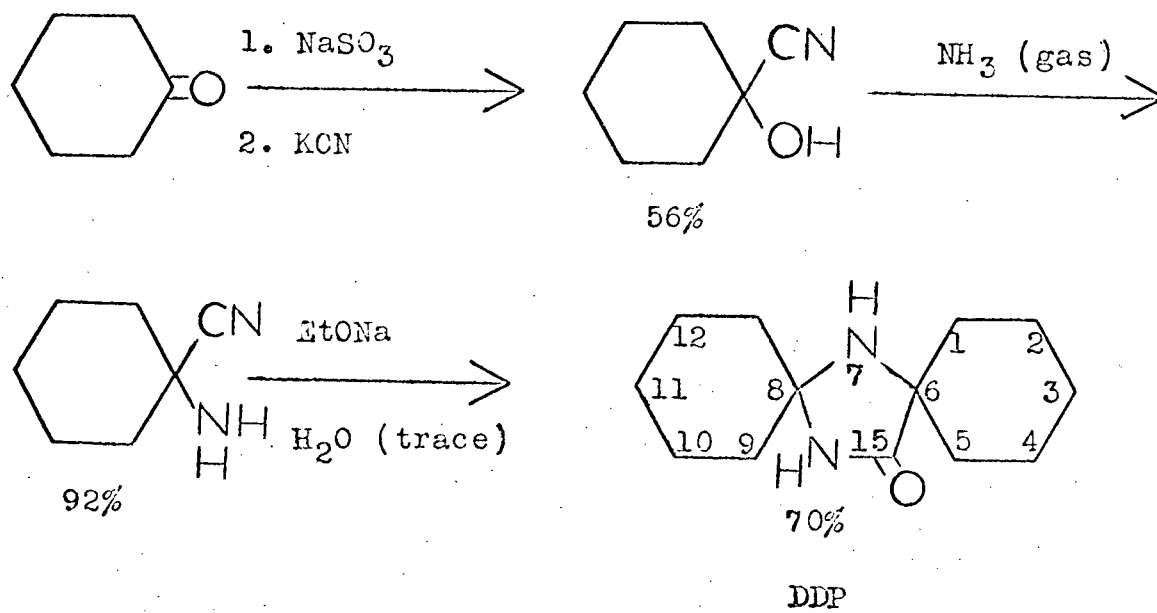
spiro[6.1.6.2]heptadec-17-one. In this laboratory, the cyclopentyl analog, 6,12-diazadispiro[4.1.4.2]tridecan-13-one, had been prepared in low yield from cyclopentanone (53) and (54).

A β-dimethylaminoethyl derivative of DDP was prepared by reacting the DDP with sodium hydride and then adding β-dimethylaminoethylbromine hydrobromide to the reaction mixture (53). Although the structure of this product shown on Infrared Spectra 10 and 11 is the 7-substituted compound, substitution on the amide nitrogen may have occurred. Under neutral conditions, the secondary nitrogen would be considerably more nucleophilic than the amide nitrogen; their pKa values would be about 11 and 0.0 respectively. The adjacent carbonyl group in the latter exerts an electron-withdrawing effect which decreases the ability of the amide nitrogen to share its unshared pair of electrons. However, in the presence of strong base the carbonyl group would help stabilize the incipient carbanion. Moreover, there appears to be some steric hindrance to attack on the secondary nitrogen, so that if a di-sodium salt formed in the reaction with sodium hydride, the amide nitrogen may be more easily alkylated. N-alkylation of amide nitrogens in the presence of sodium hydride is known; one example is the reaction of methyl iodide with a NaH treated intermediate in the synthesis of morphine (55). The lack of characteristic N-H stretching bands at 3250-3050 cm.$^{-1}$ for the lactam also suggests that substitution occurred on the amide nitrogen.

The yield of the dimethylaminoethyl derivative of DDP was increased from 11 to 17 per cent by reacting the alkyl halide with DDP at 145° and 120 p.s.i. At still higher temperature and pressure, 280° and 340 p.s.i., no product was obtained. Higher yields of the product might be obtained if the ratio of DDP to alkyl halide was 2 to 1 rather than 1 to 7 (56). The low

yields obtained are due at least partly to steric hindrance. In an analogous

reaction by F. Leung (57), the condensation of N-cyclohexyl-N-cyclohexane-

methylamine with the same alkyl halide, as well as the more reactive iodide

derivative, in the presence of sodamide, yielded no product.

The β-dimethylaminoethyl derivative of DDP was reduced with LiAlH$_4$ to

form the substituted 7,14-diazadispiro[5.1.5.2]pentadecane. As seen from

the infrared spectrum 11., the product did not contain the carbonyl function.

However, attempts to obtain a correct elemental analysis for the tripicrate

derivative of the compound were not successful.

The complete reaction sequence initially proposed for DDP is shown in

Chart 7. The synthesis of a β-dimethylaminoethyl derivative and its sub-

sequent reduction has already been described. As seen in the chart, an

alternate reaction sequence to the reduced product might begin with the

chloroacetamido derivative of DDP.

Chloroacetylation of DDP was attempted under a variety of conditions.

The apparatus, solvents, and reactants were thoroughly dried before use.

Chloroacetyl chloride was synthesized from the reaction of monochloroacetic

acid and benzoyl chloride (70) or thionyl chloride (71), the latter resulting

in higher yields. In the first series of reactions, the secondary amine, DDP,

was the hydrochloride acceptor. As seen in Table II, Part VI, no significant

difference in the yield of product was obtained when the reaction time and the

mole ratio of reactants were varied. At temperatures of 190° and 138°, no pro-

duct was obtained. In all the reactions carried out at the reflux temperature

of the solvent, benzene, about 3/4 of the starting material was recovered,

either as DDP or as its hydrochloride.

Chart 7.

7-β-Dimethylaminoethyl-DDP

β-Dimethyl-
aminoethyl-
bromine HBr

DDP

Chloroacetyl
chloride

H_3C CH_3
N
CH_2
CH_2
N

N
H

7-β-Dimethylaminoethyl-
7,14-diazadispiro-
[5.1.5.2]pentadecane

LiAlH$_4$

LiAlH$_4$

7-Chloroacetyl-DDP $\xrightarrow{\text{Dimethylamine}}$ 7-Dimethylamino-
acetyl-DDP

Methyl Iodide

CH_3
H_3C CH_3
N+
-I CH_2
C O
N

N O
H
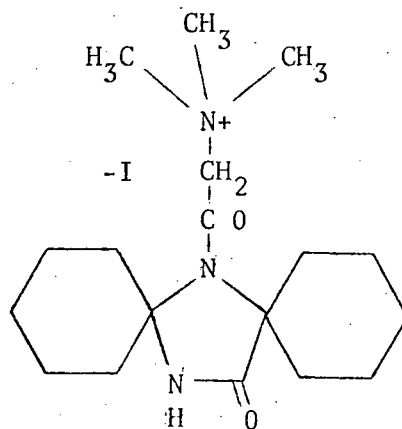
7-Trimethylammoniumacetyl-
7,14-diazadispiro[5.1.5.2]-
pentadecan-15-one Iodide

In this series of reactions as well as the ones that followed, a gum was obtained. Only after standing for several weeks could the product be obtained as a solid; the addition of acetone allowed the isolation of a white solid by suction filtration. In all the reactions tried, the solid so obtained had the same infrared spectrum. It did not contain significant quantities of the starting material or DDP HCl. No peaks are seen at 1690 cm.$^{-1}$ or 1730 and 1585 cm.$^{-1}$; but if DDP or DDP HCl are added to the product in a ratio of 1 to 100, these peaks are easily seen. The infrared spectrum did indicate that a second carbonyl peak had been added to DDP. However, a band was also seen at 1500 cm.$^{-1}$; this may be due to the presence of acyclic amide, since Amide II bands are seen in this region. Elemental analysis indicated that chlorine was present but the percent carbon obtained was too low. Thin layer chromatography showed that the product may be composed of three components. It is difficult to explain why the same infrared spectrum is obtained for the product synthesized under varying reaction conditions if this product is composed of three different compounds. It is probable that at least some acetylation is taking place on the lactam nitrogen, even under neutral conditions.

A series of model reactions was carried out to determine the reactivity of the secondary amine and the lactam nitrogen in DDP. Attempts were made to acetylate the compound using acetyl chloride in pyridine and using an excess of acetic anhydride. In both cases no significant yield of product was obtained. However this type of reaction, the acetylation of lactams, are known. For example, α-ϵ-caprolactam is acetylated in acetic anhydride at 110-120$^{\text{o}}$ (58). In a similar reaction with DDP, an intractable gum was obtained. The results indicate that the secondary nitrogen and possibly the lactam nitrogen, are sterically hindered; at a temperature high enough for the

reaction to occur to a significant extent, decomposition occurs.

The chloroacetylation of DDP was attempted in pyridine at 50° and at reflux temperature. An intractable tar was obtained in both cases.

The reaction of chloroacetyl chloride and DDP was also attempted in glacial acetic acid, according to the method of Grogan et al (38) they had successfully chloroacetylated o,o'-xylidene by this prodecure. The reaction had been carried out by another worker in this laboratory, and the product obtained gave an infrared spectrum similar to DDP except that a new peak was present at 1595 cm.$^{-1}$ (53). When the reaction was repeated in this inquiry the compound responsible for the 1595 cm.$^{-1}$ was separated from DDP by removing the latter with chloroform. Elemental analysis on the unidentified compound indicated that no nitrogen was present.

The method of Nagaten et al (59) for the benzoylation of lactams after treatment with NaH was applied to the chloroacetylation of DDP. The infrared spectrum of the product contained several peaks in the carbonyl stretching region indicating that substitution may have occurred at both nitrogens. Only very small yields were obtained and the reaction was not investigated further.

Finally, synthesis of 7-chloracetacetyl-7,14-diazadispiro[5.1.5.1]-pentadecan-15-one was attempted using potassium carbonate as the hydrochloride acceptor. This method has been used by several workers to add chloracetyl chloride to unhindered primary amines, one example is the addition of the chloroacetyl group to 2-aminotropone (60). The reaction was first run in benzene but the product was obtained in smaller yields and contained more impurity than the same reaction in acetone. Table III in Part VI shows the different reaction conditions tried. The best yield was obtained with a mole

ratio of acyl halide to DDP of 2:1. This reaction gave about 5% yield of
product with the same infrared spectrum as was obtained from the product of
previous reactions run in benzene without potassium carbonate. Over 90% of
the starting material was recovered, mostly as DDP, not the hydrochloride, as
was seen in reactions without the K_2CO_3.

Attempts were made to purify the product obtained from the reaction
of chloracetyl chloride and DDP. First the material was spotted on a 20x20 cm.
Eastman K30IR silica gel sheet with fluorescent indicator. A total of 1 ml.
of a 5 mg./ml. solution of the product in ethanol was spotted along the origin
of the sheet forming a line about 2 mm. wide under ultra-violet light. After
developing the chromatogram with a hexane, absolute ethanol, diethylamine,
6:1:2 solution, three bands could be seen under short-wave ultra-violet light.
The silica was scraped from the dark areas and then extracted with ethanol.
The ethanol was evaporated off, and the infrared spectrum of the residue was
recorded. The spectra obtained were too weak to be definitely assigned to
individual compounds.

Two attempts were made to purify the putative chloracetyl derivative
of DDP using "dry column" chromatography. The advantage of this technique
is that the same conditions found to be suitable for the separation of a
mixture by TLC can be directly transferred to the preparative system (61).
The mixture to be separated is placed on the top of the column and the
chromatogram is developed by allowing the solvent to move down the dry column
by capillary action aided by gravity. Furthermore, when the column used is
nylon and fluorescent material has been added to the adsorbent, the bands of
separating material can, under ideal conditions, be seen if the chromatogram
is developed in the dark and is irradiated with ultra-violet light. The first

attempt was made using an alumina adsorbent that had been deactivated with 4% water and had been made fluorescent by the addition of 0.5% duPont No. 609 Luminescent Chemical. The column was prepared and developed according to the method of Loev and Goodman (61). It was loaded by adsorbing the 530 mg. of material to be purified onto alumina and then distributing the alumina onto the column's top. The developing solvent was 80:18:2, acetone reagent:absolute methanol:diethylamine. Before the developing had begun, dark bands were seen under ultra-violet light that were due to the uneven packing of the column. The only band seen under irradiation with ultra-violet light while the column was developing was one that could be seen under ordinary light because it was coloured. Only a small amount of material was isolated from the first 25 ml. of solvent through the column, and no significant amount of material was isolated from subsequent fractions. The infrared spectra of the first material isolated was similar to DDP HCl. In order to recover the material from the column, the adsorbent was divided into five portions and these were extracted with hot ethanol, chloroform, and glacial acetic acid, in that order. Only small amounts of materials were extracted and the infrared spectra of these did not indicate the presence of DDP or its derivatives. It is possible that the alkyl halide group chemically reacted with the column.

A second column was prepared as before except that silica was used as the adsorbent. The gel was deactivated with 15% water (61) and the fluorescent material was added as before. The column was loaded by distributing the material to be separated directly on top of the column rather than adsorbing it onto the adsorbent as before. It was thought that denser dark bands might be obtained in this manner. The developing solvent was hexane:absolute ethanol:diethylamine, 6:1:2. Again no dark bands could be seen under short-

wave ultra-violet light except for the yellow band at the solvent front. As in the previous column, neither the fractions of the developing solvent nor the solvent extractions of the adsorbent yielded material whose infrared spectra indicated that a DDP derivative was present.

Because of the difficulties encountered in the purification of the chloroacetyl-DDP and in the synthesis of this compound in good yield, work on an analogous series of dispiro compounds was begun. Relatively little steric hindrance is present in this series because the nitrogen at which substitution occurs is primary rather than secondary. The reactions of these compounds are discussed in the following section.

B.   SYNTHESIS OF DERIVATIVES AND ANALOGS OF 7-AMINO-14-AZADISPIRO[5.1.5.2]-

PENTADECAN-15-ONE

The synthesis and structure determination of C-I, one of the starting

materials used in Section Two of the Experimental, has already been described

in Part III b. In this laboratory C-I (m.p. 272-274° after recrystallization)

was obtained in 33.8% and 16.4% yield using piperazine and pyrrolidine as

catalyst, respectively. The literature values are 47.2% (48) (m.p. 263-265.5^O,

not recrystallized) and 67% (49), using piperazine, and 23% (49) using pyr-

rolidine.

As seen in Figure 5, in Part III, the reduction of C-I, an unsaturated,

five-membered ring ketoxime N-hydroxylactam, to C-II a saturated primary

aminolactam is accomplished using nickel as a catalyst. The reduction was first

accomplished by Nightingale's group at 105-130° and 2900 p.s.i. (46), and

then by Noland and Sundberg (51) at room temperature and 30 p.s.i. In this

laboratory the latter method was used; the yield was 45.5%, m.p. 192-193°

after recrystallizations from ethanol, lit. (51) 95%, m.p. 193-195°, before

recrystallization. In some reductions attempted, unreactive starting material

and the partially reduced iminolactam were obtained.

