

OXYGEN TRANSFER REACTION FROM
CYCLIC NITRONES TO TRIPHENYLPHOSPHINE

by

FRANCO AGOLINI

LAUREA IN CHEMISTRY

UNIVERSITY OF MODENA (1958)

A THESIS SUBMITTED IN PARTIAL FULFILMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
MASTER OF SCIENCE

in the Department
of
CHEMISTRY

We accept this thesis as conforming to the
required standard

THE UNIVERSITY OF BRITISH COLUMBIA,
July, 1962.

In presenting this thesis in partial fulfilment of the requirements for an advanced degree at the University of British Columbia, I agree that the Library shall make it freely available for reference and study. I further agree that permission for extensive copying of this thesis for scholarly purposes may be granted by the Head of my Department or by his representatives. It is understood that copying or publication of this thesis for financial gain shall not be allowed without my written permission.

Department of CHEMISTRY

The University of British Columbia,
Vancouver 8, Canada.

Date 20th Aug. 1962

A B S T R A C T

The compounds in the series from triphenylphosphine to triphenylbismuthine were examined as acceptors in oxygen transfer reactions involving the 1-pyrroline-1-oxides. Triphenylphosphine was found to offer a useful route from the 1-pyrroline-1-oxides to the corresponding pyrrolines.

The second part of this work is centred on the structural investigation of Sanno's base (XV) (1), obtained as a by-product in the reductive cyclization of ethyl 2-acetyl-2-ethyl-4-methyl-3-nitromethyl valerate (a γ -nitro-ketone) and formulated by the author as having the Δ^1 -pyrroline structure; this compound has since been found to be a cyclic nitron (XVI). In the case of this complex nitron, the oxygen transfer reaction to triphenylphosphine has been successful, yielding two isomeric Δ^1 -pyrrolines. The isolation of a Δ^1 -pyrroline structure is confirmation of the proposed cyclic nitron (XVI) structure for Sanno's base and as this provides a practical application of this reaction in structural work as well as showing that triphenylphosphine will reduce N-oxides in the presence of an ester group.

ACKNOWLEDGMENT

I would like to express my deep appreciation to Drs. R. Bonnett and D. E. McGreer for their constant help and encouragement during this work.

CONTENTS

	Page:
Acknowledgment	i
Abstract	ii
Table of Contents	iii
Table of Figures	v
PART I: Introduction	1
Results and Discussion	12
PART II: Introduction	17
Results and Discussion	22
EXPERIMENTAL:	
I. Preparation of 2,4,4-trimethyl-1-pyrroline from 2,4,4-trimethyl-1-pyrroline-1-oxide	29
II. Pyrolysis of 5,5-dimethyl-1-pyrroline- 1-oxide	30
III. Preparation of 5,5-dimethyl-1-pyrroline from the corresponding nitron	31
IV. Preparation of 3-methyl-1-nitro-2-butanol	32
V. Preparation of 2-acetoxy-3-methyl-1- nitrobutene	32
VI. Preparation of 3-methyl-1-nitrobutene-2	33
VII. Preparation of Ethyl 2-acetyl-2-ethyl- 4-methyl-3-nitromethyl valerate	34
VIII. Preparation of Ethyl 4-ethyl-3-isopropyl- 5-methyl-1-pyrroline-1-oxide-4-carboxylate	34

	Page:
IX. Preparation of Ethyl 4-ethyl-3-isopropyl -5-methyl-1-pyrroline-4-carboxylate	36
X. Oxygen transfer reaction to triphenyl- phosphine	38
XI. Analysis of the components	39
BIBLIOGRAPHY	41

TABLES AND FIGURES

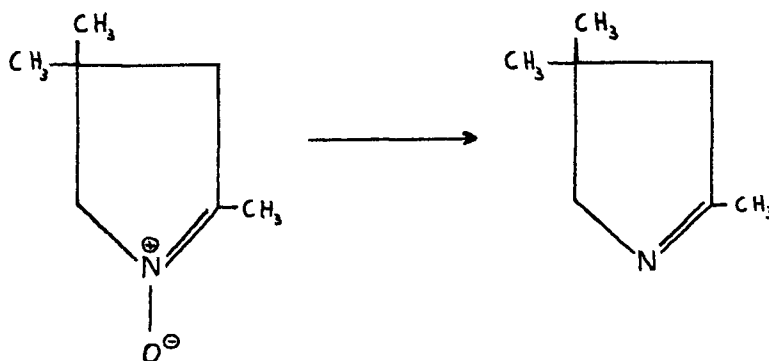
Page:

TABLE I	Oxygen transfer from 2,4,4-trimethyl- 1-pyrroline-1-oxide	14
FIGURE I	Vapour phase chromatogram of the deoxygenation of Sanno's base	28

I N T R O D U C T I O N

PART I

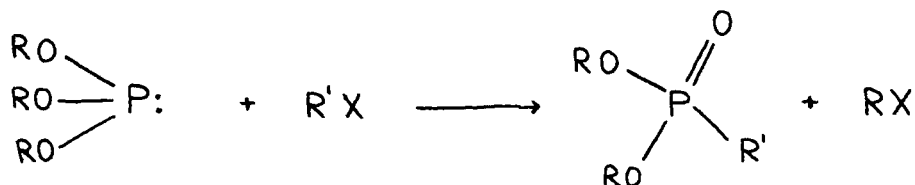
The reduction of 1-pyrroline-1-oxides (cyclic nitron^s) to the corresponding pyrrolines has previously (2) been carried out in two ways: 2,4,4-trimethyl-1-pyrroline-1-oxide, for example, on treatment with zinc and acetic acid gave a 66% yield of the corresponding pyrroline picrate, while a 15% yield was obtained when sulphur dioxide in chloroform was the reducing agent.



As the nitrones represent a reactive 1,3-system (3) and because of the necessity to stop the reduction at the pyrroline stage, investigations were carried out to find a suitable reducing agent, which would have to combine selectivity, rapidity and effectiveness.

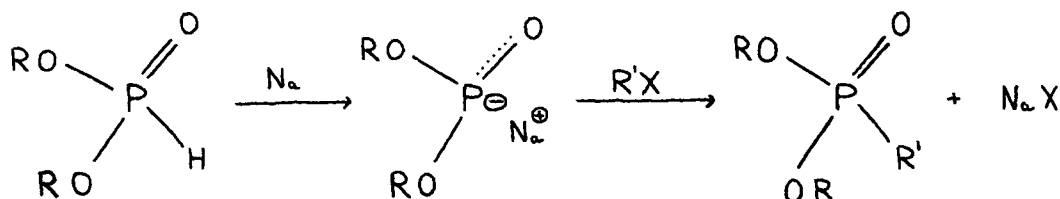
This agent has been sought among the triphenyl derivatives of group V, particularly since triphenylphosphine

has been used successfully to remove oxygen from many substrates (4). Although phosphorus follows nitrogen in Group V there is very little resemblance between the organic chemistry of these two elements. These dissimilarities arise because of the lower electronegativity of phosphorus which permits stronger bond formation with oxygen and halogens and because of the greater reactivity of the unshared electrons on the tervalent phosphorus, which results in a stronger tendency to the quinquavalency (5). These are the main differences by which the organic chemistry of the phosphorus is richer than that of the nitrogen. In all its reactions the driving force is the tendency to the quinquavalency, tendency that can be illustrated through numerous examples as in the Arbusov reaction (6), where trialkyl phosphites react with halogen derivatives to give dialkyl-alkyl-phosphonates and halogen derivatives, according to the scheme:

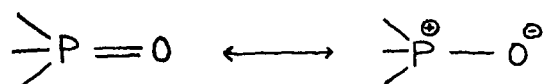


This reaction provides a useful route to prepare some alkyl halides which are not otherwise readily accessible. Another example is the Michealis reaction (7) where alkali

metal derivatives of dialkylphosphites react with alkyl halides to give dialkyl alkylphosphonates:



That the bond between phosphorus and oxygen, which is formally written as double bond, does, in fact, have a considerable amount of double bond character is shown by its dipole moment, by its short length and by its resemblance to the carbonyl group in producing α -methylene reactivity. For this reason the bond is probably better represented as the hybrid:



All the tervalent phosphorus compounds are susceptible to oxidation (8). This is particularly true of those in which the phosphorus atom has attached to it alkyl groups which, since they are electron repelling, increase the already high electron density on the phosphorus atom. Triphenylphosphine is outstanding among the triphenyl derivatives of Group V. A comparison of the dipole moments:

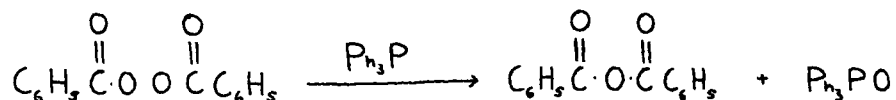
Dipole moments of the triphenyl derivatives
Group V

Ph_3N	Ph_3P	Ph_3As	Ph_3Sb	Ph_3Bi
0.22 D	1.45 D	1.07 D	0.57 D	0.00 D

shows that as the series is descended the dipole moments decrease steadily and so the nucleophilic character (9) also decreases. This has been once explained (10) on the grounds of an increase in conjugation that is expected passing from a triangular pyramid arrangement as it is in triphenylphosphine, where the phosphorus is located at the apex of the pyramid, to the planar triangular arrangement of triphenylbismuthine.

