899. *Nitrones. Part I. Cycloaddition of Unsymmetrical Olefins to the* 1-*Pyrroline* 1-*Oxides.*

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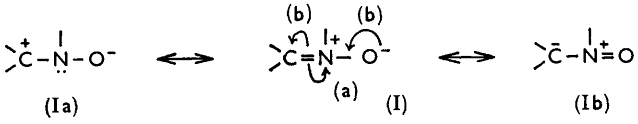
Nitrones of the 1-pyrroline 1-oxide type undergo 1,3-cycloaddition with ethyl acrylate, acrylonitrile, and allyl alcohol. By using 5,5-dimethylpyrroline 1-oxide and ethyl acrylate, it was shown that the orientation of addition was temperature-dependent, and the structures of the adducts formed at room temperature and at 100° have been determined. The results obtained can be accounted for in terms of the two possible modes of polarisation of the nitrone system. The structure of the allyl alcohol adduct has also been determined. Syntheses of 2-(5,5-dimethylpyrrolidin-2-yl)propane-1,3-diol and 3-(5,5-dimethylpyrrolidin-2-yl)propane-1,2-diol are described.

THE reaction of nitrones with olefins to form isoxazolidines is well established.[1,2] It is also known that the nitrone system (I) generally undergoes nucleophilic additions at the carbon atom [3] and it thus must polarise as indicated in (a) to form the structure (Ia).



(Ia) (I) (Ib)

Experimental evidence, however, indicates that under certain conditions back-polarisation, (b), to produce the structure (Ib) must take place.[4]

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[1] Le Bel and Whang, *J. Amer. Chem. Soc.*, 1959, **81**, 6334; Brown, Marsden, Rogers, Tylor, and Wright, *Proc. Chem. Soc.*, 1960, 254.

[2] Grashey, Huisgen, and Leitermann, *Tetrahedron Letters*, 1960, No. 12, 9.

[3] Bonnett, Brown, Clark, Sutherland, and Todd, *J.*, 1959, 2094.

[4] Brown, Clark, Lamchen, and Todd, *J.*, 1959, 2116.

Since the nitrone system is thus polarisable in two directions, two isomeric isoxazolidines are possible on reaction with unsymmetrical olefins, the product being determined by the polarisability and direction of polarisation of the olefinic bond as well as by the effect this can have on the polarisation of the nitrone under the prevailing conditions. With the exception of the two adducts formed when diphenylnitrone reacts with styrene and with allyl alcohol,[2] the position of substituents on the isoxazolidine ring has, however, not been established.

As reported by us,[5] nitrones of the 1-pyrroline 1-oxide type underwent addition with αβ-unsaturated esters. The known reactivity of hydrogen atoms at positions 2 and 3 of the nitrone [4,5] presented the possibility of a Michael-type addition. Since similar adducts were obtained when ethyl acrylate reacted with 3,3,5,5-tetramethyl- (II) and 5,5-dimethyl-1-pyrroline 1-oxide (III), reaction at position 3 is ruled out. The absence of the characteristic nitrone absorption in the infrared spectrum of these adducts indicated that the nitrone system was involved in the addition. While these results ruled out a Michael-type addition, they proved, in conjunction with published work [1,2] that 1,3-cycloaddition took place between the nitrones and ethyl acrylate. The isoxazolidines so formed from this unsymmetrical olefinic compound could be either of the two isomers or a mixture of the two.

A study of the direction of addition was carried out with 5,5-dimethyl-1-pyrroline 1-oxide (III). When the nitrone (III) and ethyl acrylate were mixed at room temperature, an exothermic reaction gave a quantitative yield of the pyrrolidinoisoxazolidine (IVa) (the position of the ethoxycarbonyl group is proved below). Reduction of this adduct with lithium aluminium hydride in boiling tetrahydrofuran for 4 hours gave a hydroxymethylisoxazolidine (IVb) which on longer treatment with the same reagent yielded an amino-glycol, to which, on the basis of the synthetic work described below, we assign the structure (V). It was hoped to prepare the amino-glycol (V) by treating the nitrone (III) with the Grignard reagent from 4-iodomethyl-2,2-dimethyl-1,3-dioxolan (VI) and reducing and hydrolysing the expected hydroxylamino-ketal. However, despite the use of activated magnesium and forcing conditions with tetrahydrofuran or the halide-entrainment method,[6] this Grignard reagent could not be prepared.

Allylmagnesium bromide reacted with the nitrone (III) to form 2-allyl-1-hydroxy-5,5-dimethylpyrrolidine (VII) which was almost certainly in the racemic form. This pyrrolidine was treated with performic acid to give, presumably, the formyloxy-hydroxy-derivative,[7] which was not isolated but was hydrolysed with sodium hydroxide and reduced with zinc and hydrochloric acid to the amino-glycol (V). The identity of this product and the amino-glycol obtained from the isoxazolidine (IVa) was established by comparison of picrates and picrolonates. The isoxazolidine (IVa) and the hydroxymethylisoxazolidine (IVb) thus have groups R at position 2.