The synthesis of 7-dimethyaminoacetamide-14-azadispiro[5.1.5.2]-

pentadecan-15-one was attempted by the addition of dimethylaminoacetic acid

hydrochloride to C-II previously treated with dicyclohexylcarbodiimide,

according to the method of Sheehan and Hess (62) proposed for peptide bond

formation. Triethylamine was used as the hydrochloride acceptor (63). The

general mechanism for this reaction is shown below (64).

$$
\begin{array}{ccccccc}
\underset{\text{RC-OH}}{\overset{O}{\|}} & + & \underset{\underset{NR'}{\|}}{\overset{NR'}{\underset{C}{\|}}} & \longrightarrow & \underset{\underset{HNR'}{|}}{\overset{\overset{NR'}{\|}}{RC\text{-}O\text{-}C}} & \xrightarrow{H^+} & \underset{\underset{NHR'}{|}}{\overset{\overset{\overset{+}{N}HR'}{\|}}{RC\text{-}O\text{-}C}} & \xrightarrow{RCO_2^-} & \underset{\underset{NHR'}{|}}{\overset{NHR'}{\underset{C}{\|}}}=O & + & \overset{RC}{\underset{RC}{}}\!\!\ce{=O}\,O
\end{array}
$$

I   II   III   IV   V   VI

III ⟶ VII   IV $\xrightarrow{NH_2R''}$ VI $\xrightarrow{NH_2R''}$

$$
\underset{\underset{NHR'}{|}}{\overset{\overset{RC\text{-}NR'}{\underset{O}{\|}\;|}}{C}}=O \qquad \xrightarrow{NH_2R''} \qquad RCO\text{-}NHR'' \;+\; \underset{\underset{NHR'}{|}}{\overset{\overset{NHR'}{|}}{C}}=O \qquad RCO\text{-}NHR'' \;+\; \underset{RC\text{-}OH}{\overset{O}{\|}}
$$

VII   VIII   V   VIII   IX
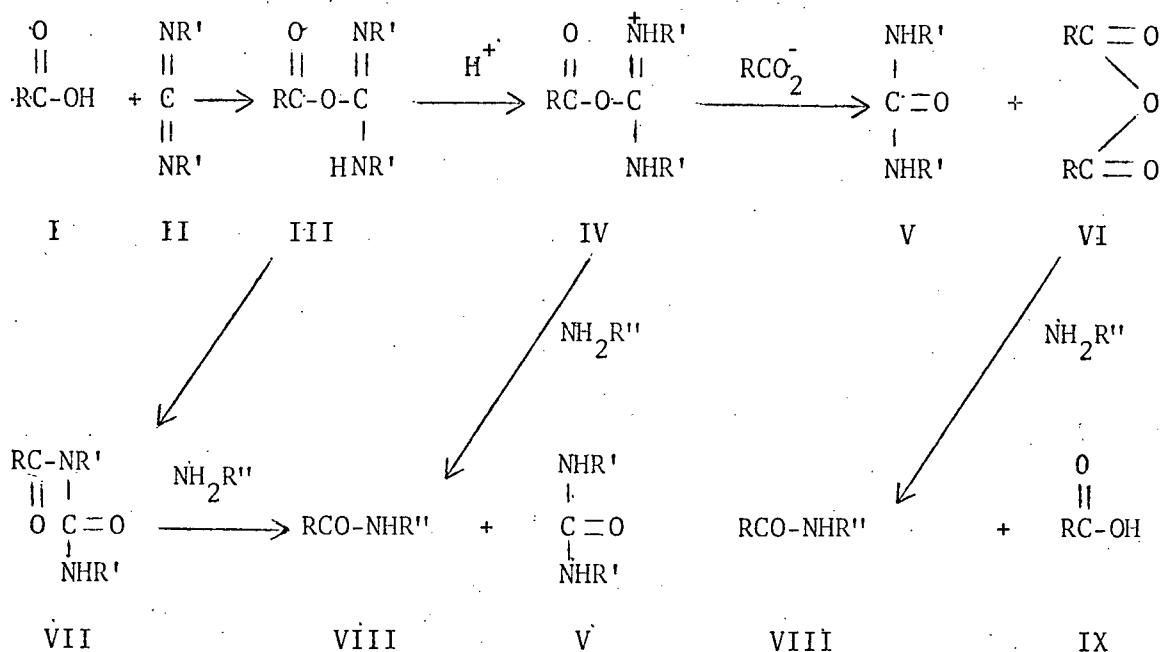
The carboxylic acid (I) reacts with the carbodiimide (II) which, in turn, could undergo either conversion to two active forms (IV and VI) of the original carboxylic acid or rearrangement via acyl transfer to an N-acylurea (VII). The latter compounds are generally quite stable and exhibit little inclination to undergo condensation, but this depends on the particular peptide derivative, carbodiimide, and solvent involved. Rearrangement of (III) to (VII) occurs via an intramolecular mechanism while the reactions (III) to (IV), (IV) to (VI) and (VIII), and (VI) to (VIII) are bimolecular; therefore, the formation of the desired products should be favored by an increase in the concentration of the reactants. Hence the amount of solvent employed should be kept to a minimum (64). The dicyclohexylurea (V) is easily separable from the product by virtue of the former's general insolubility in most of the solvents employed during the coupling step.

Only one attempt was made to condense dimethyaminoacetic acid with C-II. Approximately equimolar quantities of the carboxylic acid, C-II, triethylamine, and DCC in dichloromethane were stirred at room temperature for two weeks. No

compounds with two carbonyl peaks in the 1750-1650 cm.$^{-1}$ region were isolated from the solvent.

The same reaction was also attempted using the cycloheptyl analog of C-II, 8-amino-16-azadispiro[6.1.6.2]heptadecan-17-one. After stirring the reactants at room temperature for two days, the reaction mixture was diluted with hot dichloromethane and filtered to remove the dicyclohexyurea, and triethylamine hydrochloride. This time the filtrate yielded a white solid whose infrared spectrum showed carbonyl peaks at 1705 and 1660 cm. $^{-1}$, an Amide II peak at 1530 cm.$^{-1}$ and peaks at 2825, 2780, and 2725 cm.$^{-1}$ all of which are consistent with the desired product. However, the elemental analysis resulted in a carbon value that was too low. An attempted reduction of this compound with LiAlH$_4$ resulted in a liquid whose infrared spectrum indicated that the carbonyl groups had been reduced; however, at least one alcohol group had been formed in the same reaction.

The cycloheptyl analog of C-I, H-I, was probably first synthesized by Eckstein et al (65) in 1958 in their investigation of the reaction of cycloheptanone, nitromethane, and piperidine. But at that time it was known only as a crystalline by-product and no physical constants, elemental analyses, or yields were reported by them. The synthesis of this compound had previously been attempted by Nightingale's group but no solid product was obtained (46). Later her laboratory found that the product had formed but that the addition of acid was necessary to precipitate it from the reaction mixture (49). In this laboratory, H-I was synthesized in 22.5% yield, m.p. 246-249°, lit. (48) 51.5%, m.p. 208-209°, and lit. (49) 250-251°, using piperazine as the catalyst, and in 20% yield, m.p. 247-250°, lit. (49) 46-48%, m.p. 247-249° and 250-251°, using piperidine as the catalyst.

Shozo Miki (48) had attempted the hydrogenation of H-I as well as B-I and i-P-I (see Figure 6 for structures) but found that none of these was appreciably reduced in the presence of Raney nickel catalyst, unlike C-I, M-I, and P-I, which form C-II, M-II and P-II in good yield under the same conditions. The conditions used for the attempted hydrogenation of H-I were 1,750 p.s.i. and 162°. Miki suggested that steric hindrance may have prevented the hydrogenation of these bulkier compounds. The melting point of the H-I used by Miki, 208-209°, suggests that the piperazine salt of H-I (m.p. 225-226°) was actually the compound subjected to hydrogenation conditions.

In the present study, H-I was hydrogenated over Raney nickel at room temperature and 30-60 p.s.i. after three days shaking in absolute alcohol. The infrared spectrum showed only one unsaturation peak and the hydroxyl peak at 3200 cm.$^{-1}$ was no longer present. An elemental analysis was not obtained for H-II itself, but for its chloroacetyl derivative. The correct carbon, hydrogen, nitrogen, and chlorine values were obtained.

The chloroacetyl derivative was synthesized by adding monochloroacetyl chloride to H-II and potassium carbonate in dry benzene and refluxing for 30 minutes. The reaction mixture was filtered hot to remove inorganic salts and the product precipitated from the solvent on cooling. The infrared spectrum showed new peaks at 1665 and 1540 cm.$^{-1}$ that were assigned to the Amide I and Amide II bands, respectively, of the acyclic amide. The same reaction also yielded a product with a 1760 cm.$^{-1}$ peak; this may be the diacetylated compound, as no Amide II peak was seen. Tertiary and alicylic amides do not exhibit an Amide II band. Chart 8 shows the hydrogenation of H-I, an unsaturated, dispiro compound with a five-membered ring ketoxime N-hydroxylactam, to H-II, a primary aminolactam; the reactions attempted using H-II are also shown.

Chart 8.

H-I

H-II

Chloroacetyl
chloride

NaNH$_2$,
β-dimethyl-
aminoethyl-
bromine HBr

8-Cloroacetamido-16-azadispiro-
[6.1.6.2]heptadecan-17-one

DCC,
Dimethylamino-
acetic acid
HCl

8-Dimethylaminoacetamido-16-aza-
dispiro[6.1.6.2]heptadecan-17-one

8-Dimethylamino-
ethyl-H-II
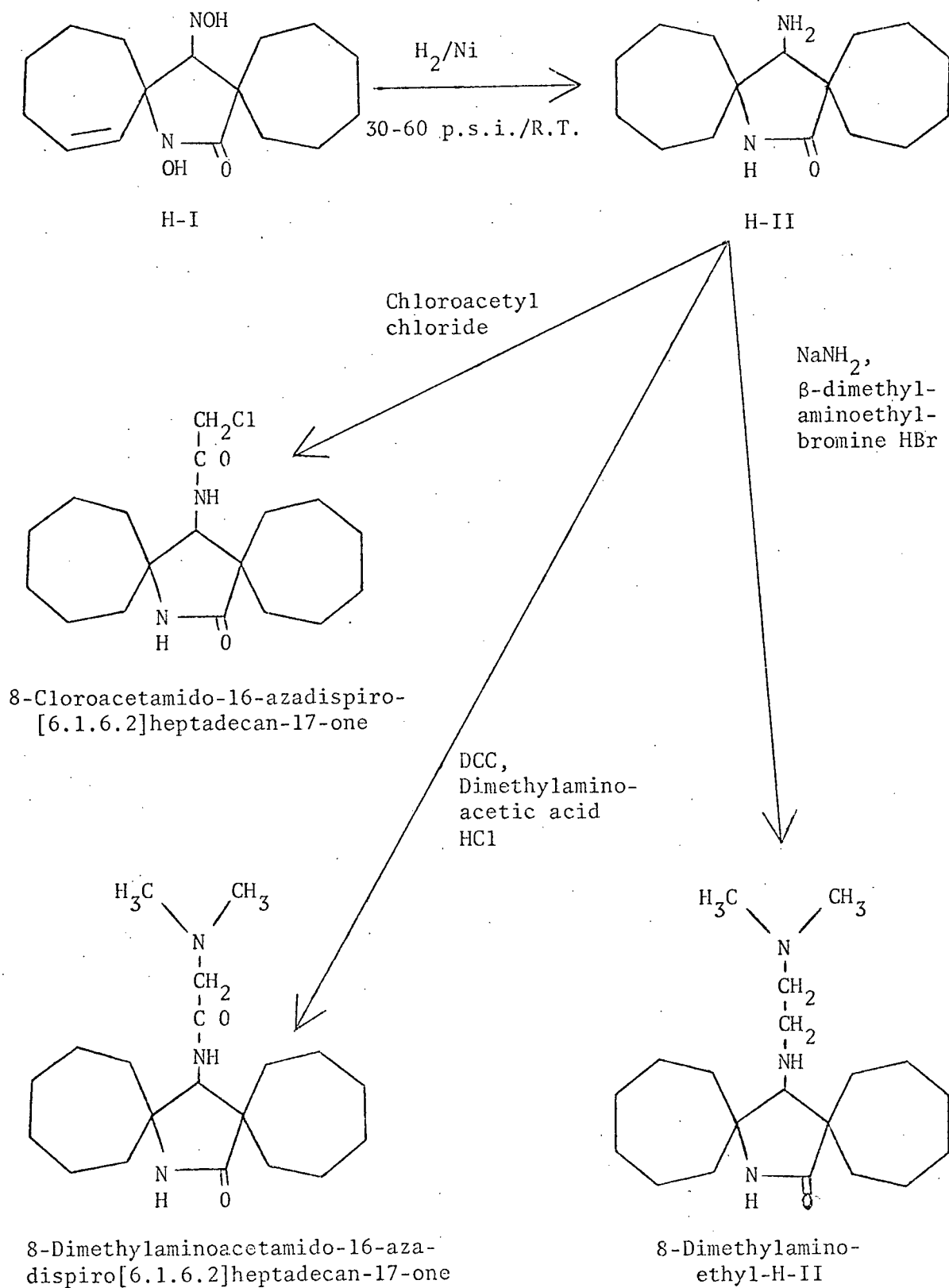
As seen in Chart 8, the synthesis of the 8-β-dimethylaminoethyl derivative of H-II was attempted using sodamide. The reaction was attempted only once and only unreacted H-II could be recovered from the reaction mixture.

The next reactions that would have been attempted are the addition of dimethylamine to the chloroacetyl derivative of H-II, and the formation of the methiodide of the product obtained; the analogous reactions with DDP are shown on Chart 7. Time did not permit these reactions to be attempted.

PART V

EXPERIMENTAL *

SECTION ONE

SYNTHESIS OF DERIVATIVES AND ANALOGS OF 7,14-DIAZADISPIRO[5.1.5.2]-

PENTADECAN-15-ONE

A.   7,14-DIAZADISPIRO[5.1.5.2]PENTADECAN-15-ONE

1. Cyclohexanone Cyanohydrin (66)

A solution of 150 g. (1.53 moles) of cyclohexanone in 900 mls. of ether

was placed in a 3-liter, three-necked flask equipped with reflux condenser,

dropping funnel and a mechanical stirrer.   To this was added, over a period

of six hours, 600 mls. of a saturated solution of sodium bisulfite.   The

bisulfite addition product was collected by suction filtration and washed

thoroughly with solvent ether.   The white solid was added to 600 ml. of

water to form a slurry and then placed in the above apparatus.   A saturated

solution of potassium cyanide (120 g. KCN in 300 mls. water) was added

dropwise until a clear solution formed.   The two layers were separated and

the aqueous layer was extracted twice with 150 ml. of ether.   The oil and

ether layers were combined and then extracted with 300 mls. of water

containing 0.75 ml. of concentrated hydrochloric acid, until neutral to red litmus. The ether-oil layer was dried over anhydrous sodium sulfate for 12 hours. The ether was removed by flash evaporation and the residue was distilled under reduced pressure, b_{2-3} 97-98°. The yield was 146 g. (1.17 mole, 56%) of title compound based on cyclohexanone.

2. 1-Aminocyclohexanecarbonitrile (51)

Cyclohexanone cyanohydrin (146 g.) was melted and placed in a 200 ml. 3-necked conical flask. Ammonia gas was bubbled through the liquid for 18 hours to form the amino compound. The excess ammonia was then removed by bubbling nitrogen gas through the product. The resulting faint yellow liquid was dissolved in 200 mls. of benzene and extracted with 75 mls. of water. The benzene solution was dried over sodium sulfate for 12 hours. The benzene was removed by flash evaporation but further purification by distillation was not attempted because 1-aminocyclohexanecarbonitrile may be unstable to heat (67). The yield of crude product was 134 g. (1.08 mole, 92%).

3. 7,14-Diazadispiro[5.1.5.2]pentadecan-15-one (DDP) (43)

To a solution of sodium ethoxide (prepared from 31.5 g. of sodium and 900 mls. of 98.4% by weight ethanol) was added 238 g. (1.77 moles) of 1-aminocyclohexanecarbonitrile. The mixture was allowed to stand at room temperature overnight. Crystals started to form after a few minutes and the mixture had solidified after 12 hours. The white solid was collected by suction filtration and recrystallized from chloroform. The yield was 138 g. (0.62 mole; 70% on 1-aminocyclohexanecarbonitrile, 36% on cyclo-hexanone) m.p. 212-217°, lit. 94%, m.p. 219-222°. After several recrystallizations from $CHCl_3$ the m.p. was 218-220°, lit. 219°.

B.   A β-DIMETHYLAMINOETHYL DERIVATIVE OF 7,14-DIAZADISPIRO[5.1.5.2]-
PENTADECAN-15-ONE

1. At Atmospheric Pressure (53)

In a 3-necked, 1000 ml. flask equipped with stirrer and reflux con-
denser, 8.0 g. (0.036 mole) of DDP and 4.48 g. (0.186) of sodium hydride in
400 mls. of dry xylene were refluxed for two hours.   To this was added
19.2 g. (1.34 mole) of β-dimethylaminoethylbromine hydrobromide.   The
mixture was refluxed with stirring for 48 hours.   The resulting red-brown
mixture was filtered and the precipitate treated with absolute alcohol to
destroy any remaining sodium hydride.   The xylene and unreacted
β-dimethylaminoethylbromine were removed by distillation at 2-3 mm. from a
water bath heated to 80°.   The residue in the flask was extracted with
anhydrous ether to separate the product from unreacted DDP.   The ether was
distilled off leaving a viscous light brown liquid.   Distillation at
148-174° at 0.7-1.0 mm. (mostly 155-156° at 0.9 mm.) yielded 1.17 g. (11%) of
clear, colorless liquid.   The infrared spectrum showed peaks at 2820 and
2760 cm^{-1} that are characteristic of the dimethylamino function.