However, on the basis of a study of the U.V. spectrum of triphenylarsine, Cullen (11) has recently suggested that there is little or no conjugation of the lone pair of arsenic with the phenyl groups and that the same is true for the compounds Ph_3M (-here $\text{M} = \text{P}, \text{Sb}, \text{Bi}$), as their spectra resemble that of triphenylarsine. A current interpretation is that as the series is descended the lone pair orbital acquires more "s" character which leads to a subsequent decrease in both the dipole moment and the nucleophilic character. Although triphenylphosphine reacts very slowly at ordinary conditions with atmospheric oxygen (12), its capacity to abstract oxygen from those substrates where there is available an oxygen atom weakly bonded is very well known. The reaction of benzoyl peroxide with tri-

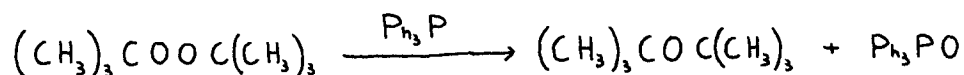
phenylphosphine to give benzoic anhydride and triphenylphosphine oxide was first discovered by Challenger and Wilson (13):



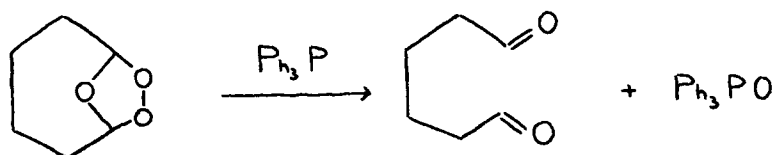
Later, Shönberg reported that dibenzoyl disulfide was reduced in similar fashion to dibenzoyl sulfide (14). Recently, Horner and Jugeleit (15) have made a thorough study of the reaction of several types of peroxides with tri-substituted phosphines.

In general, all the compounds investigated react with triphenylphosphine to give products in very high yield and purity. Hydrogen peroxide is reduced rapidly in ethereal solution to give water and triphenylphosphine oxide. n-Butyl hydroperoxide reacts with strong exothermic reaction to give the corresponding alcohol in 90% yield and in similar fashion tetralin alcohol has been obtained in 98% yield from tetralin hydroperoxide. An olefinic hydroperoxide was also reduced selectively with no affect to the double bond. On the other hand, dialkyl peroxides are in general very resistant to reduction and only in the case of the qualitative reduction of diethyl peroxide to diethyl ether has it been reported. Horner claimed that di-t-butyl peroxide after several hours of heating at 111-120° with triphenylphosphine

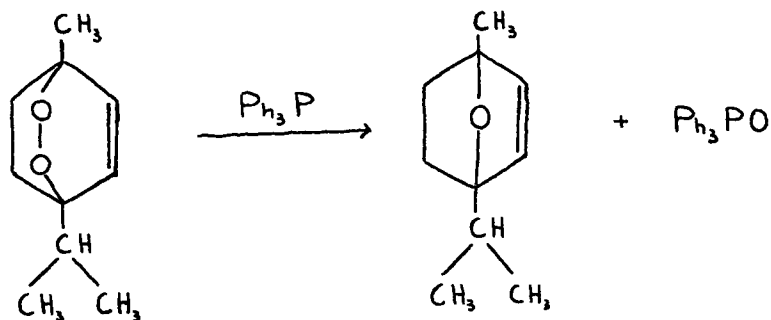
gave the corresponding ether:



However, this reaction has been reinvestigated by Walling (16) and it has been shown that the reaction goes by a free radical mechanism and triphenylphosphine does not participate. Horner reported also the satisfactory reduction of ozonides; cyclohexane ozonide gave the corresponding dialdehyde in 70% yield:

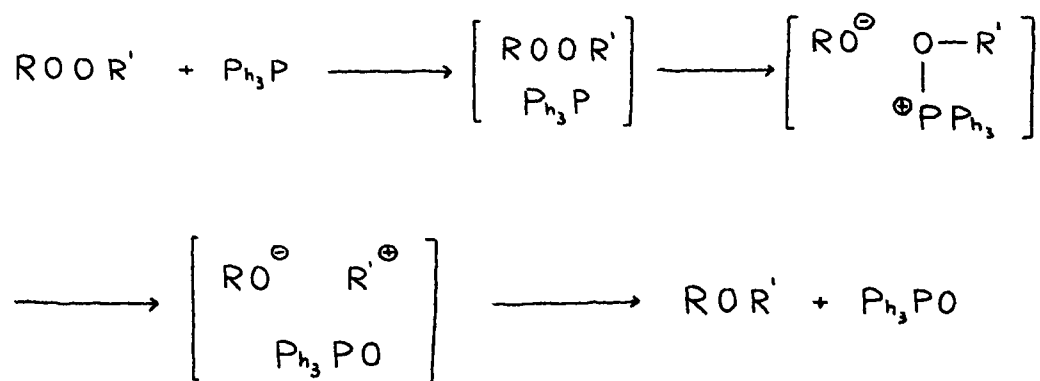


An endo peroxide (ascaridol) was reduced to the corresponding endo oxide:



The reduction of acyl peroxides, peracids, peresters, proceeds

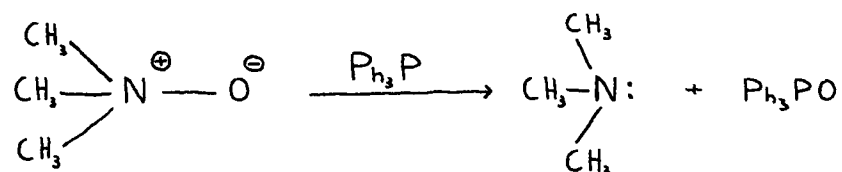
smoothly. In general, all these reactions proceed rapidly at room temperature in solvents such as pentane or ether. A free radical mechanism for these reactions does not seem likely as (a) there is no attack on the solvent (b) the products of the reaction do not correspond to those of the known radical decomposition of peroxides (c) the reaction is not prevented by the addition of radical inhibitors. Horner has suggested that the reaction proceeds by the formation of an initial adduct between triphenylphosphine and the peroxide and then subsequent attack by triphenylphosphine on one oxygen with the formation of a phosphonium ion, which can then combine to give the product and triphenylphosphine oxide according to the scheme:



Since these reactions proceed rapidly in non polar solvents, conditions which are unfavourable for ionic reactions, Hoffmann (17) investigated the reaction to determine how free any formed ions were, if indeed any ions were formed

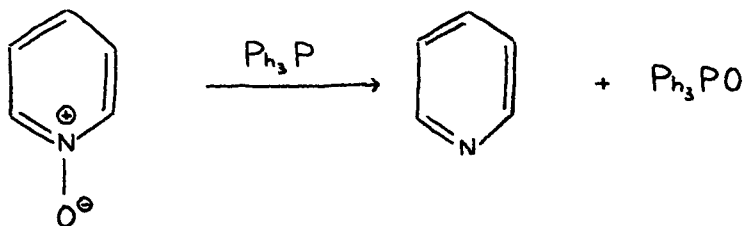
at all. He postulated the formation of an ion-pair whose rate of collapse depends to a large degree on the polarity of the solvent. In non-polar solvents the collapse is quite rapid as compared to more polar solvents where this ion-pair is "loose" enough so that a foreign ion can intervene to a larger degree and alter the nature of the products.

The effectiveness of triphenylphosphine as a selective reducing agent has also been tested on those substrates where there is an oxygen atom weakly bonded. Trimethylamine oxide (4) reacts in hot glacial acetic acid to give quantitatively trimethylamine and triphenylphosphine oxide:

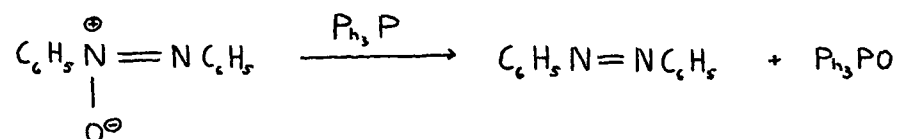


It has been observed that the ease of removal of the oxygen from the amine oxides decreases with the dipole moment.

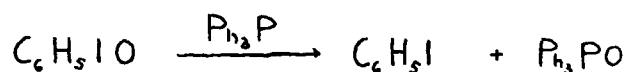
Pyridine-N-oxide and quinoline-N-oxide are resistant, however, they have been reduced (18) by mixing the reagents together in absence of solvent and using a Wood's metal bath:



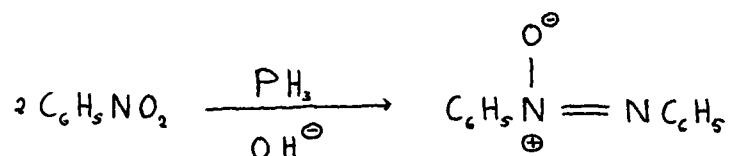
The quantitative reduction of azoxybenzene (19) to azobenzene was effected at 150°:



Iodosobenzene was reduced to iodobenzene (20):

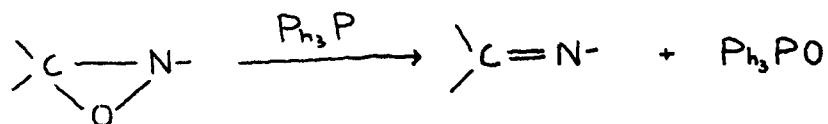
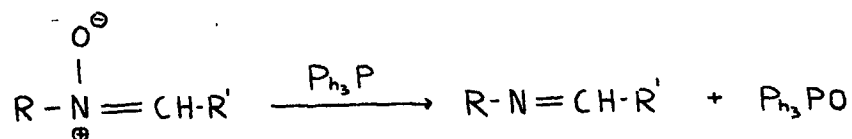


No reaction was observed with nitro compounds, although a deep colour developed on mixing nitrobenzene and triphenylphosphine. Recently (21) it has been reported that nitro aromatic compounds react with phosphine in the presence of base to give azoxybenzene in 96% yield:

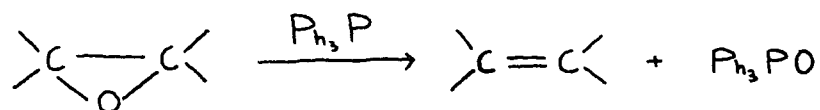


The possibility that even triphenylphosphine might be used with success can not be disregarded.