When, however, the nitrone (III) and ethyl acrylate were heated together at 100° for 4 days, a different 1 : 1 nitrone-ester adduct, was obtained, again in quantitative yield. This also had no nitrone group (infrared spectrum) and its properties were similar to those of the isoxazolidine (IV): on reduction with lithium aluminium hydride it also gave an amino-glycol, but different from the amino-glycol (V). The adduct and amino-glycol can thus be expected to have the structures (VIII) and (IX).

Various syntheses of compound (IX) were attempted. (*a*) Hydrolysis and reduction of the product from the nitrone (III) and the Grignard reagent of 1,3-dibenzyloxy-2-chloropropane should yield this glycol, but this Grignard reagent was not formed. (*b*) In many reactions nitrones behave like carbonyl compounds. Base-catalysed addition of the Knoevenagel type between the nitrone (III) and diethyl malonate was thus expected, especially since it was shown that this nitrone condensed, under basic conditions, with

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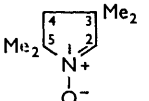
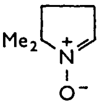
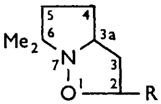
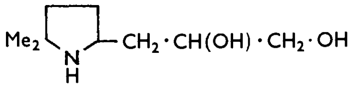
[5] Delpierre and Lamchen, *Proc. Chem. Soc.*, 1960, 386.
[6] Pearson, Cowan, and Beckler, *J. Org. Chem.*, 1959, **24**, 504.
[7] Koenigs, *Ber.*, 1898, **31**, 2364; 1899, **32**, 223.

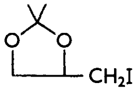
nitroalkanes.[3] However, the expected product (X) was not obtained, but, instead, an oily mixture of at least two substances having complex infrared absorption in the region 1590—1800 cm.$^{-1}$. The mixture reduced 2,3,5-triphenyltetrazolium chloride, and thus probably contained a compound with a hydroxyamino-group, but, from analytical data, this could not be the major component. (*c*) Hydroxymethylation of the methyl group of 2-picoline [8] and 2- and 4-methylquinoline [7] gave both mono- and bis-hydroxymethyl derivatives. This suggested the method by which the amino-glycol (IX) was eventually prepared. The nitro-ketone (XI) was reduced to the nitrone (XII), which was heated with paraformaldehyde. The resulting gum on reduction, first with lithium aluminium hydride and then with zinc and hydrochloric acid, gave the amino-glycol (IX), the picrate of which was identical with that of the amino-glycol obtained by reduction of the adduct (VIII). Establishment of the structure of the amino-glycol (IX) also confirmed the structure of the isoxazolidine as (VIII).

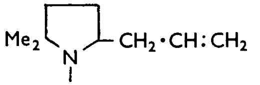

(II)

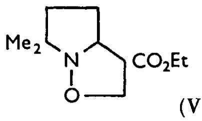

(III)

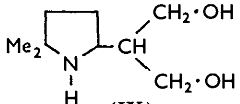

(IVa: R = CO_2Et)
(IVb: R = $CH_2\cdot OH$)

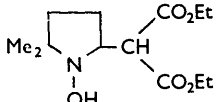

(V)

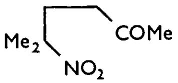

(VI)

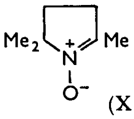

(VII)

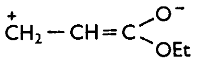

(VIII)


(IX)


(X)


(XI)


(XII)


(XIII)
$$\overset{+}{C}H_2-CH=C\begin{matrix}O^-\\OEt\end{matrix}$$

The amino-glycols (V) and (IX) have different R_F values on Whatman No. 1 paper with a butanol–ammonia eluant. Reduction of the adducts with lithium aluminium hydride, and paper chromatography of the amino-glycols so obtained, afforded a method whereby small amounts of the adducts could be characterised. In this manner it was shown that the adduct obtained at room temperature was the pure isoxazolidine (IVa), whilst the product after four days' heating at 100° was the pure isoxazolidine (VIII). Heating for only 24 hours gave a mixture of the two.