7-β-Dimethylaminoethyl-7,14-diazadispiro[5.1.5.2]pentadecan-17-one
Dipicrate: A solution of 0.3 g. of the product in 10 ml. of 95% ethanol
was added to 10 ml. of a saturated solution of picric acid.   The mixture
was heated to boiling and then allowed to cool slowly.   The yellow crystals
were filtered and recrystallized from chloroform and petroleum ether
(b.p. 60-80°) to a m.p. of 183-184°.

Anal. Calcd. for $C_{29}H_{37}N_9O_{15}$:   C, 46.34;   H, 4.96;   N, 16.77;
Found: C, 45.83;   H, 5.22;   N, 16.76.

2. At High Pressure and Temperature

The sodium salt was prepared in the same quantity and by the same procedure as above. The light orange-brown mixture was poured into an 800 ml. glass liner and the β-dimethylaminoethylbromine hydrobromide was added in the same quantity as before. The liner was placed inside of the Parr Series 4511 Pressure Reaction Apparatus and the mixture was heated to 145° at which temperature a pressure of 120 p.s.i. was reached. After stirring for 18 hours and then cooling to 20°, a pressure of 80 p.s.i. remained. At this stage the reaction mixture was divided into two portions.

(a) One-half of the volume of supernatant (174 ml.) was removed. This was worked-up as before to yield 0.9 g. (17.1%) of very viscous liquid, b.p. 148-161° at 0.7 mm. (on redistillation the b.p. was 164-168° at 1.1-1.3 mm.). The infrared spectrum was identical to that obtained from the reaction at atmospheric pressure.

(b) The remainder of the supernatant with most of the solid was exposed to 280° at 340 p.s.i. for 17 hours. A distinct odor of coal-tar was present when the bomb was opened. Distillation of the residue yielded a few drops with a b.p. 155-170° at 0.7 mm. but the infrared spectrum of this fraction showed no peaks characteristic of the dimethylamino function.

C. A β-DIMETHYLAMINOETHYL DERIVATIVE OF 7,14-DIAZADISPIRO[5.1.5.2]-
     PENTADECANE

In a 100 ml. three necked flask equipped with a mechanical stirrer, reflux condenser, dropping funnel and drying tube was placed 0.18 g. of lithium aluminum hydride in 30 ml. of anhydrous ether; this was refluxed for one hour. A solution of 1.12 g. of β-dimethylaminoethyl-DDP in 40 ml.

of anhydrous tetrahydrofuran was added to the cooled hydride slurry. After

the reaction mixture was refluxed for one hour, water was added to the cooled

solution until it just turned white. The mixture was centrifuged, the

supernatant poured off, and the precipitate extracted with ether, and the

combined oily layers were dried over $MgSO_4$. The drying agent was filtered off

and the solvent was removed by rotary evaporation. Distillation at 138-156°

at 4.5 mm. yielded 36% of reduced product. The infrared spectrum showed

no carbonyl peak at 1685 cm.$^{-1}$ and the 2820-2760 cm.$^{-1}$ peaks characteristic

of the dimethylamino function remained.

7-β-Dimethylaminoethyl-7,14-diazadispiro[5.1.5.2]pentadecane

Tripicrate: A solution of 0.3 g. of the product in 10 ml. of 95% ethanol

was added to 10 ml. of a saturated solution of picric acid. The mixture

was heated to boiling and allowed to cool slowly. The yellow crystals

were filtered and then washed with hot ethanol and benzene to remove traces

of picric acid. After recrystallization from hot water the feather shaped

crystals started to decompose about 212° and melted at 230-231°.

Anal. Calcd. for $C_{35}H_{42}N_{12}O_{21}$: C, 43.48; H, 4.38; N, 17.39;
Found: C, 39.85; H, 4.22; N, 19.24

D.   7-CHLOROACETYL-7,14-DIAZADISPIRO[5.1.5.2]PENTADECAN-15-ONE

1. Using DDP as the Hydrochloride Acceptor

In a 3-necked 2-liter flask equipped with reflux condenser, dropping

funnel, drying tube and stirrer was placed 15 g. (0.0667) of dry DDP in

900 ml. of anhydrous benzene. The chloroacetyl chloride (2.48 g., 0.0222

mole) was added dropwise in 100 ml. of anhydrous benzene to the above

solution. No immediate white precipitate formed (if the acyl halide is

not carefully redistilled, the dissolved HCl causes the immediate precipitation

of DDP hydrochloride), but after heating a heavy white precipitate was seen.

The reaction mixture was refluxed for one hour and then stirred at room

temperature for three hours. The mixture was filtered by suction to yield

5.4 g. of white solid whose infrared spectrum indicated that it was composed

mainly of DDP hydrochloride with a trace of unreacted DDP. Hydrogen

chloride was bubbled through the clear filtrate to precipitate any dissolved

amine. Suction filtration of the milky solution yielded 3 more grams of DDP

salt. The still cloudy filtrate was extracted twice with 500 ml. of water,

and the aqueous layer was made basic with 5% NaOH and then filtered to yield

2.7 g. of DDP. The clear, colorless benzene layer was dried over anhydrous

$MgSO_4$ for 48 hours. After removal of the drying agent by suction filtration,

the drying agent was extracted with hot benzene, acetone and chloroform

in succession, to determine if any product had adsorbed onto it. The

benzene yielded a few mgms. of brown gum from which DDP hydrochloride was

isolated. Similarly the acetone and chloroform extractions of the dying

agent yielded 40 mg. and 25 mg. of DDP HCl respectively. A total of the

equivalent to about 10 g. of DDP was isolated from the work-up; this is

consistent with the 1:3 ratio of acyl halide to amine used.

The benzene and HCl were then removed from the reaction product by

rotary evaporation. The viscous liquid that remained (approx. 2 g.) was

exposed to a temperature range of -70° to 100° over a period of 48 hours

in an attempt to find the best temperature to induce crystallization. Only

a few crystals could be seen after this treatment. The semi-solid was kept

in the refrigerator for one month. Next the material was dried thoroughly

at 100° and 2 mm. The addition of acetone to the gum resulted in a white

solid precipitate that could be separated from the brown acetone solution

by filtration. This solid was recrystallized from ethanol to yield color-
less cubical crystals that decomposed slowly above 180° but more rapidly at
196°, using the Fisher Stage Apparatus. In the capillary apparatus a melting
point of 212-213° (dec.) was obtained. The infrared spectrum showed peaks at
1754 and 1645 cm.$^{-1}$: The latter could be the Amide I band of a tertiary amide.
However a band at 1500 cm.$^{-1}$ was also present; this may be due to the presence
of an acyclic secondary amide. Elemental analysis showed the presence of
chlorine.

<u>Anal.</u> Calcd. for $C_{15}H_{23}N_2O_2Cl$: C, 60.29; H, 7.76; N, 9.34;
Found: C, 49.39; H, 5.32; N, 9.00

The various reaction conditions that were employed in which DDP was
the hydrochloride acceptor are summarized in Table II.

Model Reactions-Acetylation of DDP

(a) <u>Using Acetyl Chloride and Pyridine</u> In a 50 ml. mini-ware flask
equipped with condenser, stirrer, drying tube and dropping funnel were placed
4.4 g. (0.02 mole) of DDP, 0.8 g.(0.02 mole) of freshly distilled pyridine,
and 30 ml. of dry chloroform. This was cooled in an ice bath and freshly dis-
tilled acetyl chloride (0.8 g., 0.01 mole) was added dropwise in 10 ml. of
dry chloroform. The ice bath was removed and the mixture was stirred for 20
hours at room temperature. The reaction mixture was then divided into two
portions. One-half the mixture was removed and filtered, and the filtrate
was washed with 5% HCl, dried over calcium chloride, and evaporated to dryness
<u>in vacuo.</u> Only a few milligrams of solid was obtained. After two recrystal-
lizations from $CHCl_3$-petroleum ether the infrared spectrum of the solid showed
a broad peak centered at 3360 cm.$^{-1}$ indicating that a hydroxyl group is
present.

TABLE II

REACTION CONDITIONS IN THE SYNTHESIS OF THE CHLOROACETYL DERIVATIVE OF

DDP IN WHICH DDP IS THE HYDROCHLORIDE ACCEPTOR

LOT	GM. DDP USED	REACTION PROCEDURE	DDP REMOVER	WT. OR QUALITY OF PRODUCT
I	5.0	Reflux for 3 hours	5% HCl	Less than 0.1 g.
II	20.0	Reflux for 6 hours	5% HCl	Less than 0.1 g.
III	25.8	Stir for 65 hours then reflux 2 hrs	5% HCl	Less than 0.1 g.
IV	10.0	Heated with stirring to 190° under 310 p.s.i. for 11 hours	5% HCl	Intractable tar
V	10.0	Heated with stirring to 138° under 700 p.s.i. for 19 hours	5% HCl and HCl gas	DDP, DDP HCl and tar
VI*	15.0	Reflux for 1 hour then stir for 3 hours	HCl gas	0.2 g.

*   The DDP to chloroacetyl chloride mole ratio was 2 to 1 in each
     reaction except VI where it was 3 to 1. The solvent was benzene
     in all the reactions.

The second half of the reaction mixture was refluxed for 12 hours. Only DDP hydrochloride was isolated from this portion.

(b) <u>Using Acetic Anhydride</u>   In 40 ml. of acetic anhydride containing one drop of concentrated H_2SO_4 as catalyst, 5 g. of DDP was refluxed for 10 minutes. A small sample was removed and worked-up to yield DDP. The remainder of the mixture was then refluxed for 30 hours. The acetic anhydride was removed <u>in vacuo</u>. Attempts to decolorize the dark brown gum were unsuccessful. Similarly attempts to purify the material by recrystallization from $CHCl_3$-petroleum ether failed.

(c) <u>Using Acetic Anhydride at Elevated Pressure</u>   In a 100 ml. round bottomed flask with the stopper wired on, 5 g. of DDP in 40 ml. of acetic anhydride was heated under approximately 20 p.s.i. for 5 hours. The mixture was poured into 300 ml. of water and boiled to destroy the anhydride. The solvent was then removed <u>in vacuo</u> to yield a brown solid. Only DDP and uncrystallizable material could be obtained.

2.   <u>Using Pyridine as the Hydrochloride Acceptor</u>

To a solution of 100 mg. of DDP in 10 ml. of dry pyridine was added dropwise 150 mg. of chloroacetyl chloride. The solution turned purple-brown as the acyl halide was being added. After refluxing for 5 minutes the DDP HCl was filtered off and the pyridine was evaporated <u>in vacuo.</u> The material obtained was an intractable tar.

A second reaction was carried out using the above reactants. This time the chloroacetyl chloride was added rapidly enough for the reaction mixture to warm to 50°, but the solution was not refluxed. Again the only water insoluble material was a tar.

3. Using DDP and Sodium Acetate as Hydrochloride Acceptors

A solution of 3.51 g. of chloroacetyl chloride in 30 mls. of glacial acetic acid was added dropwise with stirring to a solution of 6.0 g. of DDP in 37.5 mls. of glacial acetic acid. After stirring for 10 minutes and cooling to 5° in an ice bath, 9.3 g. of sodium acetate in 37.5 mls. of water was added. The precipitate was removed by suction filtration; it was 4 g. of DDP HCl. The solvent was removed in vacuo to leave approximately 15 g. of solid. This was extracted with chloroform to yield a small amount of DDP and a second compound. An elemental analysis of this unidentified compound (the infrared spectrum of which had no 1700 cm^{-1} peak but did have a strong peak at 1600 cm^{-1}) indicated that nitrogen was absent.

4. Using the Sodium Salt of DDP

In a 3-necked flask equipped with stirrer, reflux condenser, drying tube and dropping funnel, a solution of 6 g. of DDP in 300 ml. of xylene was refluxed with 3.4 g. of sodium hydride. The heat was removed and 3.5 g. of chloroacetyl chloride in 50 ml. of dry xylene was added dropwise with stirring to the cool solution. After refluxing for 36 hours the reaction mixture was filtered and the xylene removed in vacuo. The dark brown liquid remaining was distilled at 2 mm. Three fractions were obtained with b.p. 70-75°, 90=100° and 100-115°; the infrared spectrum of each contained several peaks in the carbonyl region. These fractions were not investigated further because of the small quantities present.

The reaction was repeated as before except that excess NaH was removed by filtration through glass wool before the acyl halide was added and the reflux time was only 20 hours. Again only a few drops of xylene soluble material was obtained; the infrared spectrum was similar to that obtained in the above reaction.

5. Using Potassium Carbonate as Hydrochloride Acceptor

Chloroacetyl chloride (3.30 ml., 0.042 mole) was added dropwise to
a stirred mixture of DDP (4.44 g., 0.020 mole) and anhydrous potassium car-
bonate (6.90 g., 0.050 mole) in 500 ml. of dry acetone. The ratio of acyl
halide to amine was 2:1. The reaction mixture was refluxed for 24 hours.
The 11.01 g. of solid obtained after suction filtration, was extracted with
acetone to yield 1.18 g. of DDP. The remainder was extracted with hot 95%
ethanol to remove 2.05 g. of a mixture of 1.86 g. of DDP and 0.19 g. of
DDP HCl. The ethanol insoluble portion was completely water soluble and
after being made alkaline very little precipitate was seen, indicating that
this portion was composed of inorganic salts and not amine. The total
amount of DDP recovered was 3.36 g. (76% of the amount used). The acetone
was distilled off in vacuo to yield a viscous liquid that did not crystal-
lize after standing in the refrigerator for several days. Attempts to
extract solid from the material by the addition of ether and/or acetone in
varying proportions was not successful. After standing in a vacuum dissica-
tor for two weeks, the addition of acetone to the viscous material caused the
precipitation of 450 mg. of white solid. A 1790 cm.$^{-1}$ peak was present in
the infrared spectrum of this material. After ether extraction the solid gave
a spectrum identical to that obtained from the product of procedure 1. After
recrystallization from ethanol the m.p. was 212-213°.

Various reaction conditions were tried in which potassium carbonate
was the hydrochloride acceptor; these are summarized in Table III.

E. PURIFICATION OF 7-CHLOROACETYL-7-14-DIAZADISPIRO[5.1.5.2]PENTADECAN-
   15-ONE (Attempted)

   ### 1. Thin Layer Chromatography on Silica
   A 4x20 cm. Eastman K30IR silica gel sheet with fluorescent indicator

TABLE III

REACTION CONDITIONS USED IN THE SYNTHESIS OF THE

CHLOROACETYL DERIVATIVE OF DDP USING POTASSIUM

CARBONATE AS THE HYDROCHLORIDE ACCEPTOR *

MOLE RATIO DDP:ACYL HALIDE	GM. DDP USED	SOLVENT	PROCEDURE	PRODUCT OBTAINED
1:1	4.44	benzene	Reflux for 30 min.	Approx. 50 mg.
1:1	4.44	acetone	Reflux for 60 min.	Approx. 200 mg.
1:2	4.44	acetone	Reflux for 24 hours	450 mg.
1:1	2.22	acetone	Reflux for 8 days	Approx. 20 mg.
1:2	20.0	DMF	Stir for 12 hr. then heat to 130° for 5 min.	Trace amounts

*   In all the reactions approximately 75% of the DDP was recovered from the reaction mixture.

was activated by heating at 110° for 30 minutes and then spotted with a

5 mg./ml. solution of the product. The following solvents were tried in an

attempt to find the one that would give the best separation of the maximum

number of spots: hexane:ethanol, 19:1, 9:1, 8:1, and 6:1; absolute

ethanol alone, and the latter with petroleum ether (b.p. $65-110^o$), 1:1, 1:6,

and 1:10; absolute ethanol:petroleum ether (b.p. $65-110^o$):glacial acetic

acid, 1:6:1, 1:6:2, and 2:6:3; absolute ethanol:benzene, 1:1 and 1:4;

ethanol:glacial acetic acid, 1:2, 1:4 and 1:10; ethanol:water, 1:1, and

1:10; ethanol:acetone, 1:10; hexane:absolute ethanol:diethylamine, 6:1:2,

6:1:1 and 6:1:0.5. The 6:1:2 mixture of this last solvent system was found

to give the best separation of the three spots seen.