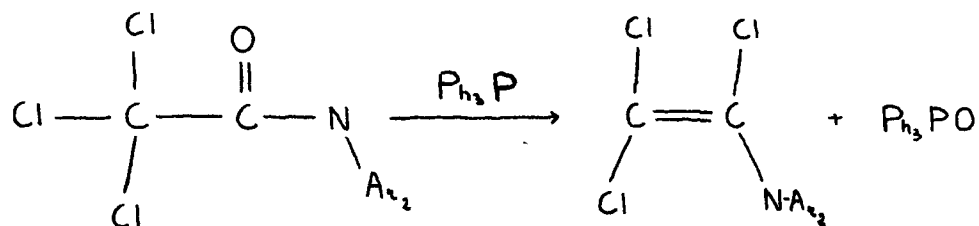
The reduction of an aldonitrone (4) and oxazirans (22) has been noted:



Ethylene oxides are more resistant, however, they have been reduced at 150° to the corresponding olefins (4):

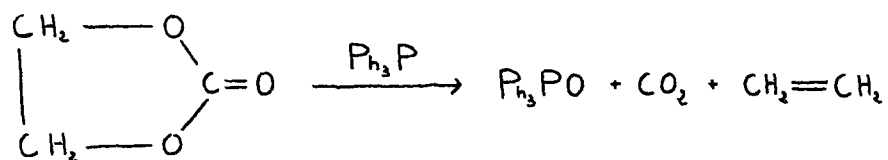


Triphenylphosphine reacts at 150° in o-xylene with N-substituted trichloroacetamides to give the corresponding vinylamine in good yield (23):



Ethylene and substituted ethylene carbonates react with triphenylphosphine (24) giving the olefin corresponding to the carbonate used. Ethylene carbonate and triphenyl-

phosphine heated over the temperature range 130-200° in the absence of solvent gave triphenylphosphine oxide in 93% yield and the olefin in 68% yield:



With higher molecular weight carbonates, phosphine oxidation and subsequent olefin synthesis occur only if a catalyst is used. Large ring carbonates do not react.

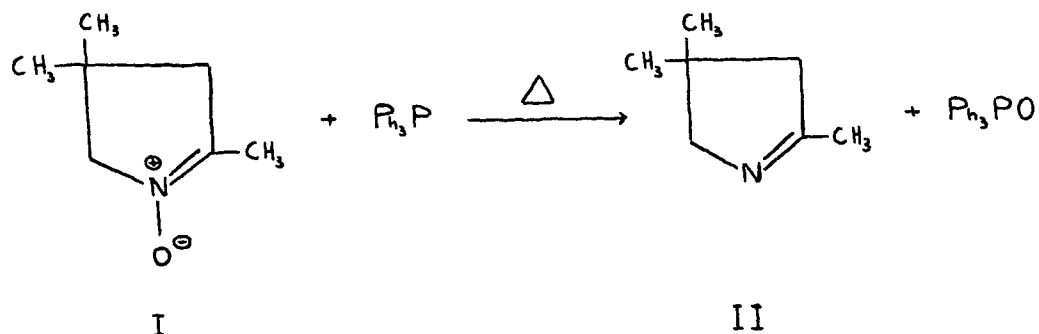
The use of triphenylarsine as an oxygen acceptor has not been so extensively investigated although the satisfactory reduction of acyl peroxides to the corresponding anhydrides has been reported (4). No information appears to be available concerning the applicability of triphenylstibine and triphenylbismuthine as oxygen acceptors.

RESULTS AND DISCUSSIONPART I

A convenient method has been sought for the reduction of nitrones to pyrrolines which would avoid aqueous or acidic conditions and which, moreover, would give the product directly under conditions that could yield a minimum of structural changes. Such a process is required for example in cases where the product of a preparative sequence is the 1-pyrroline-1-oxide from which it is then desired to make the pyrroline. Oxygen transfer from nitrogen to compounds of other elements of Group V suggested itself as a potential method, especially since triphenylphosphine has been used successfully to remove oxygen from many substrates. The reduction of an aldonitrone has been noted but no information appears to be available concerning the applicability of the reaction to purely aliphatic nitrones, including the 1-pyrroline-1-oxides.

2,4,4-trimethyl-1-pyrroline-1-oxide (I) was chosen as a model compound and was found to be reduced by triphenylphosphine. In order to determine the best conditions for the reduction experiments were carried out under a variety of conditions. It was found that the reaction did not proceed to a useful degree in refluxing

benzene or toluene. The reaction occurred rapidly, when the substances were heated together with a free flame, and the product, 2,4,4-trimethyl-1-pyrroline (II) was distilled directly from the reaction mixture:



A similar result was obtained with triphenylarsine. With triphenylstibine and triphenylbismuthine, however, extensive decomposition was evident, and in the latter case the main product in the distillate was benzene. Triphenylphosphine oxide was isolated from the residue thus confirming that the reaction involves oxygen transfer to phosphorus.

The results are summarized and some comparisons drawn in Table I. These results were not surprising, because it was expected that as this series was descended the decreasing stability of both the carbon-metal bond and metal-oxygen bond would intervene at some stage and give side reactions which would make the reaction useless as a preparative method.

TABLE I

Oxygen Transfer From 2,4,4-Trimethyl-
1-Pyrroline-1-Oxide.

Reagent	Reaction With CH ₃ l (25)	Effect of Heating Alone *	Weight of Distillate (g)	% Yield	% Yield of Picrate /
Ph ₃ P	Rapid	Refluxes	0.66	75	57
Ph ₃ As	Slow	Refluxes Slight Decomp.	0.61	70	42
Ph ₃ Sb	Nil	Decomp.	0.74 #		34
Ph ₃ Bi	Nil	Decomp.	1.6 #		Trace

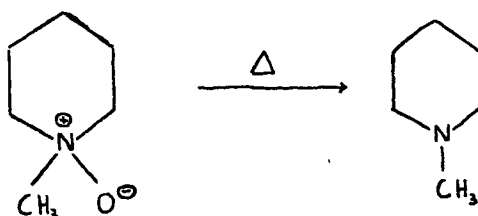
* Under the reaction conditions.

One-Gram portions of nitron heated with an equimolar amount of the reagent.

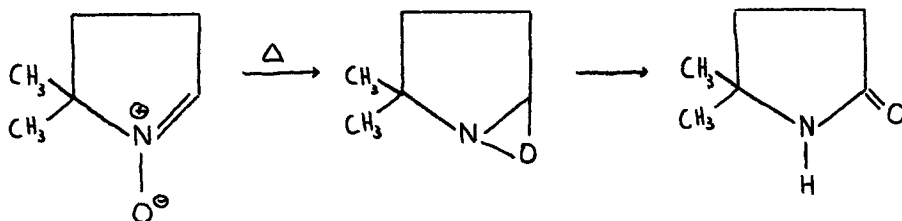
/ Prepared in moist ether.

Distillate extensively contaminated by decomposition products of the organometallic compounds.

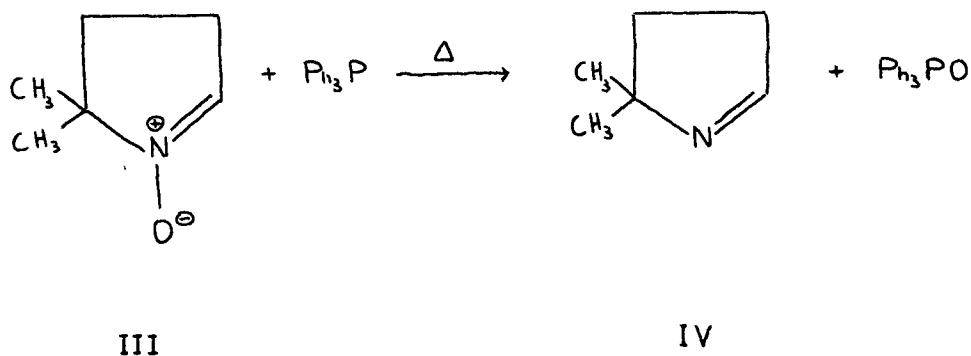
It was found that when the nitron was heated alone with a free flame for 10 minutes there was a complete recovery of unchanged starting material. This would exclude at once the possibility of a pyrolytic deoxygenation, a process which has been observed with certain amine oxides as for example N-methylpiperidine-N-oxide (26):



The reaction was also applied to 5,5-dimethyl-1-pyrroline-1-oxide (III), a cyclic aldonitrone. In contrast to the cyclic ketonitrone, I, which is fairly stable to heat, 5,5-dimethyl-1-pyrroline-1-oxide is thermolabile. The decomposition is attended by the development in the infrared spectrum of a broad absorption band in the 1660 cm⁻¹ region. This has led to the supposition that isomerization to the corresponding lactam may be one of the reactions involved:

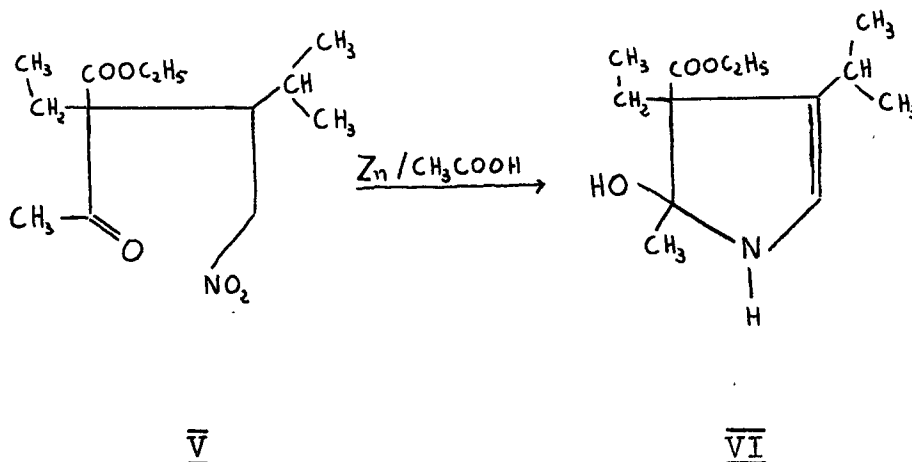


However, the oxygen transfer reaction evidently proceeds more rapidly than the isomerization, for the reaction gave a 65% yield of the crude 5,5-dimethyl-1-pyrroline (IV) (39% yield as the picrate) and triphenylphosphine oxide (57%) was isolated from the residue:



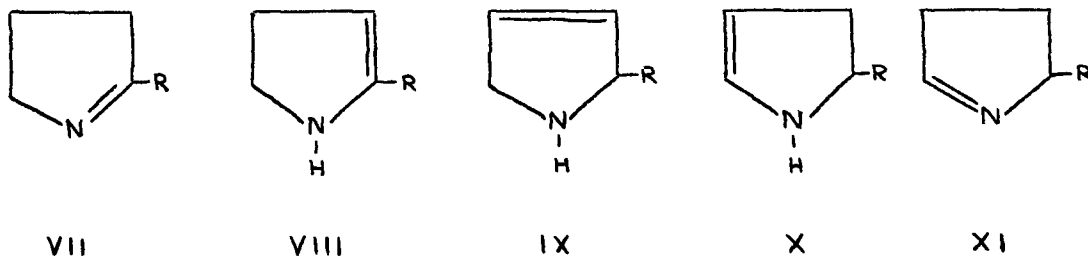
I N T R O D U C T I O NPART II

Sanno (1) reported that in the cyclization of ethyl 2-acetyl-2-ethyl-4-methyl-3-nitromethyl valerate (V), with zinc and acetic acid, there was isolated as a by-product a compound which he claimed to be the ethyl 4-ethyl-5-hydroxy-3-isopropyl-5-methyl- Δ^3 -pyrroline-4-carboxylate (VI):



This formulation may be questioned on the basis of the following more recent experimental work.

Of the five possible structures (VII-XI) which can be written for 2-substituted pyrrolines only Δ^1 and Δ^3 have been shown conclusively to exist:



There is no controversy concerning the existence and the identity of Δ^3 -pyrrolines (27). Compounds of this structure are the usual, but not the exclusive (28, 29) products obtained from the partial reduction of substituted pyrroles. However, confusion has centred around the existence of Δ^1 -pyrrolines (VII and XI) and Δ^2 -pyrrolines (VIII and X). Several workers (30-36) have arbitrarily assigned a Δ^1 -structure to their compounds, while Cloke (37, 38) suggested either the Δ^1 or Δ^2 form or a tautomeric mixture of the two. The question has been reconsidered recently (39 - 43), and in general the conclusion has been drawn that these substances exist predominantly in the Δ^1 -form.

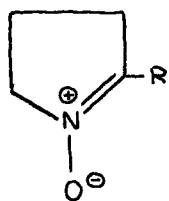
Both chemical and physical evidences have been adduced to support this formulation. The Zerewitinoff determinations (44, 45) have probably been the most significant chemical evidence since they have shown that in the examples studied, little or no active hydrogen was immediately available. Physical evidence has been based on a number of studies of ultraviolet spectra (46),

but the most significant results have come from infrared studies (39, 41, 42, 44). In general, the pyrrolines have shown little or no absorption in the N-H stretching region, but a strong band, attributed to C = N absorption, is present in the 1620-1650 cm^{-1} region. The strength of the C = N absorption band, and especially the absence of N-H absorption are of considerable importance. In the latter area difficulties have arisen in certain instances. Thus, Evans (40) reported that 2-methylpyrroline showed a weak band at 3.02μ , and Burckhalter and Short (41) considered a similar band at $3.05\text{--}3.10\mu$ in the spectrum of 2-benzylpyrroline to be anomalous since the compound did not contain active hydrogen. Other workers have considered that "the N-H region of the infrared absorption spectra of pyrrolidines and pyrrolines is difficult to interpret" (44, 47), and it is, of course, true that absorption in this region could be caused by species, notably traces of moisture or of dimer, other than the 2-pyrroline, which is presumed to be tautomeric with the Δ^1 -form. Fortunately, proton magnetic resonance proved a very useful tool. Bonnett and McGreer (48) showed for a number of cases that the pyrrolines in question did not give a signal in the olefinic proton region (2.0-5.5 τ) and this was consistent with only that structure containing the double bond in the Δ^1 -position since all possible tautomers would have at least one olefinic proton. The

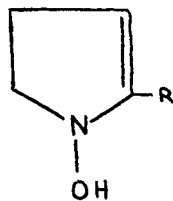
proton magnetic resonance spectra have strongly reinforced previous conclusions regarding the Δ' -structure of the pyrrolines investigated.

Furthermore, Bonnett and McGreer investigated the pyrroline-1-oxides, which are the first monomeric non-aromatic nitrones prepared by Todd (49) by reduction of γ -nitro carbonyl compounds with zinc and ammonium chloride. Todd et al (2) assigned them the Δ' -structure. Both chemical and physical evidences have been adduced to support this formulation. In fact, the nitrones were readily reduced to cyclic secondary hydroxylamine by aqueous KBH_4 ; by treatment with zinc and acetic acid they gave the Δ' -pyrroline, while with tin and hydrochloric acid they gave the corresponding pyrrolidine. The structures were supported by the physical properties that these compounds showed a single ultraviolet absorption maximum at 229-235 $\text{m}\mu$ ($\epsilon \sim 9000$) attributable to the $\text{>C} = \overset{\oplus}{\text{N}} - \overset{\ominus}{\text{O}}$ chromophore and they exhibit strong infrared absorption, the frequency ranging from 1600 to 1620 cm^{-1} for those bearing a 2-alkyl substituent and from 1570 to 1590 cm^{-1} when no such substituents were present. Bonnett and McGreer confirmed the assignment using N.M.R. methods; the lack of signal in the olefinic proton region is consistent only with structure (XII) containing the double bond in the Δ' -position since its

isomer (XIII) would have an olefinic proton:



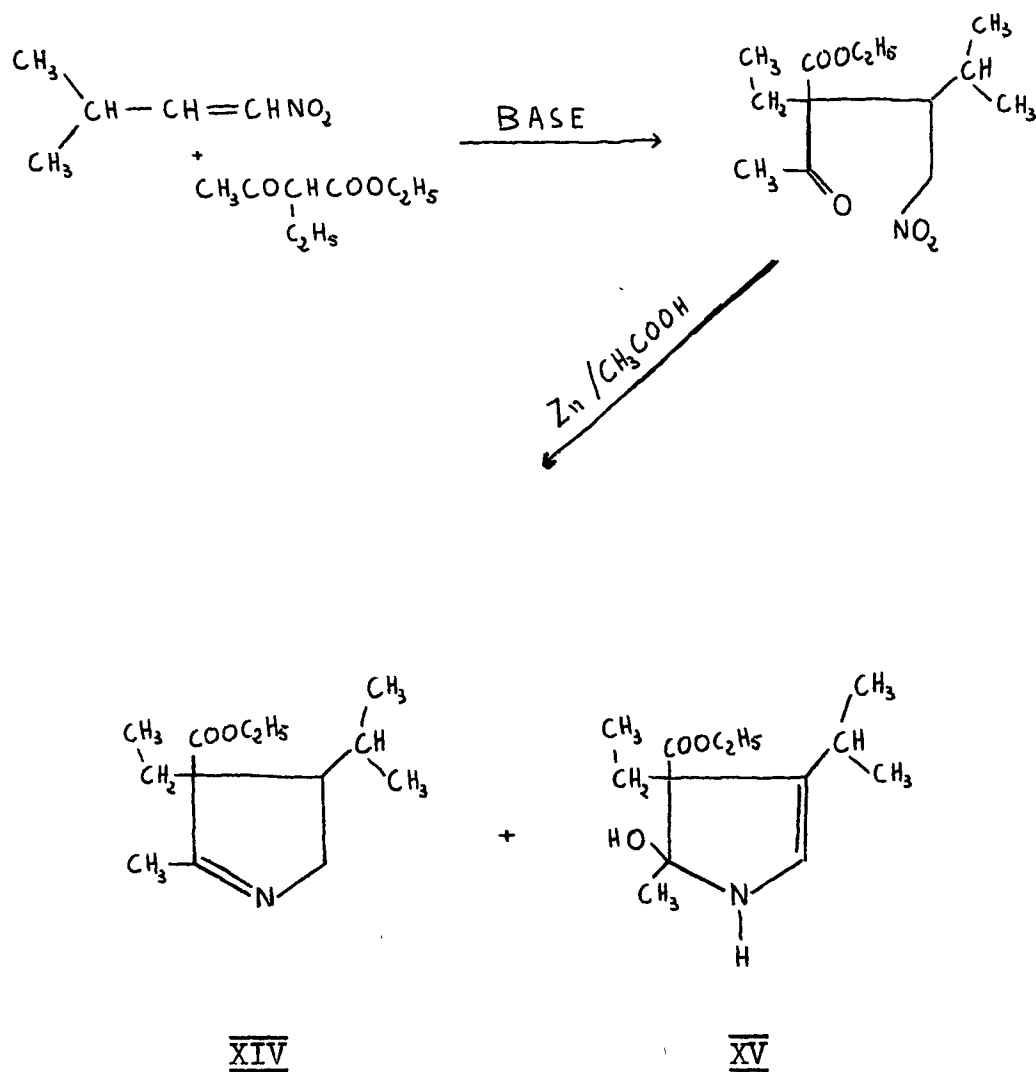
XII



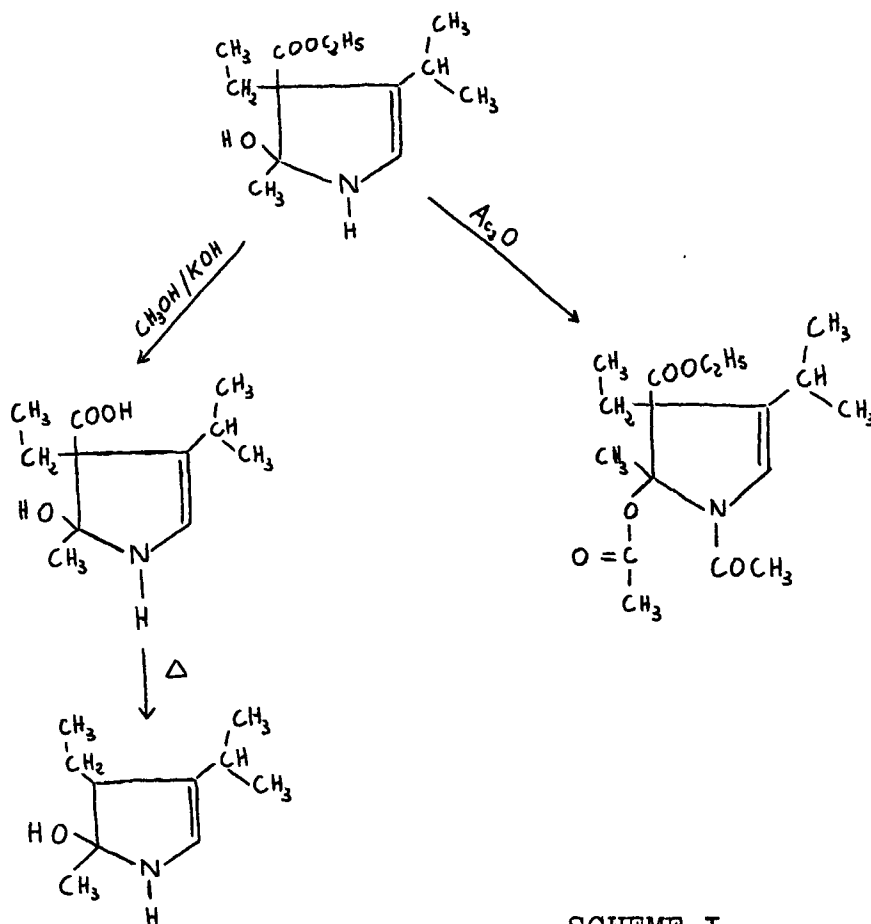
XIII

RESULTS AND DISCUSSIONPART II

Sanno (1) reported the preparation of a compound $C_{13}H_{23}NO_3$, formulated as XV, by the following route:-

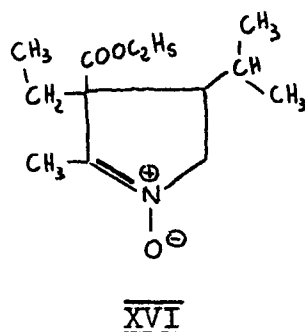


Much of the chemical evidence for this structure is summarized in the scheme I below:



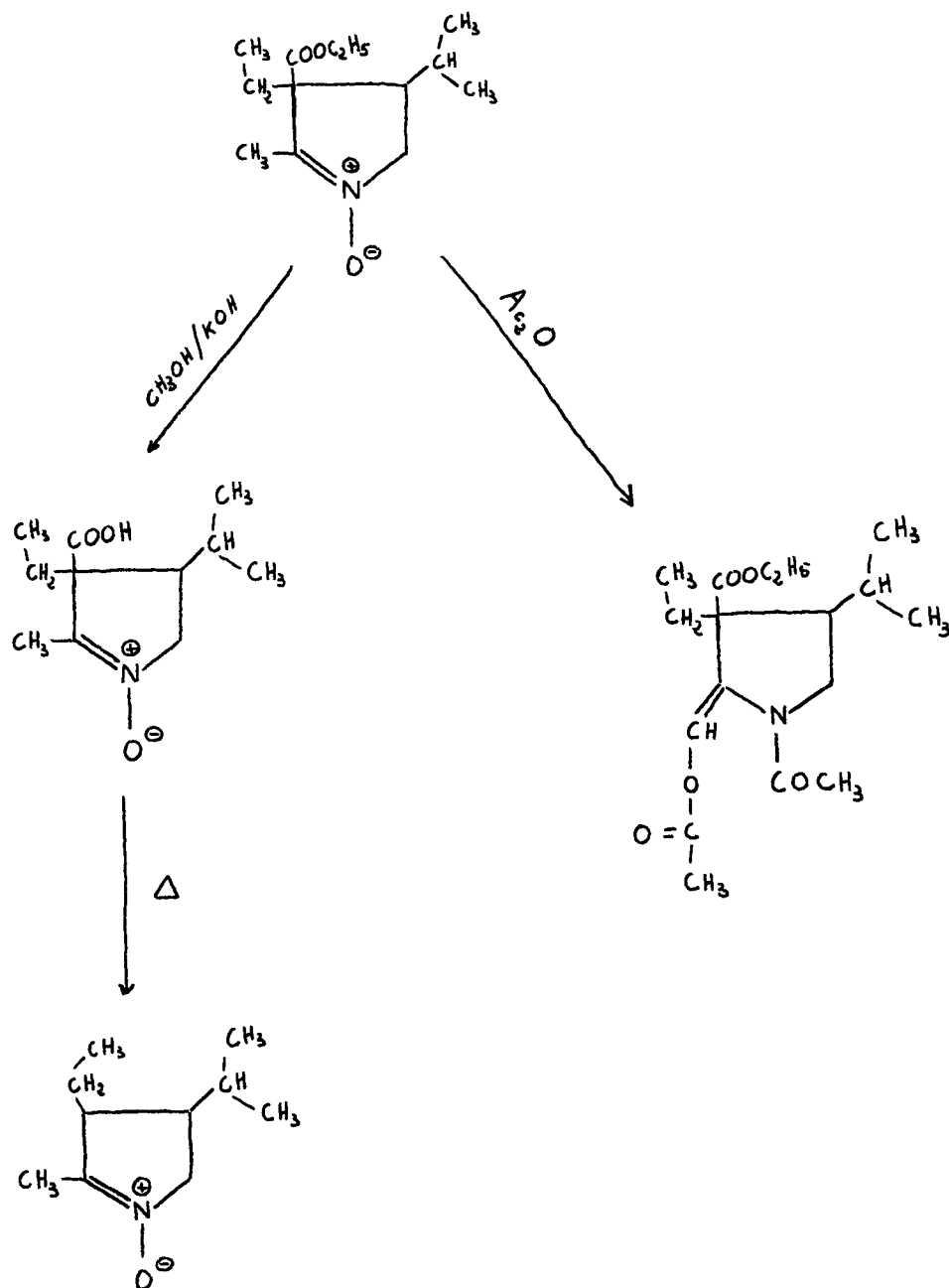
SCHEME I

Bonnett et al (50) have proved that compound XV is not a Δ^3 -pyrroline but is instead the corresponding 1-pyrroline-1-oxide (XVI):



XVI

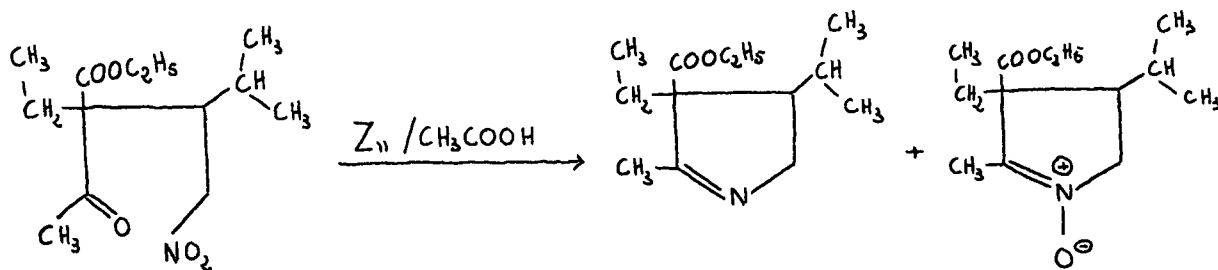
and have reinterpreted the reactions as indicated in Scheme II:



SCHEME II

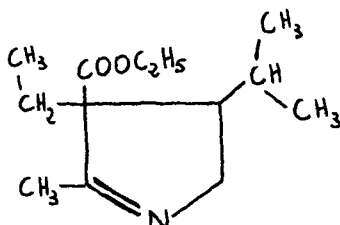
The results obtained below strongly reinforce the conclusion reached by Bonnett.

The suggestion that the Sanno product XV was a nitron provided an opportunity for the application of the oxygen transfer reaction with triphenylphosphine. Of particular interest was the possibility to investigate the reaction on a compound containing the ester group. For purposes of comparison the pyrroline was prepared by Sanno's procedure (1):



Since by ordinary distillation it was not possible to eliminate the nitron present as impurity, the pyrroline was purified by vapor phase chromatography. The chromatogram indicated the presence of two components in ratio 55 to 45%, the infrared spectra of which showed striking similarities except in the finger print region, indicating that these were cis and trans isomers. The N.M.R. spectra of both were so similar that no firm conclusion could be drawn as to the stereochemistry of each isomer. The important result was that neither of the components possessed absorption in the olefinic proton region of the

spectrum. Since analysis of the picrates indicated that the bases were isomeric, they are evidently the cis and trans -1-pyrrolines, for which the absolute stereochemistry is still unknown:



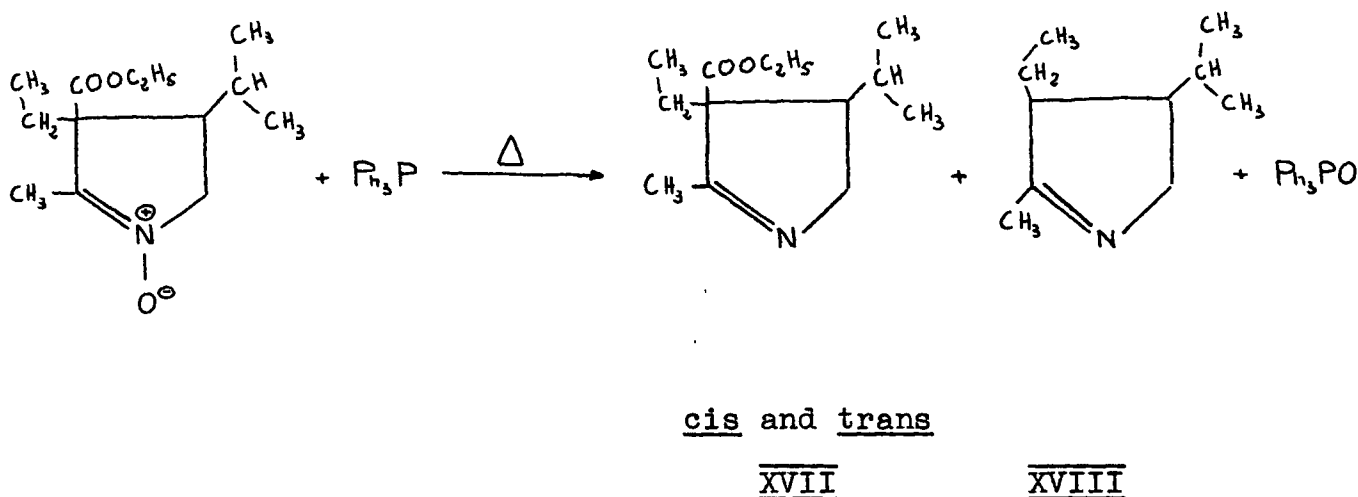
XVII

cis and trans

The nitron XVI (ethyl 4-ethyl-3-isopropyl-5-methyl-1-pyrroline-1-oxide-4-carboxylate) was subjected to the deoxygenation reaction with triphenylphosphine, and the product of the distillation was purified by vapor phase chromatography. Triphenylphosphine oxide was identified in the residue. The chromatogram of the distillate (see p.28) indicated the presence of six components; two of them were the expected two isomeric pyrrolines (XVII); a third component was identified by its infrared and N.M.R. spectra and from the analysis of its picrate to be another pyrroline (XVIII) in which the carboethoxy group at position 4 was not present. The other three components were decomposition products and were not identified. The oxygen-transfer reaction had evidently been accompanied, to the extent of about 20%, by a pyrolytic ester elimi-

nation, followed by decarboxylation, a sequence not surprising in view of the high temperatures involved.

The reaction can be summarized as follows:

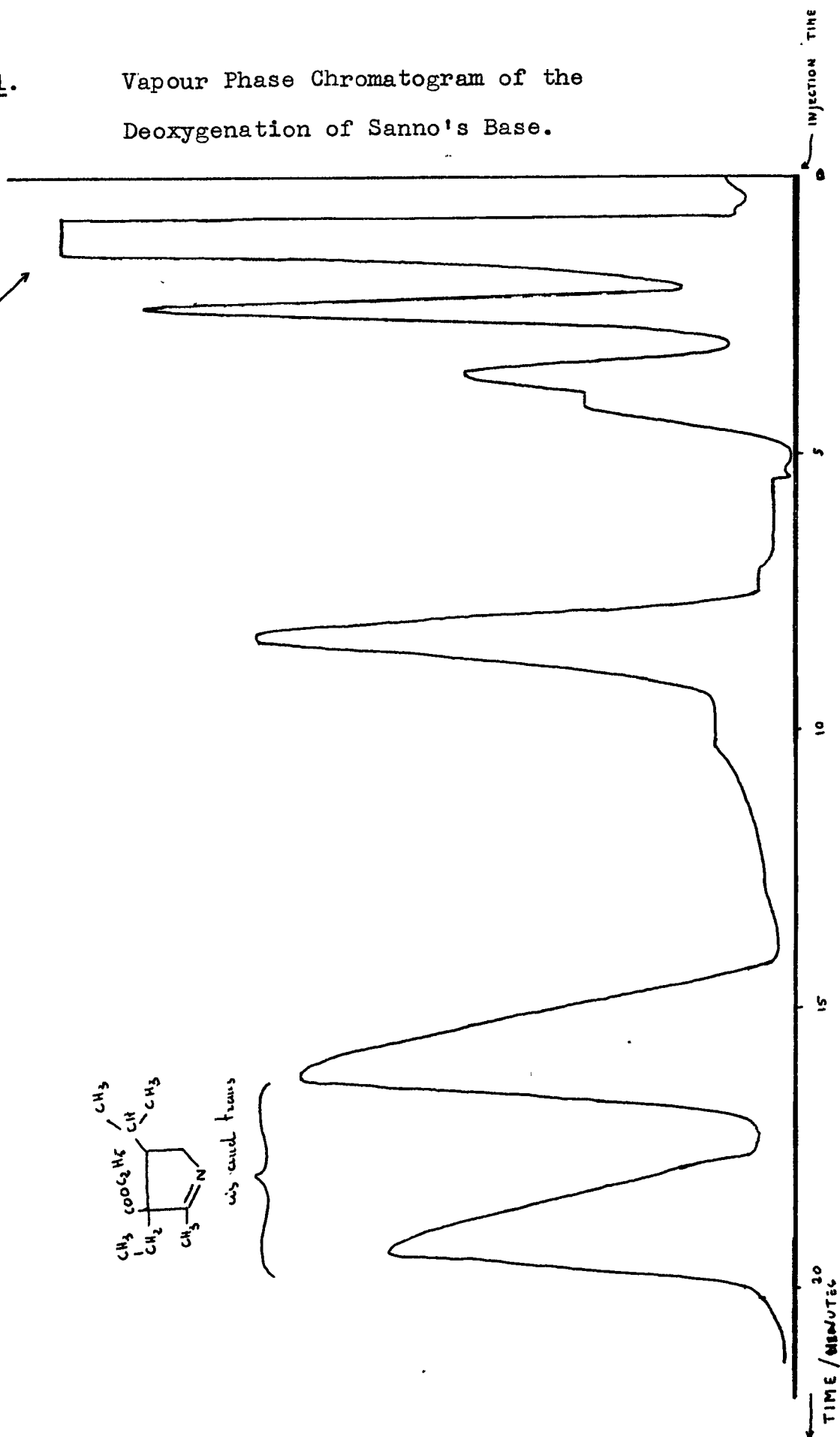
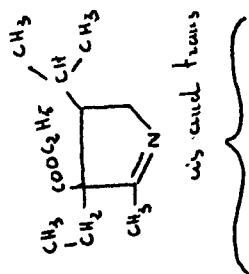
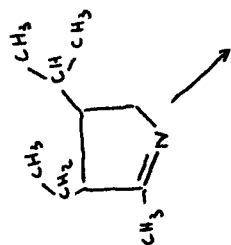


In order to prevent the pyrolysis of the ester, the nitronium was treated with triphenylphosphine in anhydrous benzene and the mixture was refluxed for 15 hours. The oxygen transfer to triphenylphosphine did not occur since triphenylphosphine was recovered and a complete recovery of nitronium was obtained.

These results show that Sanno's base is a mixture of cis and trans forms (which have been isolated and characterized at the pyrroline oxidation level), and strongly support the view that Sanno's base has the nitronium and not the Δ^2 -pyrroline structure. They also constitute the first application of the oxygen transfer reaction to structural work in the pyrroline series.

FIGURE 1.

Vapour Phase Chromatogram of the
Deoxygenation of Sanno's Base.



EXPERIMENTAL.

I. Preparation of 2,4,4-trimethyl-1-pyrroline from
2,4,4-trimethyl-1-pyrroline-1-oxide.

2,4,4-^Ttrimethyl-1-pyrroline-1-oxide (I) was prepared by the procedure of Todd et al (2).

- (a) The nitrone (I) (1 g) (0.0078 mole) and Eastman Kodak triphenylphosphine (m.p. 79°) (lit. m.p. 79°) (51) (2.5 g) (0.0095 mole) were heated (free flame) in a distillation apparatus. The volatile liquid which formed after a short time was refluxed gently for about 15 minutes and then distilled at atmospheric pressure, b.p. 110-130° (0.66 g 75%).

The infrared spectrum (film) of the basic liquid showed a band at 3620 cm⁻¹ attributed to moisture present in the hygroscopic starting material, together with a strong sharp band at 1650cm⁻¹ (C = N). No nitrone band was present since no absorption band was found at 1621 cm⁻¹, ($\text{>C} = \overset{\oplus}{\text{N}} - \overset{\ominus}{\text{O}}$). The picrate, m.p. 195-196°, was prepared in ether, and recrystallized from ethanol. No depression was obtained in the mixed melting point with an authentic sample of the pyrroline picrate obtained by the procedure of Todd et al (2). The infrared spectrum of the two picrates (Nujol mull) were identical.

The residue (2.6 g) from the distillation was extracted with cyclohexane and the solution treated with Norite. On cooling, colorless needles were formed and after crystallization from cyclohexane (0.6 g 23%) triphenylphosphine oxide, m.p. 156-158° was obtained (lit. m.p. 156°) (51).

- (b) In three trial experiments the reaction was repeated as above, except that the phosphine was replaced by equimolar quantities of triphenylarsine, triphenylstibine and triphenylbismuthine (Eastman Kodak). In the last two cases decomposition products from the organometallic compound were present in the distillates. The results of these experiments are indicated in Table I.

II. Pyrolysis of 5,5-dimethyl-1-pyrroline-1-oxide.

5,5-^Ddimethyl-1-pyrroline-1-oxide was prepared by the procedure of Todd et al (2).

A sample of 5,5-dimethyl-1-pyrroline-1-oxide was heated in a closed flask in an oil bath at 100° and the infrared spectrum of the mixture was taken at intervals. During the course of 3 hours a peak at about 1660 cm⁻¹, very weak initially, increased slightly in intensity. After a further hour at 180° the sample became very dark. The peak at 1660 cm⁻¹ had become very sharp and strong

whilst the initial peak of the nitron at 1575 cm^{-1} ($\text{>C} = \overset{\oplus}{\text{N}} - \overset{\ominus}{\text{O}}$) was now absent. Thermal pyrolysis is therefore slow at 100° but measurable at 180° . The pyrolysis product was not identified.