Since the isoxazolidine (IVa) was formed immediately at room temperature and in quantitative yield and also decomposed into the nitrone and ethyl acrylate when heated, the isoxazolidine (VIII) must have been formed from (IVa) by isomerisation (decomposition and recombination). When the pure compound (IVa) was heated overnight with an excess of ethyl acrylate, it was partly converted into its isomer. Ethyl acrylate can be expected to be polarised in one direction only, to give the polar structure (XIII); to form the isoxazolidine (IVa) the nitrone (III), in the cold, must have reacted as a carbanion (type Ib). The carbanion thus seems to be more reactive than the carbonium ion (type Ia) but this polarisation of the nitrone takes place only in the presence of highly polar compounds with a reactive C$^+$-centre, since compounds without such a strongly positive centre, *e.g.*, allyl alcohol, did not react with the nitrone in the cold. The reaction can thus be expected to occur *via* the dipolar intermediate (XIV) as shown below.

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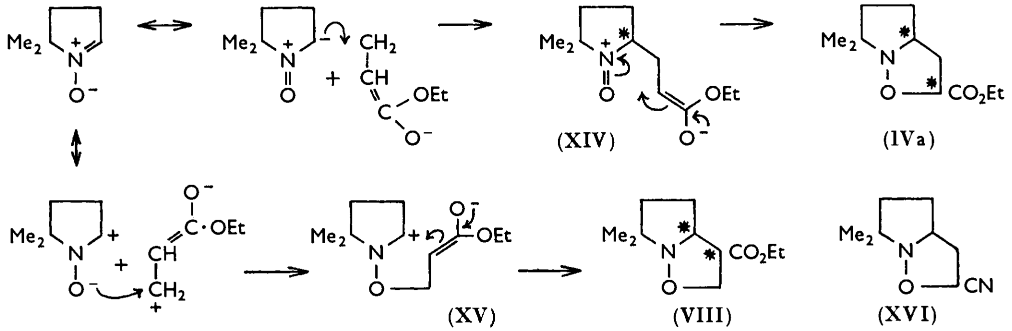
[8] Lipp and Richard, *Ber.*, 1904, **37**, 737.

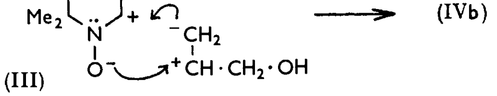
On the other hand, at 100°, the exothermic nature and reversibility of the above reaction would be expected to favour the decomposition of the adduct (IVa), and the heat could supply sufficient energy to allow the endothermic reaction between the nitrone in the form of a carbonium ion (type Ia) and ethyl acrylate. Such a reaction would produce the dipolar intermediate (XV), which would cyclise to form the thermally more stable isoxazolidine (VIII). The results obtained thus indicated that cycloaddition of nitrones with certain olefins may be subject to kinetic and thermodynamic control.



Acrylonitrile also reacted exothermally with the nitrone (III) at room temperature, to give a quantitative yield of a solid adduct. The orientation of this product has not been determined, but, since acrylonitrile could act in the dipolar form $^{+}CH_2{\cdot}CH{=}C{=}N^{-}$, on the above argument, the reacting species of the nitrone can be expected to be of the type (Ib) and the product can thus be expected to have structure (XVI).

With olefinic compounds having no strongly electron-attracting group that polarises the olefinic bond to create a highly polar C^{+}-centre, reaction does not proceed at room temperature and heat is required for formation of the adduct. In these cases where heat must be applied, sufficient energy could be available for the nitrone to react as the carbonium ion (type Ia), and the adduct will be determined by the direction of polarisation of the addend. Thus, allyl alcohol, which is considered to be polarised in such a manner as to be attacked by electrophiles on the terminal carbon atom,[9] would not be as highly polarised as the αβ-olefinic esters and would be expected to react only at high temperatures. This is found to be so, and the hydroxymethylisoxazolidine obtained at 100° proved to be identical with (IVb), indicating that the reactive form was of the type (Ia). The two reacting dipolar forms at 100° could react simultaneously at both positions, as this would produce a stable product.

The infrared absorption spectra for the adduct (IVa) (liquid film) exhibits a split carbonyl absorption peak (1740 and 1757 cm.$^{-1}$). Three possible causes could be invoked: (1) the ethoxycarbonylisoxazolidine could be a mixture of two racemates in which the steric environment of the carbonyl group could be different [10] (in the one pair inside and in the other pair outside the fold of the two fused five-membered rings); the mechanism



suggested above would be expected to give stereoisomers when the intermediate (XIV) cyclises; (2) Fermi resonance; [11] and (3) conformational isomerism of the ester-carbonyl

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[9] Winstein and Goodman, *J. Amer. Chem. Soc.*, 1954, **76**, 4368.

[10] Brooks, Eglinton, and Morman, *J.*, 1961, 106.