This solvent was then used to develop a 20x20 cm. silica sheet

spotted with a total of 1 ml. of the solution; the average spot diameter

was about 2 mm. Three bands were seen on the plate under short-wave

ultra-violet light. The Rf values were 0.64, 0.75 and 0.8. The 0.64 band

appeared to contain about 70% of the solute. The three dark areas and the

origin and solvent front were cut from the silica sheet. The silica was

scraped off the sheet and the powder was extracted with 3 mls. of hot

absolute ethanol. The ethanol was evaporated and the infrared spectra of

the solids remaining was determined. The infrared spectrum of pure silica

gel showed bands at 3400 and 1100 cm.$^{-1}$ (strong and broad) and 2900 and 800

cm.$^{-1}$ (medium). The ethanol extract of the gel where no dark band could

be seen under ultra-violet light yielded a solid with peaks at 2880 and

2800 cm.$^{-1}$ also. These latter peaks may be due to the fluorescent

indicator or the terephthalate binder. Although some of the spectra showed

carbonyl bands in the 1720-1640 cm.$^{-1}$ region, the peaks were too weak to be

assigned to any of the individual dispiro compounds.

2. Thin Layer Chromatography on Alumina

An activated 4x20 cm. alumina 6063 Eastman thin layer sheet with fluorescent indicator was spotted with a 5 mg./ml. solution of the product. The following solvents were used to develop the sheet: ethyl acetate, ethyl methyl ketone, and each of these containing 10-20% ethanol; acetone, acetone with 10% diethylamine, acetone:diethylamine:methanol, 9:0.5:1.5, 8:0.2:1.8, and 8:1:1; acetone:diethylamine:ethanol, 9:0.5:0.5 and 8:0.25:1.75. It was found that the acetone:diethylamine:methanol, 8:0.2:1.8 gave the best separation. Three spots were seen under short-wave ultra-violet light; the Rf values were 0.22-0.35 (dark), 0.42-0.48 and 0.495-0.54 (light).

3. "Dry Column" Chromatography on Alumina (61)

The column material was prepared by mixing 250 g. of Fisher Scientific No. A-540 Absorption Alumina (80-200 mesh) with 10 ml. (4%) distilled water and 1.25 g. (0.5%) E.I. duPont No. 609 Luminescent Chemical (Zinc Silicate: Manganese) on a rotary evaporator unit for 6 hours. The activity of the adsorbent was then determined by the following procedure. A melting point capillary tube was filled with the deactivated alumina and a drop of benzene placed on the open end. The tube was inverted and the closed end was snapped off. The damp end was placed into a small test tube containing a few milliliters of a 0.5% solution of p-aminobenzene in benzene until a drop of the dye solution was absorbed. The capillary was then placed in another test tube containing a few milliliters of benzene and allowed to develop. The Rf value was found to be between 0.12 and 0.24; this corresponds to an activity of II according to the Brockmann Scale. An activity of II or III is suitable for this type of chromatography.

The nylon column was heat sealed at one end and a small pad of glass wool was inserted; two or three holes were made at the bottom for drainage. The adsorbent was added to the 38 inch column in four portions, about 8 inches at a time. After the addition of each portion the column was compacted by allowing the bag to drop through the hand about six inches onto a hard surface two or three times. The tubing was "C" gauge, 1 inch flat diameter nylon made by Walter Coles and Co., Ltd., Backhouse Works, England.

The column was loaded by depositing the product on the adsorbent. This was done by dissolving 530 mg. of the product in 100 ml. of 100% ethanol and adding the solution to 5 g. of alumina. The solvent was then evaporated of _in vacuo_. The material was distributed evenly on the top of the column and then covered with a small layer of sand to prevent disturbance by the solvent.

The column was developed using a solution of 80:18:2 acetone reagent: absolute methanol:diethylamine. A constant head of 3-5 centimeters was present during the developing. The column was run in the dark and watched continuously under short-wave ultra-violet light. Before the developing had begun, dark bands could be seen under uv light; these were due to the uneven packing of the column. After solvent had been added to the column, no new bands could be seen except for one at the solvent front; this band could also be seen under visible light because it was light yellow. The first 25 ml. of solvent to come through the column was evaporated off to yield a few milligrams of viscous yellow liquid. From this was isolated a solid whose infrared spectrum was identical to DDP hydrochloride except for three new peaks at 1760, 1725 and 1640 cm.$^{-1}$. No significant amount of material was isolated from the following fractions.

Several attempts were made to recover the solid that had been loaded onto the column. This was done by cutting the column into five parts: the loading alumina and four equal portions from the remaining column. Each was extracted with 100 ml. of hot solvent, the alumina filtered off and the solvent removed in vacuo. This procedure was used to extract each portion with ethanol, chloroform and glacial acetic acid, in that order. Infrared spectra were recorded on all the material obtained. In general, very small amounts of substances were obtained and the infrared spectra of these did not indicate the presence of DDP or its derivatives. Glacial acetic acid extraction yielded 50-70 mg. of white crystalline material from each extraction, but the infrared spectrum of each was very similar and no significant carbon-hydrogen stretching peak could be seen in the 2950-2800 cm.$^{-1}$ region. An elemental analysis on the solid indicated that no nitrogen was present. Extraction of pure alumina with the same solvent yielded a material with a similar IR spectrum. A final attempt to recover the material from the column was made by soxhlet extraction of each fraction of alumina with ethanol (250 ml.) for several days. More solid like that obtained from the acid extraction was obtained but no other substance was found.

4. "Dry Column" Chromatography on Silica (61)

The column was prepared as in the above procedure except that the adsorbent was Grace-Davison Chemical Mesh 60-200 Grade 62 Silica Gel. The gel was deactivated with 15% water to give an Rf value of about 0.63 which is equivalent to an activity of III on the Brockmann Scale. In an attempt to obtain denser bands of material on the column, the product (400 mg.) obtained from the attempted chloroacetylation of DDP, was distributed evenly

on top of the column and not deposited on the adsorbent as before. The

column length was 22 inches and the solvent used was hexane:absolute

ethanol:diethylamine, 6:1:2. As in the previous column, no bands could be

seen developing except for a visible yellow band that could be seen without

ultra-violet light. After the solvent had reached the end of the column,

there still remained about half of the product at the origin. More solvent

was run through the column to a total of 180 ml. Five fractions were

collected and worked-up as before. No significant amounts of material

were obtained. The column was divided into two parts and each was extracted

with 300 ml. of hot ethanol. A small amount of material was obtained but the

infrared spectrum indicated that it was not a DDP derivative.

F.   8,16-DIAZADISPIRO[6.1.6.2]HEPTADECAN-17-ONE (Attempted)

  1. Cycloheptanone Cyanohydrin (66)

A solution of 100 g. (0.89 mole) of cycloheptanone in 540 mls of

ether was placed in a 2-liter, three-necked flask equipped with a reflux

condenser, dropping funnel and a mechanical stirrer. To this was added,

over a period of three and one-half hours, 360 mls. of a saturated solution

of sodium bisulfite. The bisulfite addition product was collected by suction

filtration and washed thoroughly with solvent ether. The white solid was

added to 360 mls. of water to form a slurry and then was placed in the above

apparatus. A saturated solution of potassium cyanide (72 g. KCN in 180

mls. water) was added dropwise until a clear solution formed. The two

layers were separated and the aqueous layer was extracted twice with 100 mls.

of ether. The oil and ether layers were combined and then extracted with

180 mls. of water containing 0.45 ml. of concentrated hydrochloric acid

until neutral to red litmus. The ether-oil layer was dried over anhydrous

sodium sulfate for 12 hours. The ether was removed by flash evaporation and the residue distilled under reduced pressure, b_2 106-108°. The yield was 58 g., 47% on cycloheptanone. The infrared spectrum showed characteristic hydroxyl and nitrile peaks at 3400 cm.$^{-1}$ and 2250 cm.$^{-1}$, respectively.

2. 1-Aminocycloheptancarbonitrile (51)

Cycloheptanone cyanohydrin (58 g.) was melted and placed in a 200 ml. 3-necked conical flask. Ammonia gas was bubbled through the liquid for 18 hours to form the amino compound. The excess ammonia was then removed by bubbling nitrogen gas through the product. The resulting faint yellow liquid was dissolved in 120 mls. of benzene and extracted with 50 mls. of water. After drying over sodium sulfate, the benzene was flashed off. The yield of crude product was 57 g., 99% on the cyanohydrin. The infrared spectrum showed peaks at 3300, 3220, 1600 cm.$^{-1}$ and 2220 cm.$^{-1}$ that are characteristic of the primary amino and nitrile groups respectively.

3. 8,16-Diazadispiro[6.1.6.2]heptadecan-17-one (attempted)

To a solution of sodium ethoxide (prepared from 7.35 g. of sodium and 210 mls. of 98.4% ethanol) was added 57 g. of 1-aminocycloheptancarbonitrile. The mixture was allowed to stand for one week but the only solid isolated on filtration was sodium cyanide. The alcohol was removed by flash evaporation, and the remaining semi-solid was taken-up in benzene, extracted three times with water and dried over sodium sulfate. The resulting semi-solid contained no nitrile peak at 2250 cm.$^{-1}$. The peak at 1690-1640 cm.$^{-1}$ could represent an imino function. Although it has been reported that certain aminonitrile compounds of this type are unstable to heat (67), a distillation was attempted. Most of the product distilled over at b_{9-10} 60-64°. The

infrared spectrum showed peaks at 1690 cm.$^{-1}$(s) and 1620-1560 cm.$^{-1}$(m). It appears that the loss of the nitrile group resulted in the formation of a cyclic imine.

SECTION TWO

SYNTHESIS OF DERIVATIVES AND ANALOGS OF 7-AMINO-14-AZADISPIRO-

[5.1.5.2]PENTADECAN-15-ONE

A.   7-AMINO-14-AZADISPIRO[5.1.5.2]PENTADECAN-15-ONE

1.   14 Hydroxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione

7-oxime (49)

(a) With Piperazine as Catalyst.   In a 250 ml. round-bottomed flask

equipped with a Stark and Dean trap were placed 24.5 g. (0.25 mole) of

cyclohexanone, 30.5 g. (0.25 mole) of nitromethane, 16.5 g. (0.25 mole)

of piperazine and 50 ml. of benzene.   Crystals began to separate after

15 minutes of refluxing.   The reaction mixture was filtered after 30 hours

of refluxing and the solid obtained was extracted with hot 1:1 hydrochloric

acid for 40 minutes.   After recrystallization from ethanol, 11.2 g.

(33.8%) of C-I, m.p. 272-274° was obtained; lit. (49) 67%, lit. (48) m.p.

263-265.5^O (not recrystallized), 47.2%.

(b) With Pyrrolidine as Catalyst.   In a one-litre round-bottomed

flask equipped with a Stark and Dean trap were placed 216 g. (2.2 mole) of

cyclohexanone, 146.5 g. (2.4 mole) of nitromethane, 36 mls. of pyrrolidine

and 328 mls. of benzene.   The catalyst was added in three portions; the

remainder of the 37.5 g. (0.6 mole) was added in two equal 4 ml. portions

after 27 and 43 hours of refluxing.   After thoroughly washing with ether,

47 g. (16.4%) of solid (m.p. 270-272°) was obtained; lit. (48) 23%, m.p.

262-263°; after recrystallization from ethanol the m.p. was 274-275°; lit.

(49) 273-274°; lit. (51) 275-275°.

2. 7-Amino-14-azadispiro[5.1.5.2]pentadecan-15-one (51)

C-I (11 g.) in 200 ml. of absolute ethanol was hydrogenated in the conventional Parr apparatus at 30-60 p.s.i. over 6 g. of Raney nickel. After shaking for 3 days the alcohol was decanted off the catalyst and the catalyst was washed with 100 mls. of hot ethanol. The combined alcohol fractions was filtered through kieselguhr and the alcohol was concentrated; hot water was added to cause the precipitation of fine white needles. After five recrystallizations from ethanol and water the melting point was 192-193°, lit. 192-193° (40), 195-196° (51). The yield was 45.5% lit. 95%, m.p. 193-195° (51).

In several of the hydrogenation reactions the product was the 14-azadispiro[5.1.5.2]pentadecane-7,15-dione 7-imine as indicated by its infrared spectrum with peaks at 1700 and 1670 cm.$^{-1}$, lit. 1698 and 1661 cm.$^{-1}$ (51), and by the melting point 196-208°. Unreacted starting material and a solid with a melting point of 295-300° were also isolated in some reactions.

B. 7-DIMETHYLAMINOACETAMIDO-14-AZADISPIRO[5.1.5.2]PENTADECAN-15-ONE
   (Attempted) (62)

To a suspension of 1.4 g. (0.01 mole) of N,N-dimethylglycine hydrochloride in 25 ml. of dichloromethane was added 1.01 g. (0.01 mole) of triethylamine, 2.84 g. (0.012 mole) of C-11 and 2.06 g. (0.01 mole) of dicyclohexylcarbodiimide. After being stirred for two weeks at room temperature, the reaction mixture was diluted with 75 ml. of hot dichloromethane and then filtered to remove the dicyclohexylurea, and triethylamine hydrochloride. The solvent was removed in vacuo to yield a white semi-solid. This was recrystallized from acetone to yield several compounds, none of

which had an infrared spectrum with two carbonyl peaks in the 1750-1650 cm.$^{-1}$ region and peaks in the 2850-2725 cm.$^{-1}$ region characteristic of the dimethyl-amino function.

C.   8-AMINO-16-AZADISPIRO[6.1.6.2]HEPTADECAN-17-ONE

1. 16-Hydroxy-16-azadispiro[6.1.6.2]heptadec-10-ene-8,17-dione 8 oxime (49)

(a) With Piperazine as Catalyst. Cycloheptanone (71.0 g., 0.63 mole), nitromethane (42.2 g., 0.69 mole), piperazine (25.8 g., 0.3 mole) and 150 ml. of benzene were placed in a 500 ml. round-bottomed flask equipped with a Stark and Dean trap and refluxed for 80 hours. Solid began to separate after 2 hours of refluxing. The solid was collected by suction filtration and washed with ether and then with hot benzene. The yield of piperazine salt of H-I was 32 g., m.p. 223-225°, lit. 225-226°, after recrystallization from hot ethanol, lit. (48) 51.1%, m.p. 208-209°, before recrystallization. When the salt was extracted with hot 1:1 hydrochloric acid for 40 minutes it yielded 20.5 g. (22.5%) of H-I, m.p. 246-249°, lit. (49) m.p. 250-251°.

(b) With Piperidine as Catalyst. In a 2000 ml. round-bottomed flask fitted with a Stark and Dean trap were placed 112.17 g. (1.0 mole) of cycloheptanone, 67.14 g. (1.1 mole) of nitromethane, 85.15 g. (1.0 mole) of piperidine, and 500 ml. of benzene, and the solution was refluxed for 90 hours. No solid separated during the reaction time, but after acidifica-tion of the reaction mixture with hydrochloric acid, crystals separated from the solution. They were collected by suction filtration, washed with hot water and recrystallized from 95% ethanol to yield 29 g. (20%) of H-I m.p.

247-250°, lit. (49) 46-48%, m.p. 247-249° and 250-251°.

2. 8-Amino-16-azadispiro[6.1.6.2]heptadecan-17-one

H-I (20 g.) in 200 ml. of absolute alcohol over 12 g. of Raney nickel was hydrogenated in the conventional Parr apparatus at 30-60 p.s.i. After shaking for three days the alcohol was decanted from the catalyst and the catalyst was washed with 100 mls. of hot ethanol. The combined alcohol fractions was filtered through kieselguhr and the solution was concentrated. The addition of hot water caused the crystallization of a white solid that decomposed above 180°. After several recrystallizations from ethanol and water the material melted at 183-185°d. The yield was 71.6%. The infrared spectrum showed only one unsaturation peak. This was seen at 1685 cm.$^{-1}$

A second hydrogenation reaction starting with 27 g. of H-I yielded a small portion (1.3 g.) of unreacted H-I and an unidentified solid (0.5 g.) melting at 290-300°, as well as the solid assumed to be H-II.

D. 8-CHLOROACETAMIDO-16-AZADISPIRO[6.1.6.2]HEPTADECAN-17-ONE

In a three-necked 100 ml. flask equipped with stirrer, dropping funnel, and reflux condenser was placed 5.29 g. (0.02 mole) of H-II and 3.45 g. (0.025 mole) of potassium carbonate in 50 ml. of dry benzene. To this was added dropwise 1.65 ml. (0.021 mole) of chloroacetyl chloride in 5 mls. of dry benzene. The mixture was refluxed for 30 minutes. A dense white precipitate was seen as soon as the acyl halide was added and its appearance did not change after heating. The reaction mixture was filtered hot to remove the inorganic salts and any hydrochloride salt that may have formed. On cooling the filtrate yielded 320 mg. of a white solid m.p.