III. Preparation of 5,5-dimethyl-1-pyrroline (IV) from the corresponding nitron III.

5,5-^Ddimethyl-1-pyrroline-1-oxide (III) (1 g) (0.0088 mole) was treated with triphenylphosphine (2.62 g) (0.01 mole) as above, and the volatile liquid boiling up to 104° was collected as crude 5,5-dimethyl-1-pyrroline (IV) (0.55 g 65%), the infrared spectrum of which showed a sharp peak at 1618 cm^{-1} ($\text{C} = \text{N}$). That nitron band was present was shown by the lack of a band at 1575 cm^{-1} ($\text{>C} = \overset{\oplus}{\text{N}} - \overset{\ominus}{\text{O}}$). The yield was not improved by using a Wood's metal bath at 300° in place of a free flame. After purification by vapor phase chromatography the product had the same infrared spectrum as a similarly purified sample of the authentic base prepared according to the procedure of Todd et al (2).

The pyrroline IV (0.37 g) was treated with a saturated solution of picric acid in moist ether to give the picrate (1.13 g 37%) which was identical with an authentic sample. The residue (2.5 g) was dissolved in a very small quantity of methanol (5 ml) and this solution was poured onto a column of dry alumina. Elution with petrol-ether ($65-110^\circ$) gave colorless needles, which were crystallized from cyclo-

hexane to give 1.52 g (57%) of triphenylphosphine oxide, m.p. 156-158°.

IV. Preparation of 3-methyl-1-nitro-2-butanol.

To a mixture of 100 g (1.63 mole) of nitromethane, 11.4 g (0.082 mole) of potassium carbonate and 70 ml of water, there was added dropwise, with stirring at a temperature kept below 50° (the reaction is slightly exothermic - no heating is needed) 76 g (1.05 mole) of isobutyraldehyde. As the reaction proceeded the mixture became red-orange. After the addition the reaction mixture was stirred at room temperature for a further 2 hours. Then it was cooled in an ice bath and brought to a pH of 3 by adding dilute hydrochloric acid. The resulting mixture was extracted with ether, washed with water, aqueous sodium bicarbonate and again with water. The ethereal extract was dried over magnesium sulfate, then concentrated and distilled under reduced pressure to give 105 g (80%) of the nitro alcohol (b.p.₂ 72-74°, n_D^{25} 1.4462) (lit. (52) b.p.₂ 72-74°). The product showed infrared bands at 3472 cm⁻¹ (OH), 1560 cm⁻¹ (asymmetric NO₂) and 1387 cm⁻¹ (symmetric NO₂).

V. Preparation of 2-acetoxy-3-methyl-1-nitrobutane.

To a solution of 100 g (0.75 mole) of the nitro-alcohol in 65 ml of chloroform there was added dropwise

with stirring at room temperature 59 g (0.75 mole) of acetyl chloride dissolved in 60 ml of chloroform. After the addition was completed, the reaction mixture was refluxed for 2 hours and then allowed to stand overnight. The solvent was distilled off and the oil thus obtained was distilled under reduced pressure to give 120 g (91%) of product (b.p._{0.5} 78-80°, n_D^{25} 1.4345) (lit. (52) b.p._{2.5} 82-85°, n_D^{25} 1.4345). The infrared spectrum showed bands at 1754 cm^{-1} (C = O), 1563 cm^{-1} (asymmetric NO_2), 1381 cm^{-1} (symmetric NO_2) and 1238 cm^{-1} (C - O acetate group).

VI. Preparation of 3-methyl-1-nitrobutene-2.

The olefin was prepared by a procedure similar to that reported by Drake and Ross (53).

A mixture of 110 g (0.628 mole) of the nitro acetate, 69 g (0.728 mole) of anhydrous sodium carbonate and 800 ml of benzene were stirred vigorously under reflux until no more water was collected in a water-trap connected to the refluxing flask. After 6 hours the reaction was completed. The excess of sodium carbonate and the sodium acetate were filtered off and washed with benzene. The solvent was distilled off and the oil distilled under reduced pressure to give 50 g (72.3%) of olefin (b.p.₁₃ 66-67°) (lit. (52) b.p.₁₃ 66-67°). The infrared spectrum showed bands at 1650 cm^{-1} (C = C), 1538 cm^{-1} (NO_2) and 1357 cm^{-1} (NO_2).

VII. Preparation of Ethyl 2-acetyl-2-ethyl-4-methyl-3-nitromethyl valerate (V).

1-Ethylacetoacetic acid ethyl ester was prepared by a similar procedure to that reported by Robinson (54).

To a solution of 76 g (0.481 mole) of 1-ethylacetoacetic acid ethyl ester in 140 ml anhydrous ether and 40 ml 2% NaOEt-EtOH there was added 36.5 g (0.385 mole) of 3-methyl-1-nitrobutene-2 in 40 ml anhydrous ether dropwise with stirring at room temperature. After the addition was completed the solution was stirred for a further 3 hours and then allowed to stand at room temperature for 24 hours. Then the solution was neutralized with acetic acid, diluted with water and extracted with ether. The ether extract was washed with 8% sodium bicarbonate, with water and then dried over magnesium sulfate. After evaporation of the solvent, the oil was distilled under reduced pressure to give 36 g (41.6%) of product b.p.₁ 135° (lit. (52) b.p.₁ 135°).

VIII. Preparation of Ethyl 4-ethyl-3-isopropyl-5-methyl-1-pyrroline-1-oxide-4-carboxylate. (XVI)

To a mixture of 10 g (0.036 mole) of ethyl 2-acetyl-2-ethyl-4-methyl-3-nitromethyl valerate, 2 g (0.373 mole) of ammonium chloride in 60 ml tetrahydrofuran and 20 ml of water, there was added portionwise 13.4 g of zinc dust with vigorous stirring while the temperature was kept between 25-30°. After the addition was completed the reaction

mixture was stirred for a further 3 hours. The solid was then filtered off and washed with 60 ml of hot methanol. The filtrate was concentrated and then distributed between 50 ml of 5N hydrochloric acid and 50 ml of ether. The ether layer was discarded and the aqueous layer was made alkaline by the addition of potassium hydroxide. The basic product was extracted several times from the aqueous solution with dichloromethane and the dichloromethane solution was dried over magnesium sulphate. The solvent was distilled off and the residual oil was distilled at reduced pressure through a Vigreux column to give 5.5 g (63.7%) of a very viscous yellow-green liquid b.p.₃ 180-182°. The product showed ultraviolet absorption (determined in 95% ethanol solution) at λ_{max} 237.5 ($\epsilon = 7935$) ($\text{>C} = \overset{\oplus}{\text{N}} - \overset{\ominus}{\text{O}}$ chromophore) and the infrared spectrum of the pure liquid (film) showed a band at 1608 cm^{-1} ($\text{>C} = \overset{\oplus}{\text{N}} - \overset{\ominus}{\text{O}}$). The N.M.R. spectrum determined in CCl_4 showed a quartet centred at 5.86 τ (CH_2 in $\text{COOCH}_2\text{CH}_3$) an unresolved broad band in the region 8 to 8.35 τ (corresponding to 5 H), a triplet centred at 8.75 τ (CH_3 in $\text{COOCH}_2\text{CH}_3$) and two singlets at 9.05 and 9.15 τ , and no peaks attributable to olefinic hydrogen atoms.

The picrate was made from a saturated solution of picric acid in ethanol and after crystallization from ethanol it had m.p. 106-107° (lit. (52) m.p. 102°).

IX. Preparation of Ethyl 4-ethyl-3-isopropyl-5-methyl-1-pyrroline-4-carboxylate. (XIV)

To a mixture of 17 g (0.062 mole) of ethyl 2-acetyl-2-ethyl-4-methyl-3-nitromethyl valerate in 90 ml of acetic acid there was added portion-wise 23.35 g zinc dust with vigorous stirring while the temperature was kept at 85-90°. After the addition was completed the reaction mixture was stirred for a further 2 hours on a steam bath. Then it was poured into 400 ml of cool water and neutralized with sodium hydroxide and extracted several times with ether. The ether extract was concentrated and distributed between 50 ml 1 N hydrochloric acid and 50 ml of ether. The ether layer was discarded while the aqueous layer was made alkaline and then extracted with ether. The ether extract was dried over magnesium sulfate and then concentrated to a residual oil which was distilled under reduced pressure. Two fractions were collected; the first one (6 g) boiling at 100-107°/3 mm and the second one (2 g) at 178-183°/3 mm. The infrared spectrum of the first crude fraction exhibits a strong band at 1647 cm⁻¹ (C = N) together with a small although sharp band at 1608 cm⁻¹ ($\text{C} = \overset{\oplus}{\text{N}} - \overset{\ominus}{\text{O}}$). The infrared spectrum of the second fraction showed a strong band at 1608 cm⁻¹. Thus the first fraction was mainly pyrroline and the second fraction was the 1-oxide prepared above. The ultraviolet spectrum of the second fraction (determined in 95% ethanol solution) showed a maxima at 237.5 mμ

($\epsilon = 7935$) ($>C = \overset{\oplus}{N} - \overset{\ominus}{O}$). The picrate, m.p. 106-107°, of this last fraction was made as before and there was no depression for a mixture melting point with the picrate of ethyl 4-ethyl-3-isopropyl-5-methyl-1-pyrroline-1-oxide-4-carboxylate. The N.M.R. of the 1-oxide fraction (determined in CCl_4) showed no absorption attributable to olefinic hydrogen.