[11] Allen, Ellington, and Meakins, *J.*, 1960, 1909; Jones, Angell, Ito, and Smith, *Canad. J. Chem.*, 1959, **37**, 2007.

group with respect to the ring C–O bond.[12] Of these three, the last is preferred because solution spectra showed that the intensity of absorption is related to the polarity of the solvent, the band of high frequency gaining in intensity with respect to that of lower frequency in polar solvents, but losing intensity in non-polar solvents. This would rule out the first cause suggested, since the relative intensities of the two peaks should remain constant in all solvents. In a case of Fermi resonance, solvent effects are the reverse of that found here,[11] but the same effect has been observed in the case of split carbonyl absorption due to conformational isomerism.[10,13]

The adduct (VIII) (liquid film) gave an infrared spectrum with a single carbonyl absorption peak at 1742 cm.$^{-1}$, as is to be expected from its structure which lacks an electronegative atom on the carbon atom bearing the carbonyl group. In this case, conformational effects must be of negligible importance.

Nuclear magnetic resonance spectra of the adducts (IVa) and (VIII), apart from further confirming their non-identity, were of no material value in structural assignment, as the spectra were considerably involved owing to spin–spin coupling of the ring protons. Peaks due to protons of the *gem*-dimethyl groups and ester ethyl groups were, however, clearly recognisable.

There is some evidence that the adduct (IVa) is a mixture of stereoisomers, as the picrate of the amino-glycol (V) obtained from the adduct (IVa), although giving correct analyses, had m. p. 116—119°, which can be raised by repeated crystallisations to 123—125° without change in composition and is not depressed on admixture with the picrate of the same amino-glycol obtained from the allyl alcohol adduct, m. p. 125—126°. Since the formation of the adduct (IVb), as suggested, confers asymmetry on carbon atoms 2 and 3a simultaneously, it can be expected that one racemate will be formed more readily than the other (allyl alcohol is known to react stereospecifically with cyclopentadiene [14]) and the higher m. p. of the amino-glycol picrate obtained from the allyl alcohol adduct is thus also to be expected. The formation of the adduct (VIII) by ring-closure of the intermediate (XV) would confer asymmetry on carbon atoms 3 and 3a simultaneously, and this reaction may, as models also suggest, again be stereospecific.

Cycloaddition products were also obtained from 2,4,4-trimethyl-1-pyrroline 1-oxide and ethyl acrylate, as well as from the nitrone (III) and acraldehyde diethyl acetal. In neither of these two cases were studies carried out on the orientation of addition. In the former case, however, it was shown that the adduct decomposed when heated and this, in conjunction with the short time of heating, suggests that a fair amount of the adduct was the isomer with the 2-ethoxycarbonyl group.

EXPERIMENTAL

Nuclear magnetic resonance spectra were obtained at 40 Mc./sec. by using a Varian Associates V4300B spectrometer and 12 in. electromagnet with flux stabilisation and sample spinning. Positions of reference are as chemical shifts on the τ scale ($SiMe_4$ = 10·00), and have been measured against tetramethylsilane as an internal reference, with side-bands generated by a Muirhead–Wigan D695 decade oscillator.

Reaction of the Nitrones with Ethyl Acrylate.—(*a*) 3,3,5,5-*Tetramethyl*-1-*pyrroline* 1-*oxide* (II). This oxide (2·68 g.) and ethyl acrylate (20 ml.) were heated on a steam-bath for 26 hr. Unchanged ester was removed under reduced pressure, and the residual oil shaken with water (10 ml.). Light petroleum (b. p. 30—50°; 10 ml.) was added, the mixture shaken, and the aqueous layer discarded. The petroleum layer was washed with water (4 × 10 ml.), dried (Na_2SO_4), and evaporated. Distillation of the residue in a short-path still at 100—110°/0·2—0·3 mm. gave the adduct (2·89 g.), $\nu_{max.}$ 1745 cm.$^{-1}$ (Found: C, 64·3; H, 9·6; N, 6·2. Calc. for $C_{13}H_{23}NO_3$: C, 64·7; H, 9·6; N, 5·8%), probably a mixture of two isoxazolidine esters. A

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[12] Brown, *Spectrochim. Acta*, 1962, **18**, 1615.

[13] Bellamy and Williams, *J.*, 1957, 4294; 1958, 3465.

[14] Alder and Windemuth, *Ber.*, 1938, **71**, 1939.

picrolonate was formed in ethanol–light petroleum (b. p. 100—120°) and, recrystallised from butanol, had m. p. 162—163° (decomp.) (Found: C, 54·7; H, 6·2; N, 13·9. $C_{23}H_{31}N_5O_8$ requires C, 54·6; H, 6·2; N, 13·9%).