210-212° after recrystallization from benzene. The infrared spectrum showed new peaks at 1665 cm.$^{-1}$ and 1540 cm.$^{-1}$ that could represent the Amide I and Amide II bands of acyclic secondary amide.

Anal. Calcd. for $C_{18}H_{29}N_2O_2Cl$: C, 63.42; H, 8.58; N, 8.22; Cl, 10.40. Found: C, 63.74; H, 8.70; N, 8.24; Cl, 10.26.

The benzene from the reaction was evaporated off to yield 700 mg. of a mixture of the compound whose analysis appears above and at least two other compounds. One appears to be the diacetylated product. Its infrared spectrum shows a 1760 cm. peak and no Amide II peak. The latter indicates that no alicyclic monosubstituted amide is present. The melting point of this compound was 176-184°. The third compound had a melting point of 2950300°; this could be the hydrochloride salt of H-II.

E.   8-DIMETHYLAMINOACETAMIDO-16-AZADISPIRO[6.1.6.2]HEPTADECAN-17-ONE
      (Attempted) (62)

To a suspension of 1.4 g. (0.01 mole) of N,N-dimethylglycine hydro-chloride in 25 ml. of dichloromethane was added 1.01 g. (0.01 mole) of triethylamine, 3.18 g. (0.012 mole) of H-II and 2.06 g. (0.01) of DCC. After being stirred for two days at room temperature, the reaction mixture was diluted with 75 ml. of hot dichloromethane and then filtered to remove the dicyclohexylurea, and the triethyamine hydrochloride. The precipitate was extracted twice with 10% hydrochloric acid and the aqueous solution was made alkaline. A white precipitate appeared but it could not be removed by suction filtration. The precipitate was removed by ether extraction but the dried ether layer yielded only a few mg. of solid. Hexane extraction of this material yielded a small amount of solid believed to be the desired product.

The filtrate obtained from the reaction mixture yielded a semi-solid after the solvent was removed in a rotary evaporator. This material was dissolved in hot acetone and a solid was precipitated from it by the addition of pet. ether (b.p. 65-110°). After recrystallization from acetone and further acetone washing a white solid was obtained m.p. 136.5-137.5°, 700 mg. After several recrystallizations from acetone the m.p. was 138-139.5°.

$\underline{Anal}$. Calcd. for $C_{20}H_{35}N_3O_2$: C,68.73; H, 10.09; N, 12.02: Found: C, 57.47; H, 9.68; N, 12.34.

The infrared spectrum showed 2825 cm.$^{-1}$, 2780 cm.$^{-1}$, and 2725 cm.$^{-1}$ peaks characteristic of the dimethylamino function, and carbonyl peaks at 1705 cm.$^{-1}$ and 1660 cm.$^{-1}$ as well as an Amide II band at 1530 cm.$^{-1}$ all of which are consistent with the title compound.

F. 8-DIMETHYLAMINOETHYLAMINO-16-AZADISPIRO[6.1.6.2]HEPTADECANE
    (Attempted)

The material obtained from the previous reaction (0.63 g., 0.0019 mole) was added to a stirred suspension of LiAlH$_4$ (0.15 g., 0.004 mole) in 25 ml. of THF. After refluxing with stirring for 24 hours, the excess hydride was destroyed by the addition of 30% aqueous potassium hydroxide. The mixture was filtered and the coagulated white precipitate was extracted with hot THF. The combined solvent layers were dried over MgSO$_4$ and then the solvent was evaporated off at 50° $\underline{in\ vacuo}$. The product was distilled at 79-81° at 0.4 mm. The two carbonyl peaks were no longer present but a large peak at 3600-3000 cm.$^{-1}$ indicated that an alcohol was present. The strong peak at 1055 cm.$^{-1}$ indicates that the alcohol could be primary.

G.   8-DIMETHYLAMINOETHYLAMINO-16-AZADISPIRO[6.1.6.2]HEPTADECAN-17-ONE
      (56) (Attempted)

A mixture of sodium amide (1.42 g., 0.036 mole) in dry toluene (10 ml.)
was stirred and heated to 100° in a 50 ml. 3-necked flask.   Then 7.93 g.
(0.03 mole) of H-II was added to the amide mixture, and the mixture was
refluxed for 3 hours.   The bath was removed and 10 ml. of toluene was added
to the dark brown paste.   The β-dimethylaminoethylbromine hydrobromide
(3.49 g., 0.015 mole) was added and the mixture was refluxed for 48 hours.
After the mixture had cooled, 20 ml. of water was added and the toluene
layer was separated.   The precipitate was washed with ether and the water
layer was saturated with potassium carbonate and then extracted twice with
25 ml. of solvent ether.   The combined toluene and ether layers were dried
over MgSO$_4$.   The drying agent was filtered off and the solvent removed <u>in</u>
<u>vacuo</u>.   The semi-solid remaining was diluted with a few mls. of anhydrous
ether and filtered to yield 1.8 g. of H-II, m.p. 180-185° after recrystalli-
zation from ethanol-water.   The very ether soluble portion was distilled at
1-2 mm. and 225° to yield a semi-solid with an infrared spectrum essentially
the same as the starting material, H-II.

H.   MISCELLANEOUS

  1. <u>Raney Nickel Catalyst W-4</u> (68)

In a 2 liter erlenmeyer equipped with a thermometer and a Hershberg
stirrer was placed 209 g. of NaOH in 815 ml. of water.   The flask was
immersed in a cold running water bath and 163 g. of Ni-Al alloy was added in
2-4 g. portions keeping the temperature at 50°±2° and collapsing the foam
with ethanol if necessary.   The cooling bath was then removed and the

suspension was digested at 50° for 50 minutes with gentle stirring. The catalyst was washed in the flask by decantation several times with distilled water and then it was transferred to a 1 liter graduate cylinder. The catalyst was then suspended to a depth of 3/4 the length of the water column in the cylinder by stirring. About 24 1. of water was flushed through the catalyst in a 3-4 hour period, or until the wash water was neutral to litmus. The catalyst was allowed to settle and then the water was decanted. The sludge was transferred to a 250 ml. centrifuge tube and washed three times with stirring not shaking, with 200 ml. of 95% ethanol and then three times with 200 ml. absolute ethanol, centrifuging after each washing. The catalyst was stored under absolute alcohol in a refrigerator.

2. N,N-Dimethylglycine Hydrochloride (69)

In a 500 ml. round-bottomed flask equipped with reflux condenser were placed 45 g. (0.6 mole) of glycine, 150 ml. of 90% formic acid and 120 ml. of formalin. The reactants were gently boiled under reflux for 17 hours. On cooling, 60 ml. of concentrated hydrochloric acid was added and the mixture was evaporated to a sirup under reduced pressure. After cooling, the precipitate which formed was removed by suction filtration and then washed thoroughly with acetic acid. The yield was 22.8 g. (27%) m.p. 187-190°, lit. 64-67%, m.p. 189-190°, after recrystallization from water. The low yield could have been due to the old formalin that was used.

3. Chloroacetyl Chloride

(a) Using benzoyl chloride (70)   Finely ground, dry monochloro-acetic acid (9.46 g., 0.1 mole) and freshly distilled benzoyl chloride (28.1 g., 0.2 mole) were placed in 50 ml. round-bottomed flask equipped with a heated Vigreux column and distillation collection apparatus. The mixture

was heated with an oil bath at 190°; the column temperature was 90°. The product was distilled over as rapidly as possible consistent with good separation. The fraction coming over at 102-110° (12 g.) was collected and stored in a salt-ice bath until used.

(b) Using thionyl chloride (71)   In a 200 ml. round bottomed flask equipped with a reflux condenser fitted with a drying tube were placed finely ground, dry monochloroacetic acid (84 g., 0.89 mole) and thionyl chloride (115 g., 0.963 mole). The reactants were refluxed gently on a water bath for three hours and then boiled vigorously until the evolution of gas had ceased. The excess thionyl chloride was distilled off on a steam bath. Distillation yielded 47.5 g. product with no significant infrared peak at 1230 cm.$^{-1}$ indicating no contamination with thionyl chloride. The fractions that were not pure were added to the unreacted chloroacetic acid in the reaction vessel along with 35 ml. of thionyl chloride and the reaction was run as before. A further 33 g. of product was collected (b.p. 101-109°) to give a total yield of 80.5 g. (80%) based on the acid.

PART VI

INFRARED SPECTRA

Infrared Spectrum 1.   Cycloheptanone Bisulphite Addition
                        Product.
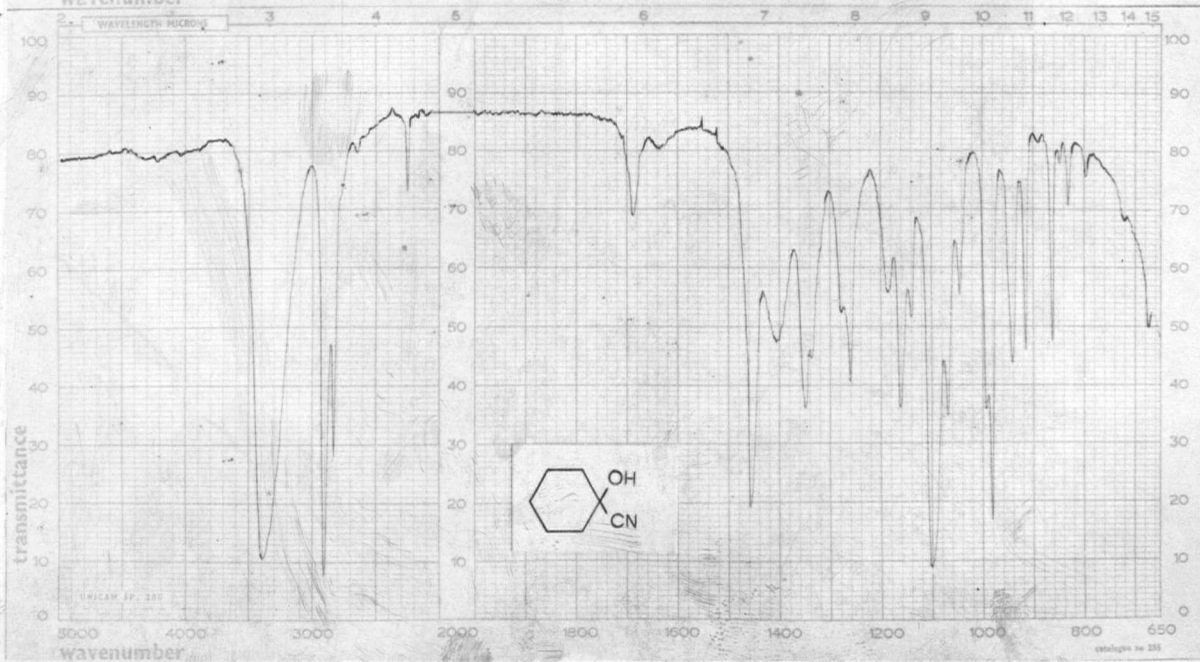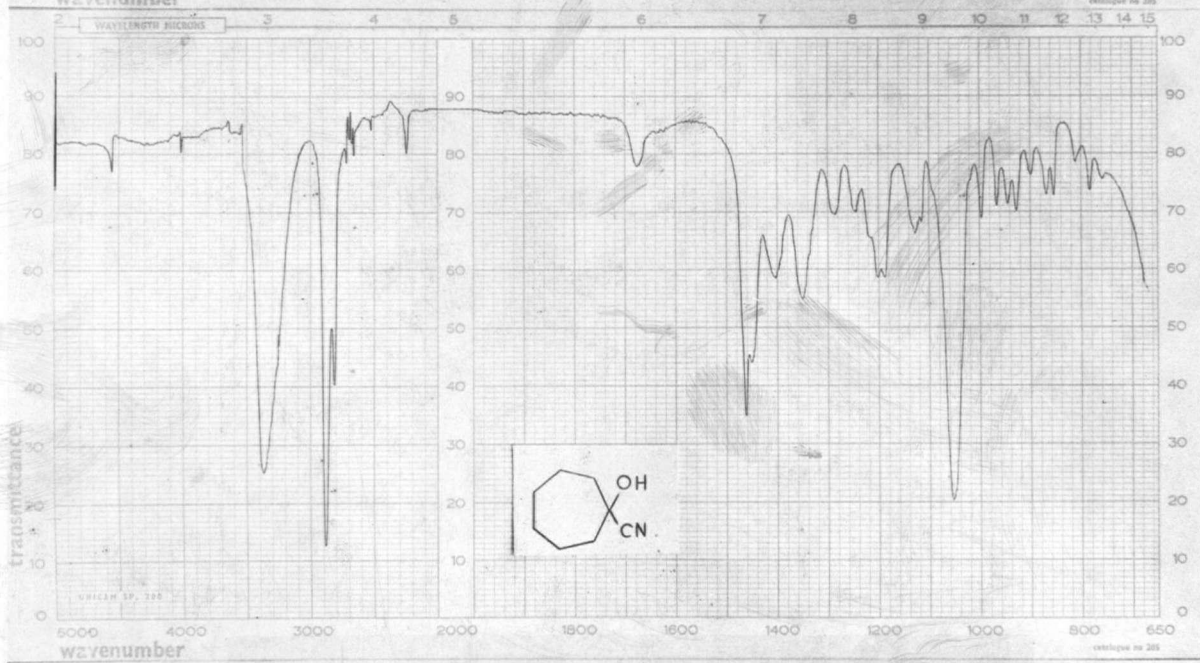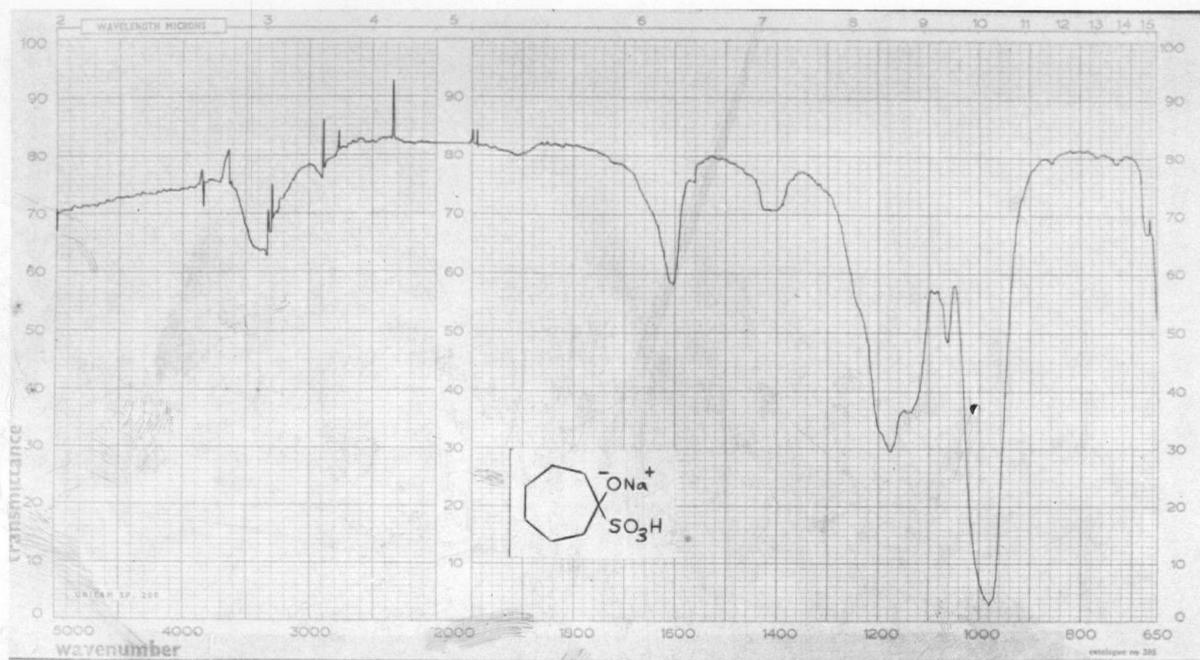   Solid in potassium bromide disk.

Infrared Spectrum 2.   Cycloheptanone Cyanohydrin
                        Liquid film between sodium chloride
                        plates.