The first fraction was redistilled three times, but it was not possible to eliminate the 1-oxide impurity. At this stage, a gas chromatogram through a 5-ft Uconpolar column at 175° with a helium flow rate of 67 cc./min. gave two peaks at 15, 16.3 min. in ratio 55 to 45%, determined by the weight of paper cuts of the peaks (the 1-oxide was not eluted at this temperature). Separation gave each with a purity of 95 and 91% respectively. The infrared spectra (films) of these two components showed absorption bands at 1733 cm^{-1} ($C = O$) and at 1647 cm^{-1} ($C = N$) common to both of them but it revealed also significant differences in the finger print region: thus, the first component had absorption bands at 1309, 1142 and 971 cm^{-1} which were not present in the spectrum of the second base. The 1-oxide band at 1608 cm^{-1} was now absent. It is thus apparant that the two components are isomeric pyrrolines. The N.M.R. spectrum determined in CCl_4 showed for the first component a quartet centred at 5.85 τ (CH_2 in $-COOCH_2CH_3$), an unresolved broad band between 7.8 and 8.5 τ (corresponding

to 5 H), a triplet at 8.75 τ (CH_3 in $\text{COOCH}_2\text{CH}_3$) and two singlets at 9.05 τ and 9.15 τ . The N.M.R. for the second component showed a quartet centred at 5.85 τ (CH_2 in $\text{COOCH}_2\text{CH}_3$) an unresolved broad band at 7.8 and 8.5 τ (corresponding to 5 H), a triplet at 8.75 τ (CH_3 in $-\text{COOCH}_2\text{CH}_3$) and two singlets at 9.05 τ and 9.15 τ and no absorption attributable to olefinic hydrogen. It was concluded that these two components are cis and trans isomers but ^{the} absolute geometry ^{was} not determined.

The picrate of the first component was prepared from a saturated solution of picric acid in ethanol and was recrystallized three times, m.p. 159-161°. The infrared spectrum of the picrate (Nujol mull) showed bands at 1629 cm^{-1} ($\text{C} = \text{N}$), 1695 cm^{-1} ($\text{>C} = \overset{\oplus}{\underset{|}{\text{N}}} - \text{H}$) and at 1745 cm^{-1} ($\text{C} = \text{O}$).

Anal.-Calcd. $\text{C}_{19}\text{H}_{26}\text{N}_4\text{O}_3$: C, 50.21; H, 5.77; N, 12.33.

Found: C, 50.32; H, 5.84; N, 12.42.

The picrate of the second fraction was prepared in a similar manner, m.p. 150-151°. The infrared spectrum (Nujol mull) was similar with that of the first component. The mixed melting point ^{of the isomeric picrates} was 148-149° (lit. (1) m.p. 144°).
Anal. - Found: C, 50.20; H, 5.84; N, 12.40.

X. Oxygen transfer reaction to triphenylphosphine.

Ethyl-3-isopropyl-4-ethyl-5-methyl-1-pyrroline-1-oxide-4-carboxylate (1 g) (0.00415 mole) and triphenylphosphine (1.3 g) (0.00475 mole) were heated (free flame)

in a distillation apparatus. The mixture became dark after 10 minutes. It was refluxed for 15 minutes and then distilled, to give 0.466 g b.p. 84-180°, of product. Six components were identified by vapor chromatography of this product using a 5-ft Uconpolar column at 170°. The percentage of the total products was determined by the weights of paper cuts of the peaks. The residue (1.4 g) from the triphenylphosphine reaction was dissolved in cyclohexane, heated with Norite and gave, on cooling, 0.58 g (42.34%) of triphenylphosphine oxide m.p. 156-158° (lit. (51) m.p. 156°).

XI. Analysis of the volatile components.

Isolation of the first component (19.6% of the total) gave a compound which was shown by chromatography to have a purity of 97%. The infrared spectrum showed a strong peak at 1647 cm^{-1} ($\text{C} = \text{N}$) and no absorption in the carbonyl region. The N.M.R. spectrum (determined in CCl_4) did not have a signal in the olefinic proton region and the quartet and the triplet of the CH_2 and CH_3 of the carboethoxy group were not present. It is apparent that ester pyrolysis and decarboxylation has occurred. The picrate was made in the usual manner, m.p. 128-129°. The infrared spectrum of the picrate (Nujol mull) showed bands at 1634 cm^{-1} ($\text{C} = \text{N}$) and 1684 cm^{-1} ($\text{>C} = \overset{\oplus}{\underset{|}{\text{N}}} - \text{H}$).
 Anal.-Calcd. $\text{C}_{16}\text{H}_{22}\text{N}_4\text{O}_7$: C, 50.24; H, 5.80; N, 14.65.
 Found: C, 50.24; H, 5.75; N, 14.60.

The chromatogram gave the second, third and fourth components in the following percentage ratio: 10.5-10.5-17.9. These three components could not be isolated in sufficient purity for identification. The last two components obtained in the following percentage ratio: 23.27 and 18.16 were identified by means of their infrared spectra, N.M.R. spectra and picrates, and found to be identical with the two isomeric pyrrolines isolated from the zinc dust and acetic acid reduction of ethyl 2-acetyl-2-ethyl-4-methyl-3-nitromethyl valerate. The picrates (m.p. 159-161° and 150-151° respectively) showed no depression in m.p. when mixed with the two corresponding pyrrolines prepared by synthesis.

BIBLIOGRAPHY

1. Y. Sanno, Yakugaku Zasshi 78, 1113 (1958); Chem. Abstr., 53, 5238 (1959)
2. R. Bonnett, R.F. C. Brown, V.M. Clark, I.O. Sutherland and A. Todd, J. Chem. Soc., 2094 (1959).
3. L. J. Smith, Chem. Rev., 23, 193 (1938).
4. L. Horner and H. Hoffmann, Angew. Chem., 68, 473 (1956).
5. P. C. Crofts, Quart. Rev., 12, 341 (1958).
6. A. E. Arbusov, J. Russ. Phys. Chem. Soc., 38, 697 (1906).
7. A. Michealis and Th. Becker, Ber., 30, 1003 (1897).
8. G. M. Kosolapoff - "Organophosphorus Compounds" John Wiley and Sons, Inc., New York, 1950, p.96.
9. L. Horner and K. Klüpfel, Ann., 591, 69 (1955).
10. E. Min and N. Kanay, Doklady Akad. Nauk, U.S.S.R. 73 709 (1930).
11. W. R. Cullen and R. Hochstrasser, J. Mol. Spectroscopy, 5, 1189 (1960).
12. P. D. Bartlett, E. F. Cox and R.E. Davis, J. Am. Chem. Soc., 83, 103 (1961).
13. F. Challenger and V. K. Wilson, J. Chem. Soc., 213 (1927).
14. A. Schonberg, Ber., 68, 163 (1935).
15. L. Horner and W. Jurgeleit, Ann., 591, 138 (1955).
16. C. Walling, O.H. Basedow and E.S. Savas, J. Am. Chem. Soc., 82, 2181 (1960).
17. M. A. Greenbaum, D.B. Denney, and A.K. Hoffmann, J. Am. Chem. Soc., 78, 2563 (1956).
18. E. Howard and W. F. Olszewsky, J. Am. Chem. Soc., 81, 1483 (1959).
19. H. Schaefer, Diplomarbeit-Mainz, 1955.
20. K. Klupfel - Dissertation Mainz, 1954.

21. S. A. Buckler, L. Doll, F.K. Lind and M. Epstein, J. Org. Chem., 27, 794 (1962).
22. L. Horner and E. Jurgens, Ber., 90, 2184 (1957).
23. A. J. Speziale and R. C. Freeman, J. Am. Chem. Soc., 82, 903 (1960).
24. P.T. Keough and M. Grayson, J. Org. Chem. 27, 1817 (1962).
25. W.C. Davies and W.P. Lewis, J. Chem. Soc., 1599 (1934).
26. A. C. Cope and N.A. LeBel, J. Am. Chem. Soc., 82, 4656 (1960)
27. H. Fisher and H. Orth, "Die Chemie des Pyrroles", Vol. I, Leipzig, 1934, p.319.
28. G. G. Evans, J. Am. Chem. Soc., 73, 5230 (1951).
29. A. Sonn, Ber., 68, 148 (1935); 72, 2150 (1939).
30. S. Gabriel, Ber., 42, 1238 (1909).
31. R. Hichshen, Ber., 31, 277 (1898).
32. H. Rupe and F. Gisiger, Helv. Chem. Acta., 8, 338 (1925).
33. E.B. Knott, J. Chem. Soc., 186 (1948).
34. J.B. Cloke, J. Am. Chem. Soc., 51, 1174 (1929).
35. P. Lipp and H. Seeles, Ber., 62, 2456 (1929).
36. L. C. Craig, H. Bulbrook and R.M. Hixoil, J. Am. Chem. Soc., 54, 3971 (1932).
37. J. B. Cloke and T.S. Learly, J. Am. Chem. Soc., 67, 1249 (1945).
38. J. B. Cloke, E. Stehr, T.R. Steadman and L. C. Westcott, J. Am. Chem. Soc., 67, 1587 (1945).
39. B. Witkop, J. Am. Chem. Soc., 76, 5597 (1954).
40. G. G. Evans, J. Am. Chem. Soc. 73, 5230 (1951).
41. J. H. Burckhalter and J. H. Short, J. Org. Chem. 23, 1278 (1958).
42. R. Bonnett, V.M. Clark, A. Giddey and A. Todd, J. Chem. Soc., 2087 (1959).

43. M. C. Kloetzel, J.L. Pinkus and R.M. Washburn, J. Am. Chem. Soc., 79, 4222 (1957).
44. P. M. Maginnity and J.B. Cloke, J. Am. Chem. Soc., 73, 49 (1951).
45. P. M. Maginnity and T. J. Gair, J. Am. Chem. Soc., 74, 4958 (1952).
46. P.J.A. Demoen and P.A.J. Jannsen, J. Am. Chem. Soc., 81, 6281 (1959).
47. W. Davey and D.J. Tivey, J. Chem. Soc., 2276 (1958).
48. R. Bonnett and D.E. McGreer, Can. J. Chem., 40, 177 (1962).
49. R.F.C. Brown, V.M. Clark and A. Todd, Proc. Chem. Soc., 1957, 97.
50. R. Bonnett et al, Unpublished results.
51. Handbook of Chemistry and Physics, 40th Ed. (1958-59), Chemical Rubber Publishing Co., Cleveland.
52. Y. Sanno, A. Kurita and K. Imai, J. Pharm. Soc., Japan, 75, 1461 (1955).
53. N.L. Drake and A.B. Ross, J. Org. Chem. 23, 717 (1958).
54. R. Robinson, J. Chem. Soc. 1044 (1916).