(*b*) 2,4,4-*Trimethyl*-1-*pyrroline* 1-*oxide*. This oxide [3] (2·0 g.) and ethyl acrylate (10 ml.) were heated on a steam-bath for 24 hr. and worked up as described under (*a*), to yield the adduct (2·19 g.) (Found: C, 63·4; H, 8·95; N, 6·8. Calc. for $C_{12}H_{21}NO_3$: C, 63·4; H, 9·3; N, 6·2%), probably a mixture of two isomers, $\nu_{max.}$ 1745 cm.$^{-1}$. A *picrolonate*, formed and recrystallised as above, had m. p. 134—136° (Found: C, 53·8; H, 6·0; N, 13·7. $C_{22}H_{29}N_5O_8$ requires C, 53·8; H, 6·0; N, 14·3%).

This adduct (5·0 g.) was refluxed under nitrogen at 120—130° (bath)/3 mm. for 1 hr. A carbon dioxide–acetone trap inserted between the pump and the apparatus collected ethyl acrylate, identified by its b. p. and infrared spectrum. The residual oil was dissolved in light petroleum (b. p. 30—50°; 20 ml.) and shaken with water (20 ml.). Evaporation of the water under reduced pressure, followed by addition of ethanolic picric acid gave, after recrystallisation from butanol, 2,4,4-trimethyl-1-pyrroline 1-oxide picrate, m. p. and mixed m. p. 116—117°.

(*c*) 5,5-*Dimethyl*-1-*pyrroline* 1-*oxide* (A). This oxide [3] (2·0 g.) and ethyl acrylate (10 ml.) were mixed and left at room temperature for 24 hr. Removal of the ethyl acrylate below 30° under reduced pressure gave *ethyl hexahydro*-6,6-*dimethylpyrrolo*[1,2-*b*]*isoxazole*-2-*carboxylate* (IVa) (3·8 g., 100%) as a liquid free from the parent nitrone (no infrared absorption at 1575 cm.$^{-1}$) (Found: C, 60·2; H, 8·9; N, 6·2. $C_{11}H_{19}NO_3$ requires C, 61·9; H, 9·0; N, 6·6%). Rapid distillation in a short-path still at 110—120° (bath)/1 mm. did not change the infrared absorption. When the ester was refluxed at 110° (bath)/1 mm. for 1 hr., or when 10 g. or more were distilled at 100° (bath)/below 0·1 mm. in a conventional distillation apparatus, much decomposition to the nitrone occurred.

The nitrone-free oil was appreciably hygroscopic, and partially miscible with water. It had no detectable optical activity. It had n_D^{21} 1·4671, and $\nu_{max.}$ (liquid film) 1730vs and 1754s, (in acetonitrile) 1740s and 1758vs, (in $CHCl_3$) 1736s and 1754vs, (in CCl_4) 1739vs and 1764m, (in dioxan) 1764vs, and (in hexane) 1748vs and 1772m cm.$^{-1}$. Change of concentration did not change the position of absorption or the relative strengths of the two carbonyl peaks. Significant nuclear magnetic resonance peaks were observed with chemical shifts at τ 9·0 (*gem*-dimethyl), triplet at 8·8 (methyl of OEt) quartet at 5·85 (CH_2 of OEt), and complex series of multiplets in range 5·5—8·9. The picrolonate, prepared in ethanol–ether and recrystallised from butanol, had m. p. 140—141°, $\nu_{max.}$ (KCl) (broad) 1760 cm.$^{-1}$ (Found: C, 52·9; H, 5·7; N, 14·7. $C_{21}H_{27}N_5O_8$ requires C, 52·8; H, 5·7; N, 14·7%).

(*d*) 5,5-*Dimethyl*-1-*pyrroline* 1-*oxide* (B). The oxide (10 g.) and ethyl acrylate (60 ml.) were heated for 4 days at 100°. The excess of ethyl acrylate was removed on the water-bath under reduced pressure, and the residual oil dissolved in light petroleum (b. p. 30—50°; 60 ml.). This solution was washed with water (10 ml.), dried ($MgSO_4$), and evaporated, to give the *ethyl hexahydro*-6,6-*dimethylpyrrolo*[1,2-*b*]*isoxazole*-3-*carboxylate* (VIII) (18·5 g., 98%). A sample was distilled in a short-path still at 105—110° (bath)/0·5 mm., to give a colourless oil, n_D^{21} 1·4676, $\nu_{max.}$ 1742 cm.$^{-1}$ (Found: C, 61·4; H, 9·0; N, 6·4. $C_{11}H_{19}NO_3$ requires C, 61·9; H, 9·0; N, 6·6%). Significant nuclear magnetic resonance peaks had chemical shifts at τ 9·0 (*gem*-dimethyl), a triplet at 8·75 (Me of OEt), and a quartet at 5·9 (CH_2 of OEt). Complex series of multiplets in range τ 5·4—8·8. A 30% solution in ethanol showed no detectable optical rotation.