Infrared Spectrum 3.   Cyclohexanone Cyanohydrin
                        Liquid film between sodium chloride
                        plates.

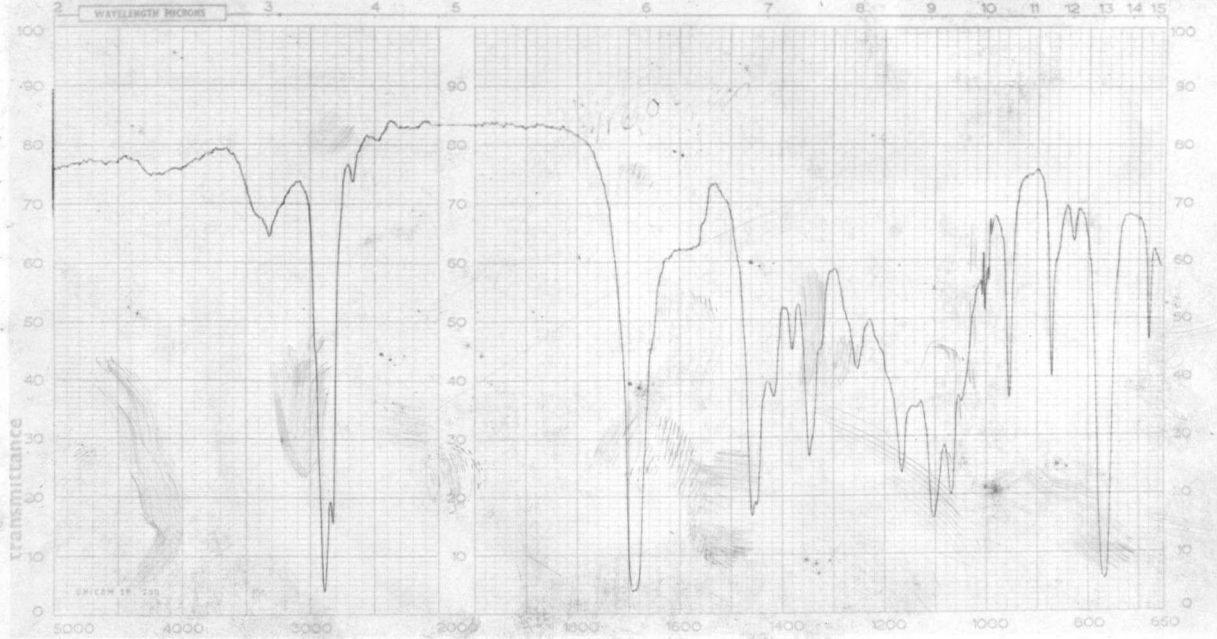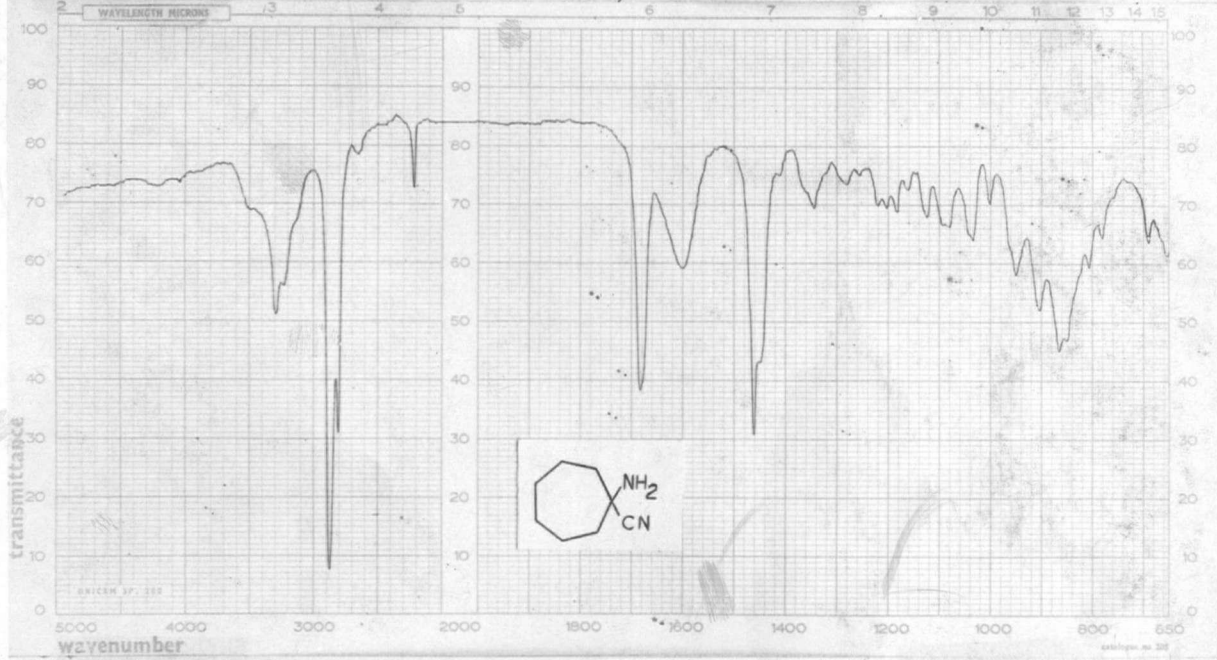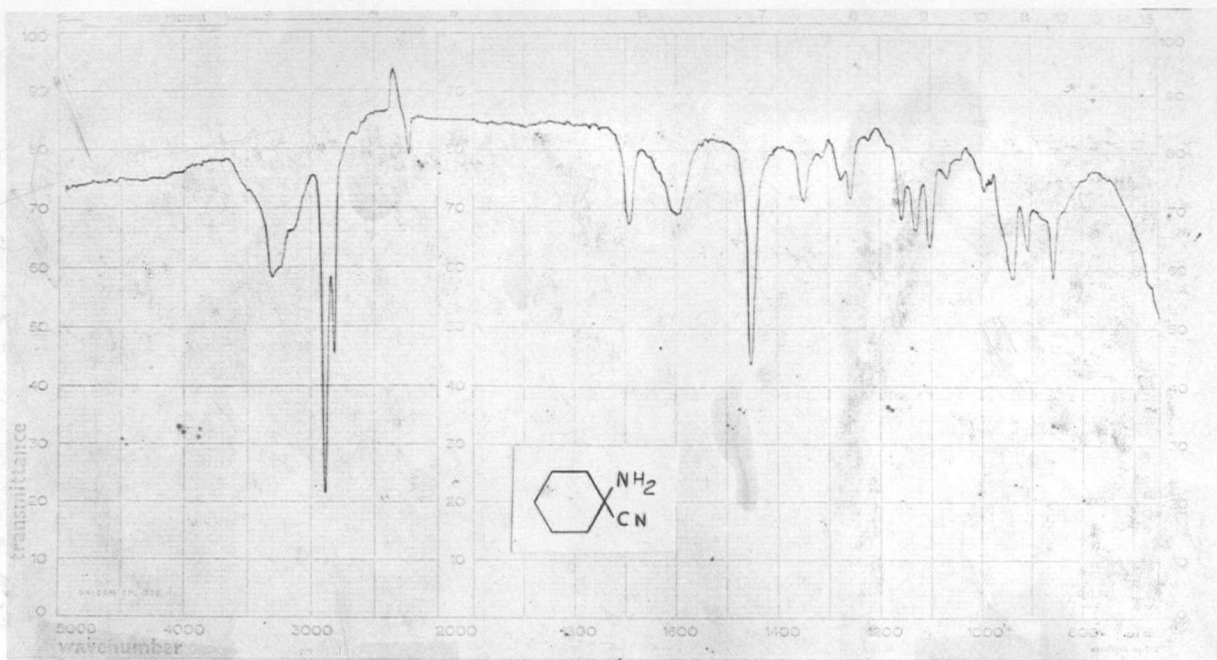Infrared Spectrum 4. 1-Aminocyclohexanecarbonitrile.

Liquid film between sodium chloride plates.

Infrared Spectrum 5. 1-Aminocycloheptanecarbonitrile.

Liquid film between sodium chloride plates.

Infrared Spectrum 6. Product from the Attempted Synthesis of 8,16-Diazadispiro[6.1.6.2]hepta-decan-17-one.
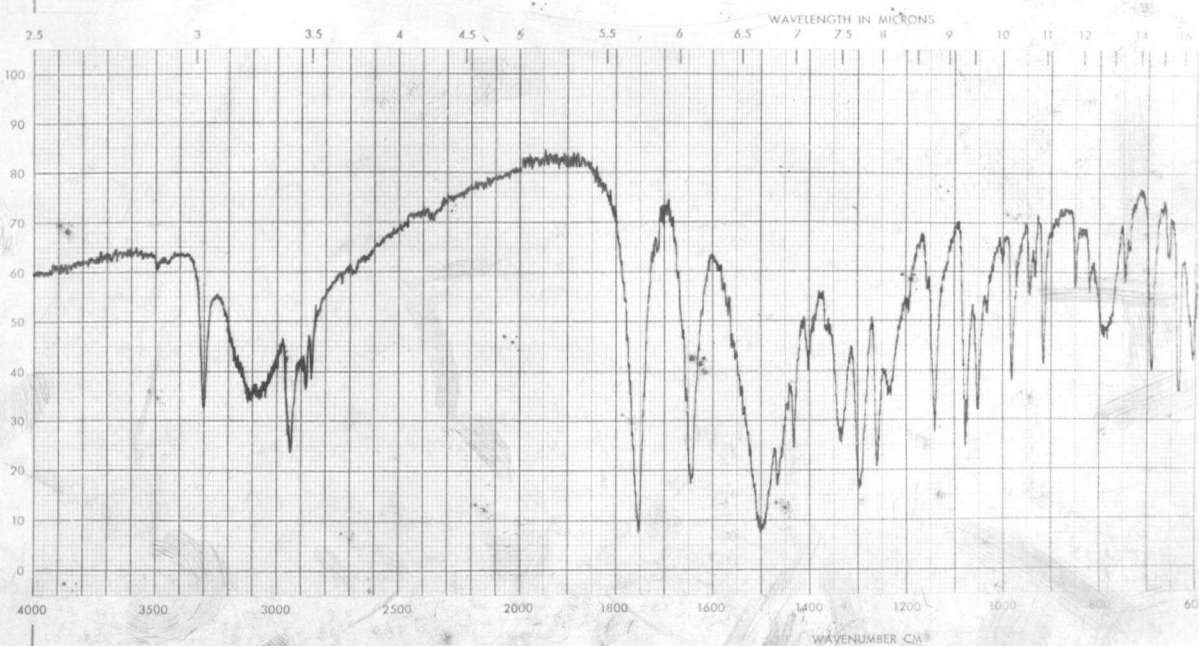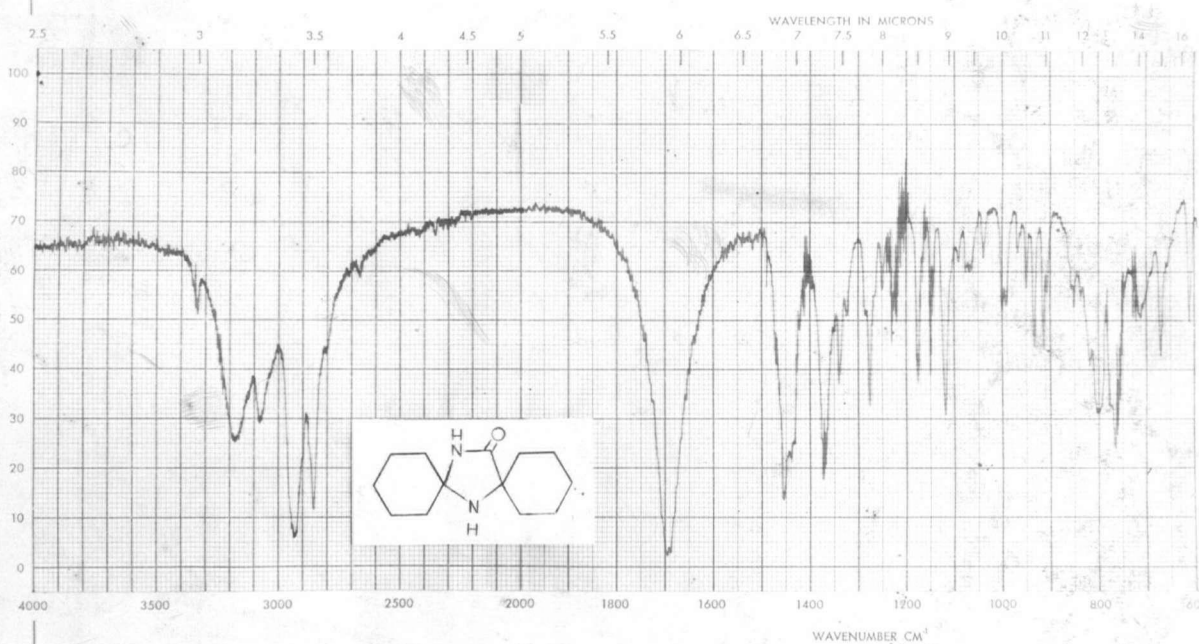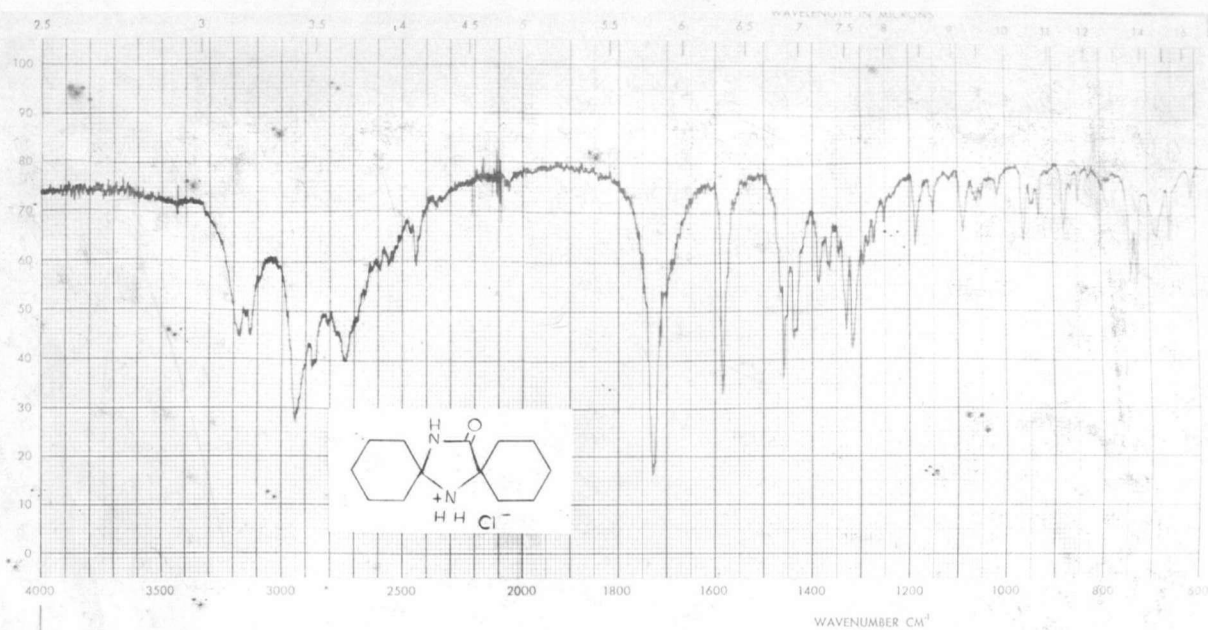
Liquid film between sodium chloride plates.

transmittance

wavenumber

WAVELENGTH MICRONS

transmittance

wavenumber

WAVELENGTH MICRONS

transmittance

Infrared Spectrum 7.   7,14-Diazadispiro[5.1.5.2]pentadecan-

15-one Hydrochloride.

Solid in potassium bromide disk.

Infrared Spectrum 8.   7,14-Diazadispiro[5.1:5.2]pentadecan-

15-one.

Solid in potassium bromide disk.

Infrared Spectrum 9.   Product from the Attempted Synthesis

of 7-Chloroacetyl-7,14-diazadispiro-

[5.1.5.2]pentadecan-15-one.

Solid in potassium bromide disk.

Infrared Spectrum 10.   A β-Dimethylaminoethyl Derivative of
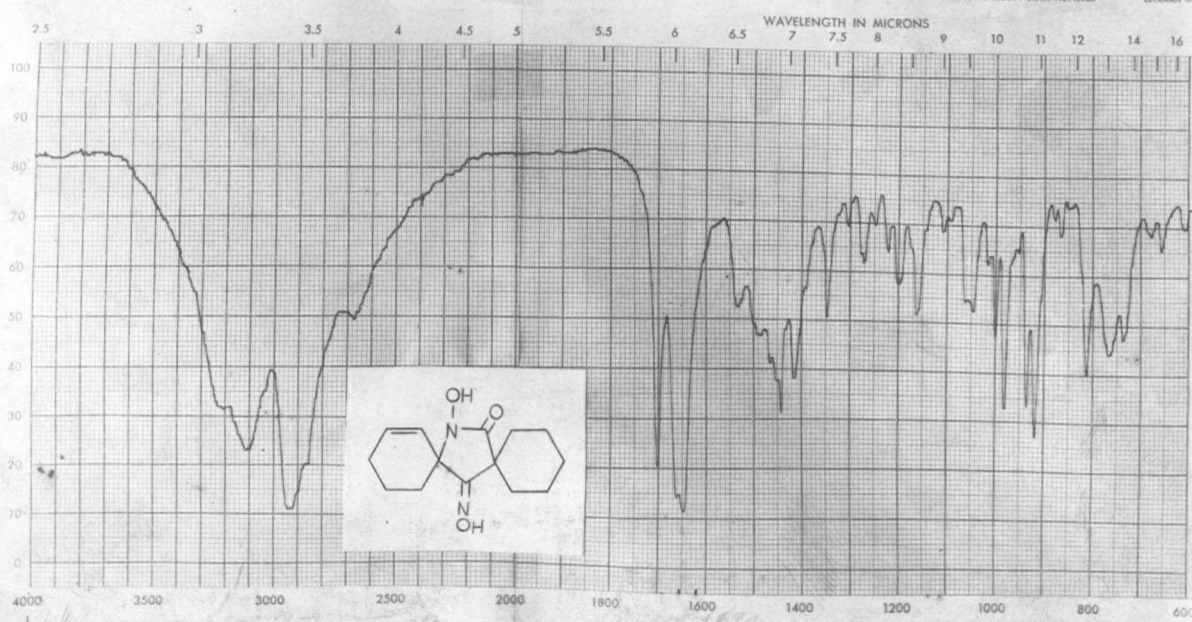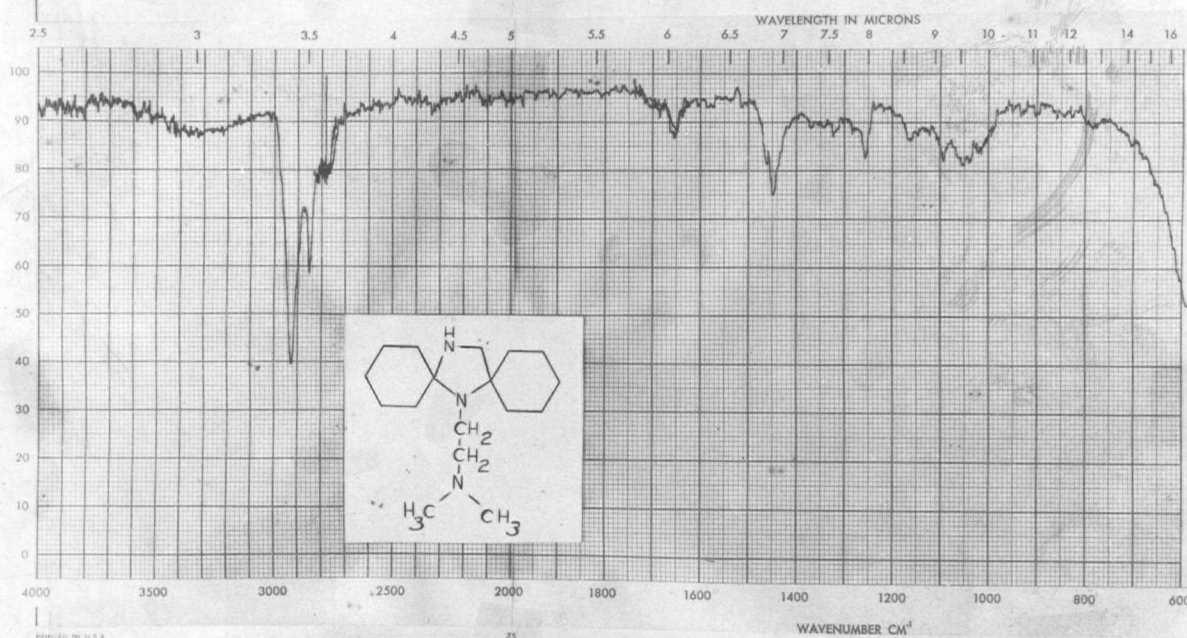7,14-Diazadispiro[5.1.5.2]pentadecan-
15-one.
Liquid film between sodium chloride
plates.

Infrared Spectrum 11.   A β-Dimethylaminoethyl Derivative of
7,14-Diazadispiro[5.1.5.2]pentadecane.
Liquid film between sodium chloride
plates.

Infrared Spectrum 12.   14-Hydroxy-14-azadispiro[5.1.5.2]-
pentadec-9-ene-7,15-dione 7-oxime.
Solid in potassium bromide disk.

WAVELENGTH IN MICRONS

WAVENUMBER CM⁻¹

WAVELENGTH IN MICRONS

WAVENUMBER CM⁻¹

PRINTED IN U.S.A.   75   WHEN REORDERING SPECIFY CHART NO. 104411   BECKMAN INC.

WAVELENGTH IN MICRONS
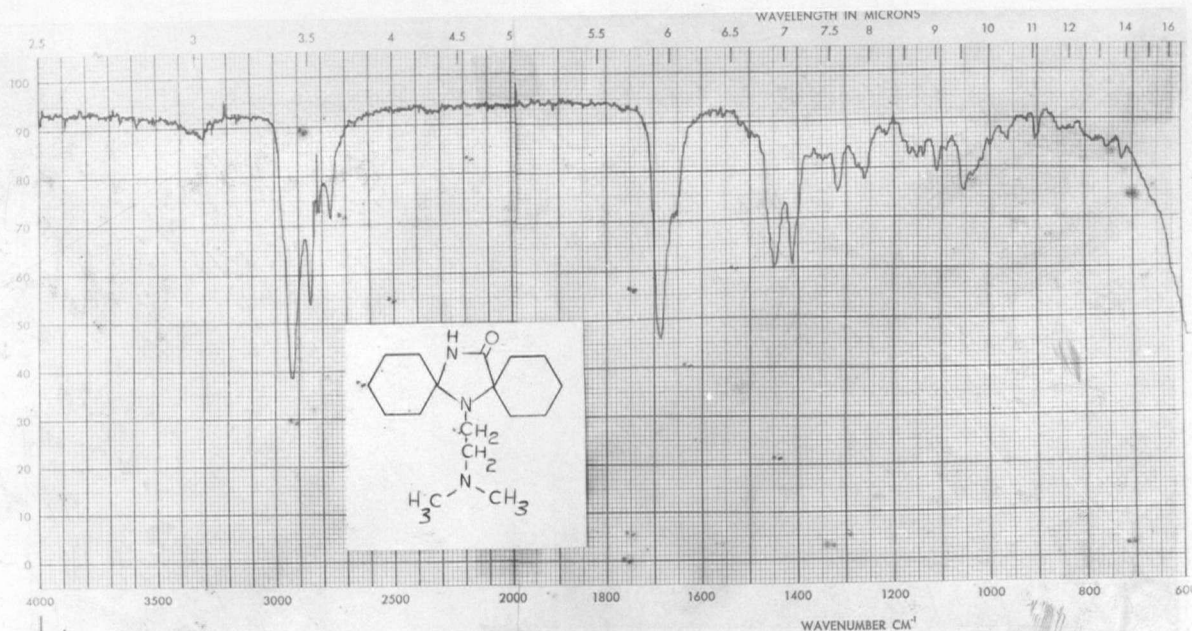
Infrared Spectrum 13.   7-Amino-14-azadispiro[5.1.5.2]penta-

decan-15-one.

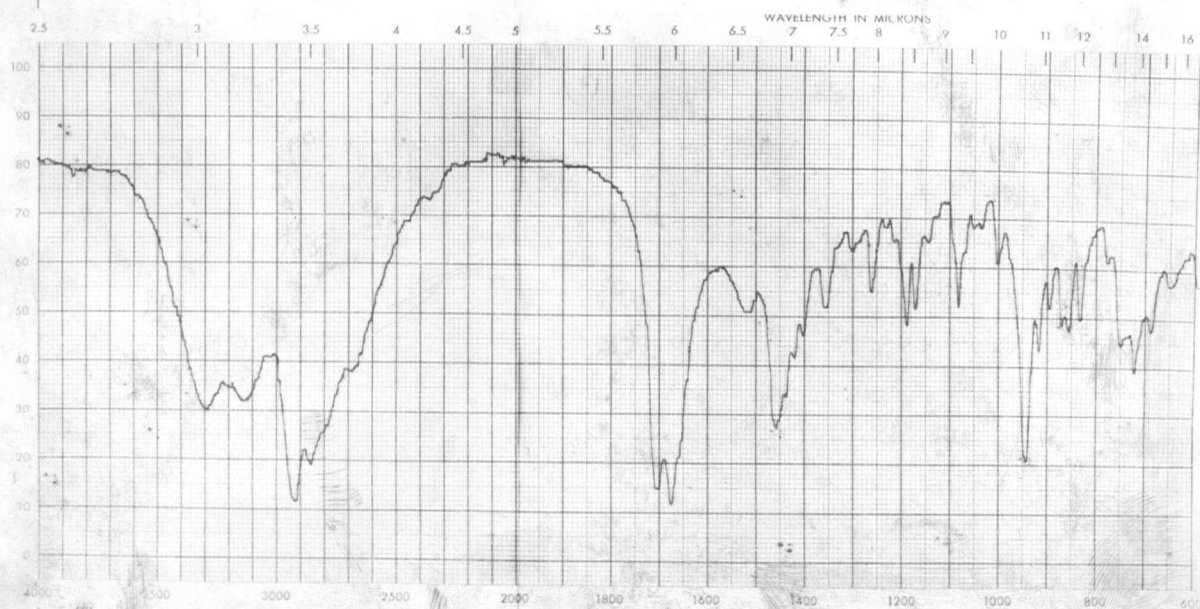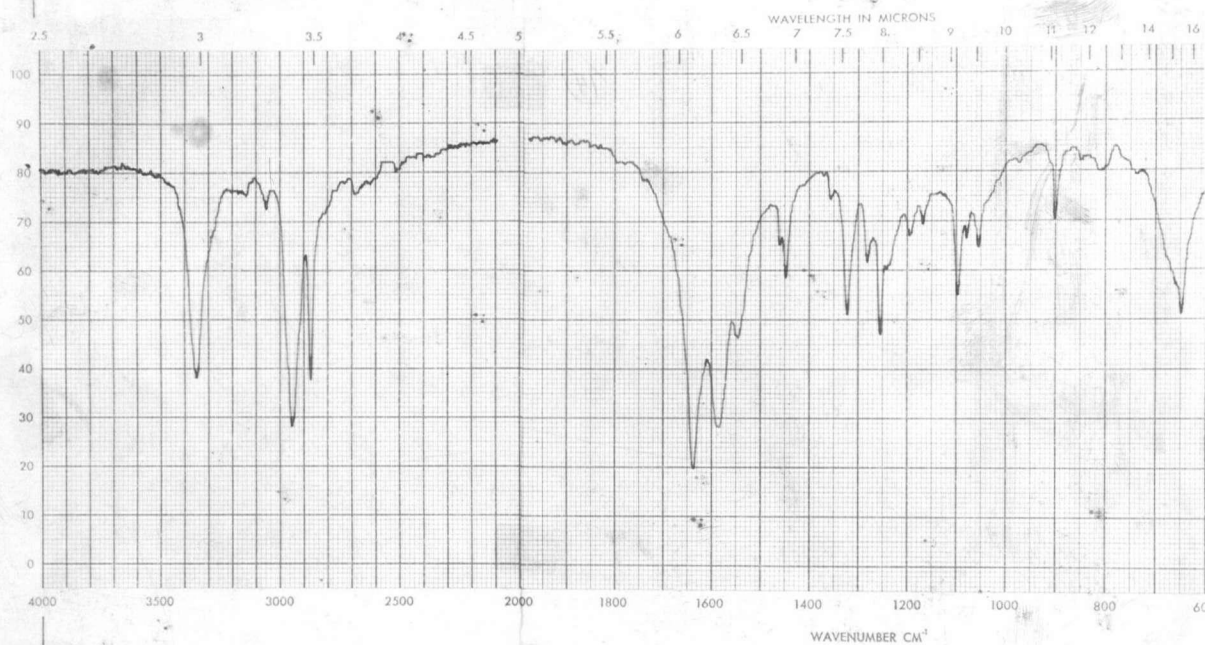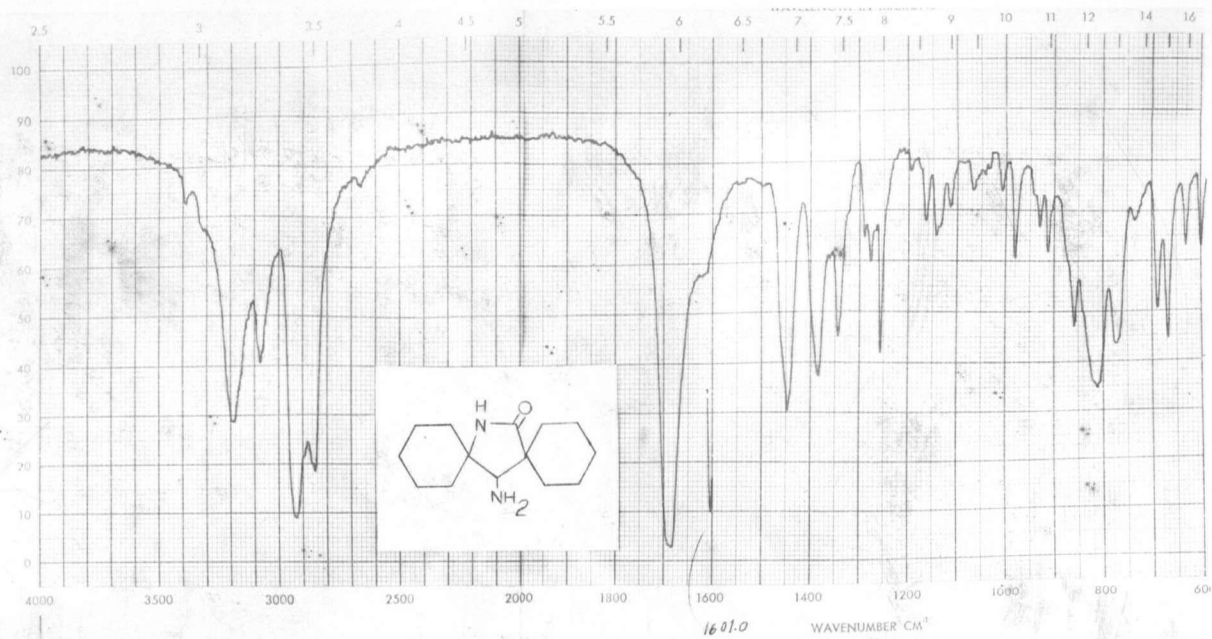Solid in potassium bromide disk.

Infrared Spectrum 14.   A Product obtained from the Reaction of

N,N-Dimethylglycine Hydrochloride, DCC,

and 7-Amino-14-azadispiro[5.1.5.2]penta-

decan-15-one.

Solid in potassium bromide disk.

Infrared Spectrum 15.   Piperazine Salt of 16-Hydroxy-16-aza-

dispiro[6.1.6.2]heptadec-10-ene-8,17-

dione 8-oxime.

Solid in potassium bromide disk.