Isomerisation of the Ester (IVa).—The ester (1 g.) was heated in ethyl acrylate (10 ml.) at 100° for 12 hr. The excess of ethyl acrylate was removed *in vacuo*, the residue dissolved in light petroleum ether (b. p. 30—60°; 10 ml.) and shaken with water, and the hydrocarbon layer dried ($MgSO_4$). Evaporation of the solvent gave a 67% recovery of the esters. Reduction with lithium aluminium hydride, followed by paper chromatography as described below, showed that the above material consisted of the esters (IVa) and (VIII), the latter predominating.

Other Cycloadditions of 5,5-*Dimethyl*-1-*pyrroline* 1-*Oxide*.—(*a*) *With allyl alcohol*. The oxide (22 g.) and anhydrous allyl alcohol (100 ml.) were heated at 100° overnight. The excess of alcohol was removed *in vacuo*, and the residual oil diluted with ether (50 ml.). After washing of the ethereal solution with 30% aqueous potassium carbonate (5 × 25 ml.), drying (Na_2SO_4), and evaporation, the residue was distilled at 100—103°/3—4 mm. to give *hexahydro*-2-*hydroxymethyl*-6,6-*dimethylpyrrolo*[1,2-b]*isoxazole* (IVb) (23 g., 84%). This solidified to a highly hygroscopic solid, m. p. 43—44° [from light petroleum (b. p. 40—60°)] (Found: C, 61·4; H, 9·65;

N, 7·9. $C_9H_{17}NO_2$ requires C, 63·1; H, 10·0; N, 8·2%). The *picrate*, prepared in ethanol, recrystallised from butanol as needles, m. p. 150—152° (Found: C, 45·1; H, 5·1; N, 14·7%; Equiv., 399. $C_{15}H_{20}N_4O_9$ requires C, 45·0; H, 5·0; N, 14·0%; Equiv., 400).

(*b*) *With acrylonitrile.* The oxide (2·0 g.) and acrylonitrile (10 ml.) were mixed with cooling and left at room temperature for 24 hr. The excess of nitrile was removed under reduced pressure at room temperature. Upon cooling and trituration, the residual oil solidified (3·3 g., 100%). This adduct, probably 2-*cyanohexahydro*-6,6-*dimethylpyrrolo*[1,2-b]*isoxazoline* (XVI), recrystallised from light petroleum (b. p. 100—120°) as white cubes, m. p. 57—58° (Found: C, 64·6; H, 8·8; N, 16·5. $C_9H_{14}N_2O$ requires C, 65·0; H, 8·5; N, 16·9%). A *picrolonate* was formed in ethanol and, recrystallised from butanol, had m. p. 147° (Found: C, 52·7; H, 5·5. $C_{19}H_{22}N_6O_6$ requires C, 53·0; H, 5·1%).

(*c*) *With acraldehyde diethyl acetal.* 5,5-Dimethyl-1-pyrroline 1-oxide (2·3 g.) and the acetal[15] (5 ml.) were heated on the water-bath for 24 hr. The excess of acetal was rapidly removed under reduced pressure, and water (10 ml.) was added. The insoluble oil was dissolved in light petroleum (b. p. 30—50°; 10 ml.) and washed with water (3 × 10 ml.). After drying ($MgSO_4$), and removal of the solvent, the residual oil was distilled in a short-path still at 100—110° (bath)/0·5 mm., to give the *adduct* (2·8 g.) (Found: C, 64·4; H, 10·3; N, 5·8. $C_{13}H_{25}NO_3$ requires C, 64·2; H, 10·4; N, 5·8%). A *picrate* was formed in ethanol and recrystallised from butanol as needles, m. p. 102—103° (Found: C, 48·9; H, 6·2; N, 12·0. $C_{19}H_{28}N_4O_{10}$ requires C, 48·3; H, 6·0; N, 11·9%).

Reduction of Isoxazolidine Ester (IVa).—The ester (10 g.) in dry tetrahydrofuran (100 ml.) was refluxed for 14 hr. with lithium aluminium hydride (8 g.). The unused hydride was destroyed with methanol, and the whole was evaporated under reduced pressure to a paste. Saturated aqueous sodium potassium tartrate (50 ml.) was added, and the resulting granular solid extracted with boiling chloroform (5 × 25 ml.). The chloroform extract was dried ($MgSO_4$) and evaporated, and the residual viscous oil distilled in a short-path still at 150—180° (bath)/1 mm. to give 3-(5,5-dimethylpyrrolidin-2-yl)propane-1,2-diol (V) (5·7 g., 70%), indefinite m. p. (25—50°). This material is very hygroscopic (Found: C, 60·9; H, 10·9; N, 7·5. Calc. for $C_9H_{19}NO_2$: C, 62·4; H, 11·1; N, 8·1%). When tested by paper chromatography as described below, the diol moved as a single spot of R_F 0·61.

The *picrate* was prepared from benzene and recrystallised from butanol as needles, m. p. 116—119° (Found: C, 45·2; H, 5·7; O, 36·7%; Equiv., 403. $C_{15}H_{22}N_4O_9$ requires C, 44·8; H, 5·5; O, 35·8%; Equiv., 402). The m. p. of this picrate was gradually raised to 123—125° on repeated recrystallisation from butanol.

The *picrolonate* was prepared from ethanol, and recrystallised from butanol as needles, m. p. 160—162° (Found: C, 51·2; H, 6·0; N, 15·6. $C_{19}H_{27}N_5O_7$ requires C, 52·1; H, 6·2; N, 16·0%).

A *tritoluene*-p-*sulphonyl derivative* was prepared in very low yield from toluene-*p*-sulphonyl chloride in pyridine. Recrystallisation from butanol–cyclohexane gave white fluffy needles, m. p. 153—154° (Found: C, 57·1; H, 5·2; S, 14·9. $C_{30}H_{37}NS_3O_8$ requires C, 56·7; H, 5·9; S, 15·1%).

Reduction of the Isoxazolidine Alcohol (IVb).—The alcohol (IVb) (6·4 g.), reduced as above with lithium aluminium hydride (6·5 g.) and worked up as before, gave 4·91 g. (76%) of 3-(5,5-*dimethylpyrrolidin*-2-*yl*)*propane*-1,2-*diol*, b. p. 170—180° (bath)/4 mm., m. p. 64—66° [from light petroleum (b. p. 100—120°)] (Found: C, 61·8; H, 11·0; N, 8·0%). This material was hygroscopic. Paper chromatography (see below) showed the presence of a single basic component, R_F 0·61.

The picrate formed needles, m. p. 125—126°, alone or mixed with picrate described above of m. p. 116—119°, 116—118°, or 123—125° (Found: C, 45·1; H, 5·5; O, 36·2%; Equiv., 402).

Reduction of the Isoxazolidine Ester (VIII).—The ester (10 g.), reduced with lithium aluminium hydride and worked up as above, gave 2-(5,5-*dimethylpyrrolidin*-2-*yl*)*propane*-1,3-*diol* (IX) (5·9 g., 73%), b. p. 150—180° (bath)/0·1 mm., very hygroscopic. Paper chromatography as described below showed the presence of a single basic component, R_F 0·71 (Found: C, 60·5; H, 10·5; N, 7·6. $C_9H_{19}NO_2$ requires C, 62·4; H, 11·1; N, 8·1%). The *picrate* was prepared in benzene and recrystallised from butanol as yellow-orange needles, m. p. 165—166° (Found:

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[15] Van Allan, *Org. Synth.*, 1952, **32**, 5.

C, 45·1; H, 5·6; O, 35·5%; Equiv., 402. $C_{15}H_{22}N_4O_9$ requires C, 44·8; H, 5·5; O, 35·8%; Equiv., 402).

Paper Chromatography of the Amino-glycols (V) *and* (IX).—A small sample of amino-glycols (V) and (IX) were spotted on Whatman No. 1 paper, and the chromatogram was developed with 1 : 1 butanol–3N-aqueous ammonia. After drying, the paper was dipped in a 5% solution of ninhydrin in acetone, and heated at 110° for 5 min. The diol (V) formed a purple spot, R_F 0·61, and the diol (IX) a purple spot, R_F 0·71.

For the detection of the esters in mixtures, they were reduced with an excess of lithium aluminium hydride in tetrahydrofuran under reflux for 14 hr., and the diol or mixture of diols was isolated as described above and examined chromatographically.

Partial Reduction of the Isoxazolidine Ester (IVa).—The ester (1·0 g.), reduced for 4 hr. with lithium aluminium hydride in boiling tetrahydrofuran and worked up as above, gave 0·5 g. of product. Paper chromatography on Whatman No. 1 paper, with butanol–acetic acid–water (77 : 6 : 17), followed by ninhydrin, revealed two components, the slower-moving of which corresponded to the amino-glycol (V). The faster-moving component was obtained by chromatography of 2·4 g. on a cellulose column (Whatman normal grade) with the above solvent as eluant. On distillation at 0·1 mm. (free flame) a viscous oil (1·6 g.) was obtained. Seeding with the alcohol (IVb) caused the oil to solidify to a low-melting basic substance.

A picrate was formed in benzene and recrystallised from butanol as needles, m. p. 154—155°, mixed m. p. with picrate of (IVb) 151—152° (Found: C, 45·4; H, 5·1; N, 13·9%; Equiv., 399. Calc. for $C_{15}H_{20}N_4O_9$: C, 45·0; H, 5·0; N, 14·0%; Equiv., 400).

The above base (1 g.) gave, on further reduction with lithium aluminium hydride and working up in the usual way, 0·4 g. of 3-(5,5-dimethylpyrrolidin-2-yl)propane-1,2-diol, identified as its picrate, m. p. and mixed m. p. 116—119°.