16 01.0   WAVENUMBER CM⁻¹

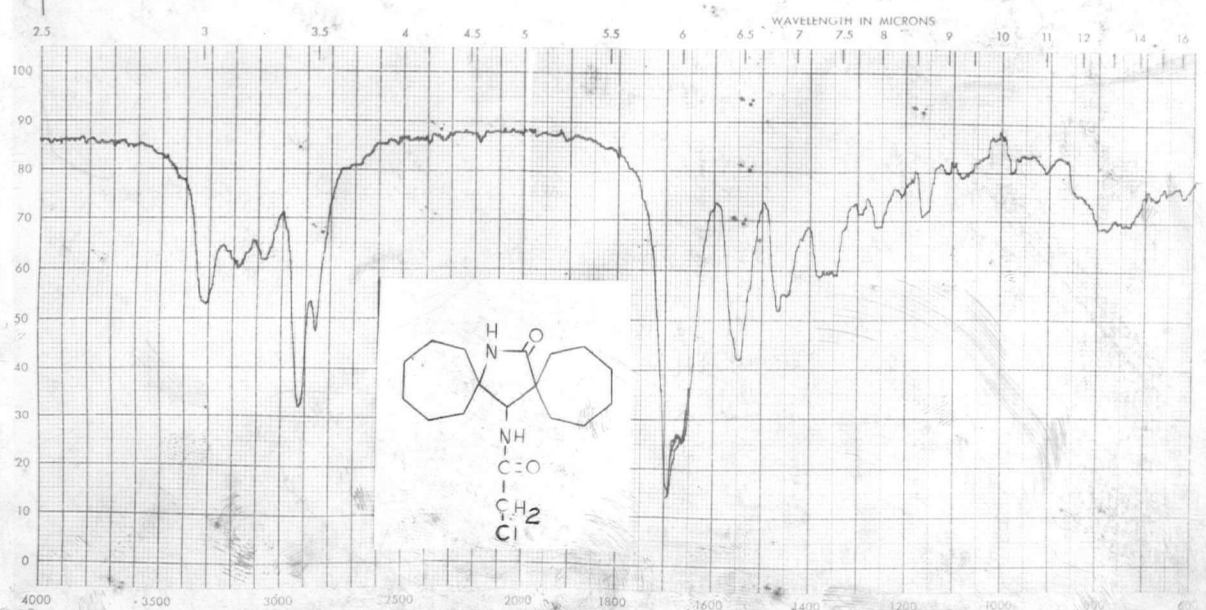Infrared Spectrum 16.   16-Hydroxy-16-azadispiro[6.1.6.2]hep-

tadec-10-ene-8,17-dione 8-oxime.

Solid in potassium bromide disk.

Infrared Spectrum 17.   8-Amino-16-azadispiro[6.1.6.2]hepta-

decan-17-one.

Solid in potassium bromide disk.

Infrared Spectrum 18.   8-Chloroacetamido-16-azadispiro[6.1.6.2]-

heptadecan-17-one.

Solid in potassium bromide disk.

2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 9 10 11 12 14 16

100 90 80 70 60 50 40 30 20 10 0

4000 3500 3000 2500 2000 1800 1600 1400 1200 1000 800 600

WAVENUMBER CM⁻¹

WAVELENGTH IN MICRONS

2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 9 10 11 12 14 16

100 90 80 70 60 50 40 30 20 10 0

4000 3500 3000 2500 2000 1800 1600 1400 1200 1000 800 600

WAVENUMBER CM⁻¹

WAVELENGTH IN MICRONS

2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 9 10 11 12 14 16

100 90 80 70 60 50 40 30 20 10 0

4000 3500 3000 2500 2000 1800 1600 1400 1200 1000 800 600
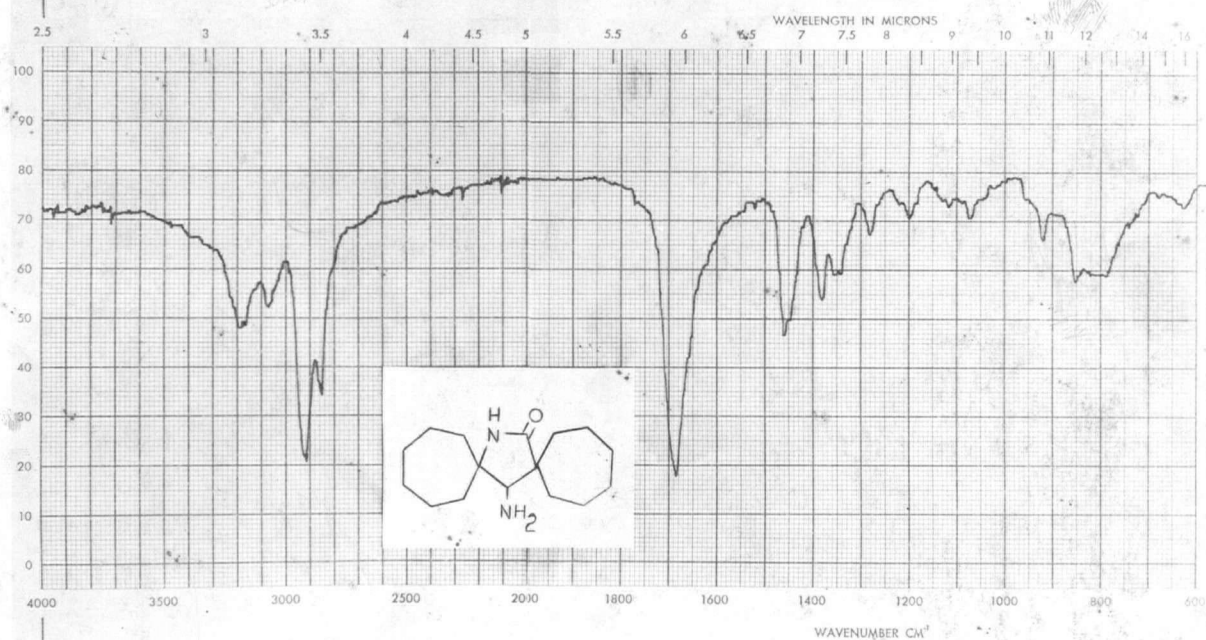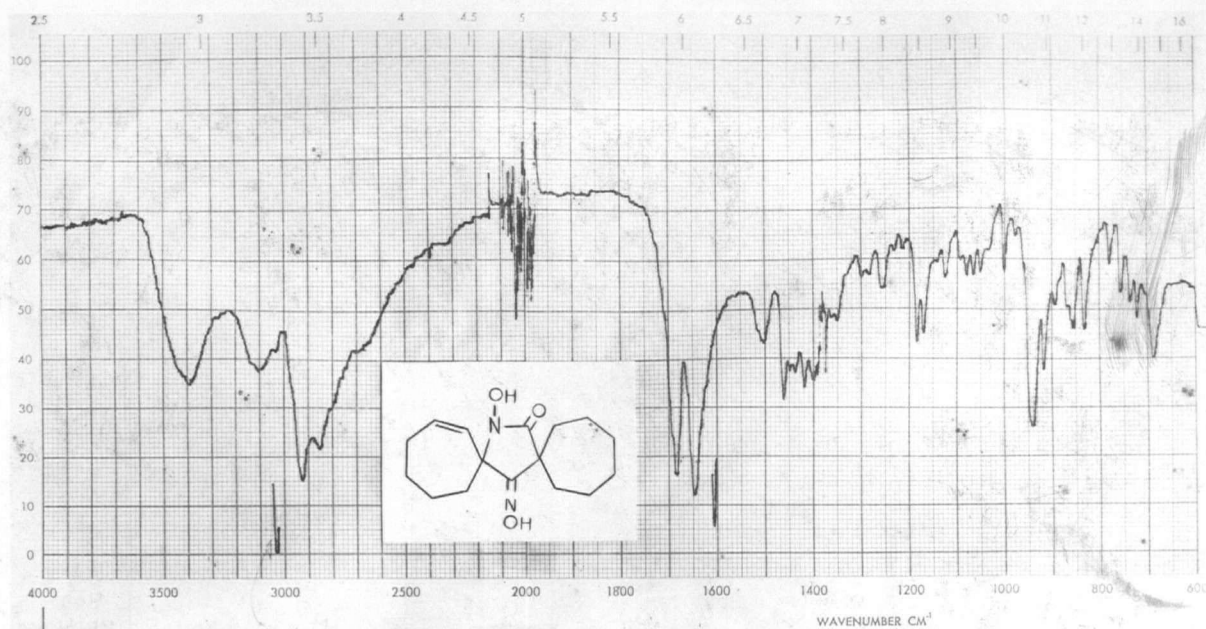
Infrared Spectrum 19.   A Product obtained from the Reaction

of Monochloroacetyl Chloride and

8-Amino-16-azadispiro[6.1.6.2]hepta-

decan-17-one.

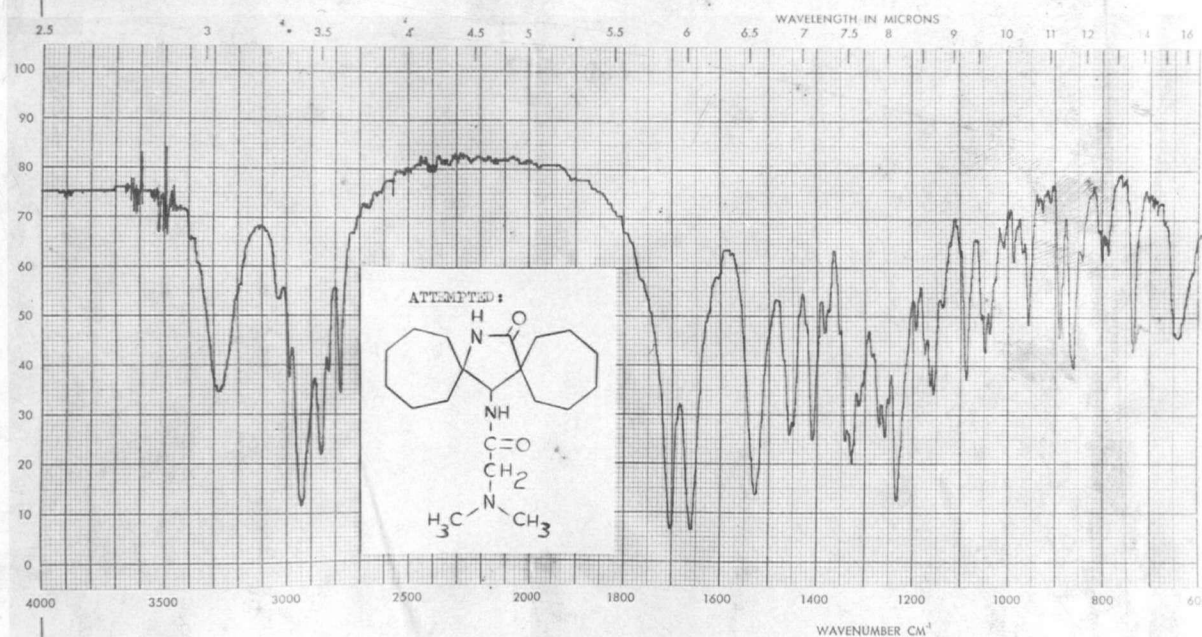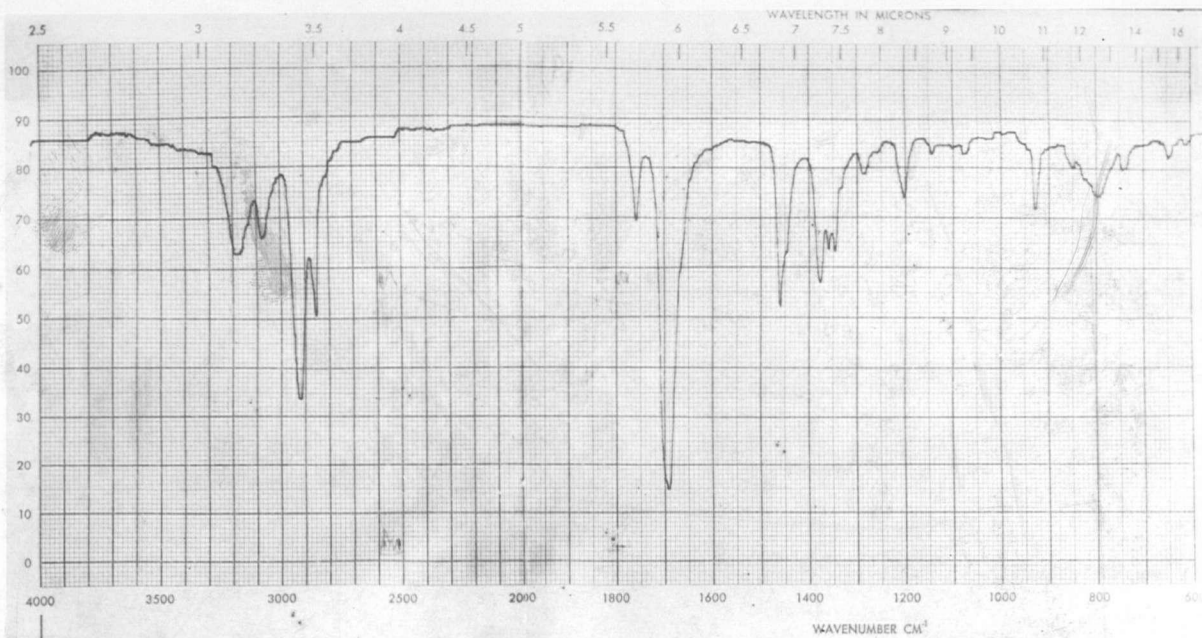Solid in potassium bromide disk.

Infrared Spectrum 20.   Product from the Attempted Synthesis

of 8-Dimethylaminoacetamido-16-aza-

dispiro[6.1.6.2]heptadecan-17-one.

Solid in potassium bromide disk.

Infrared Spectrum 21.   Product from the Attempted Synthesis

of 8-Dimethylaminoacetamido-16-aza-

dispiro[6.1.6.2]heptadecane.

Liquid film between sodium chloride

plates.

ATTEMPTED:

PART VII

SUMMARY

A β-dimethyaminoethyl derivative of 7,14-diazadispiro[5.1.5.2]-pentadecan-15-one was synthesized by adding β-dimethyaminoethylbromine hydrobromide to the latter compound after it had been treated with an excess of sodium hydride. This derivative was then reduced using lithium aluminum hydride, as indicated by infrared spectroscopy. A correct elemental analysis was obtained for the lactam but not for the reduced analog. It was not determined if substitution had occurred at the secondary of lactam nitrogen. The synthesis of the chloroacetyl derivative of 7,14-diazadispiro[5.1.5.2]-pentadecan-15-one was attempted so that it could be used as an intermediate in the synthesis of the dimethyaminoacetyl dispiro compound. The reaction of chloroacetyl chloride with the above-named dispiro compound was attempted using a variety of reaction conditions. The use of potassium carbonate as the hydrochloride acceptor and acetone as the solvent gave the best yields, but even these were very low. Thin layer chromatography indicated that the product obtained from the reaction was a mixture of three components, but attempts to separate these on alumina and on silica columns failed. Because of the difficulty experienced in trying to obtain and purify this intermediate, and in the failure of 8,16-diazadispiro[6.1.6.2]heptadecan-17-one to form under the same conditions used to synthesize the cyclohexyl analog, attention was turned to the synthesis of analogous dispiro compounds that differed from the first series by the presence of a primary amino group rather than a secondary one. This series of dispiro compounds lack the steric hindrance around the amino group which may be the cause of the low yields of the condensation reactions.

The primary aminolactams used as starting material were obtained by Raney nickel hydrogenation at room temperature of the unsaturated dispiro compounds that contained a five-membered ring ketoxime N-hydroxylactam. The cyloheptyl analog had not been previously reported. The one-step additions of the dimethylaminoacetic acid to 7-amino-14-azadispiro[5.1.5.2]-pentadecan-15-one and 8-amino-16-azadispiro[6.1.6.2]heptadecan-17-one using dicyclohexylcarbodiimide as the condensing agent were attempted. The infrared spectrum of the product obtained from the former reaction indicated that the condensation product did not form. In the case of the latter reaction, the product obtained did not result in a correct elemental analysis although its infrared spectrum was consistent with the desired product. The addition of β-dimethylaminoethylbromine hydrobromide, to the 8-amino dispiro compound named above after pretreatment with sodamide, was not successful. The intermediate for the synthesis of the 8-dimethyaminoacetyl derivative, 8-chloroacetamido-16-azadispiro[6.1.6.2]heptadecan-16-one was synthesized by the method found to give the best yields of chloroacetylated product in the first series of dispiro compounds. It was identified by its infrared spectrum and elemental analysis.

PART VIII

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