2-*Allyl*-1-*hydroxy*-5,5-*dimethylpyrrolidine* (VII).—5,5-Dimethyl-1-pyrroline 1-oxide (32 g.) in dry ether (50 ml.) was added during 30 min. with stirring to ethereal allylmagnesium bromide (from allyl bromide, 42 g.), and the whole was refluxed with stirring for 2 hr. 5N-Ammonium chloride (100 ml.) was added, and the ether layer separated. The aqueous layer was washed with ether (2 × 500 ml.), and the combined ether extracts were dried (Na_2SO_4). Evaporation, followed by distillation, gave the *hydroxylamine*, b. p. 80—82°/5 mm. (16 g., 36%) (Found: C, 69·4; H, 11·0. $C_9H_{17}NO$ requires C, 69·45; H, 11·0%).

3-(5,5-*Dimethylpyrrolidin*-2-*yl*)*propane*-1,2-*diol* (V).—The above hydroxylamine (6·5 g.) in "AnalaR" 99% formic acid (50 ml.) was cooled in ice and mixed with hydrogen peroxide (100-vol.; 5·5 ml.). After being kept in ice for 10 min., the mixture was heated at 40° for 16 hr. The formic acid was removed under reduced pressure, and the residue refluxed for 1 hr. with potassium hydroxide (14 g.) in 96% ethanol (80 ml.). Acetic acid (25 ml.) was added, and after evaporation under reduced pressure, the residue was heated at 100° overnight with zinc dust (30 g.) and 20% hydrochloric acid (75 ml.). After filtration, the solution was made alkaline with sodium hydroxide (100 g.) in water (100 ml.), this being followed by saturated aqueous sodium potassium tartrate (100 ml.), and was extracted with ether continuously for 4 days. After drying (K_2CO_3), the extract was evaporated, and the residue distilled in a short-path still at 150—180° (bath)/1 mm. to give a viscous, hygroscopic oil (3·4 g.), which soon solidified to a low-melting, waxy solid on seeding with the product of reduction of either (IVa) or (IVb). The picrate, prepared from benzene, recrystallised from butanol as needles, m. p. and mixed m. p. 116—119°. The m. p. was raised to 123—125° (mixed m. p. not depressed).

The picrolonate, prepared in ethanol–ether and recrystallised from butanol, had m. p. and mixed m. p. 160—162°.

2,5,5-*Trimethyl*-1-*pyrroline* 1-*Oxide* (XII).—5-Methyl-5-nitrohexan-2-one [16] (94 g.) was stirred with a solution of ammonium chloride (26 g.) in water (710 ml.), while zinc dust (130 g.) was added in 2 hr. The temperature was kept below 15° (ice-bath and by occasional addition of ice). After filtration, the cake of zinc oxide was washed with hot water, and the combined washings and filtrate were evaporated under reduced pressure at 70—75°. The residual oil was saturated with potassium carbonate and extracted with chloroform. After drying (Na_2SO_4) the solution was evaporated, and the residue distilled. The nitrone (58 g., 77%) was obtained as an almost colourless oil, b. p. 71—72°/2 mm. The picrate was formed from an aqueous solution of picric acid, and recrystallised from butanol as needles, m. p. 99—100° (lit.,[3] 98°).

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[16] Schechter, Ley, and Zeldin, *J. Amer. Chem. Soc.*, 1952, **74**, 3664.

2-(5,5-*Dimethylpyrrolidin*-2-*yl*)*propane*-1,3-*diol* (IX).—Freshly distilled 2,5,5-trimethyl-1-pyrroline 1-oxide (20 g.) and paraformaldehyde (9·2 g.) were heated for 18 hr. at 100°. The resulting gum was dissolved in tetrahydrofuran (100 ml.), and heated under reflux with lithium aluminium hydride (10 g.) in tetrahydrofuran (100 ml.) for 6 hr. The excess of hydride was destroyed with methanol, and the mixture evaporated to a paste. 20% Hydrochloric acid (100 ml.) and zinc dust (50 g.) were added, and the mixture was heated at 100° overnight. After filtration, the solution was made alkaline by addition of potassium hydroxide (50 g.) in water (50 ml.), followed by saturated aqueous sodium potassium tartrate solution (100 ml.) and the resulting solution was extracted with ether for 4 days. The ether extract was dried ($MgSO_4$) and evaporated, and the residual oil distilled in a short-path still at 120—180° (bath)/1 mm., to give 6·8 g. of a viscous hygroscopic oil. Paper chromatography showed this oil to consist mainly of 2-(5,5-dimethylpyrrolidin-2-yl)propane-1,3-diol. The picrate had m. p. and mixed m. p. 165—166°.

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