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2-*ETHYL*- AND 2-*ETHYL*-3-*NITROSOTETRAHYDRO*-1,3-*OXAZINES*—SYNTHESIS AND STRUCTURAL DETERMINATION

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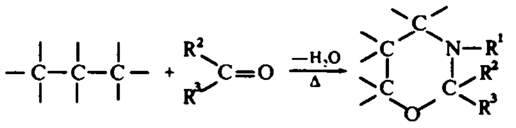
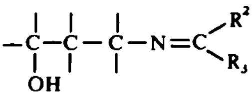
Abstract—The reaction of 3-amino-1-propanol with propionaldehyde yielded as the main product 2-ethyltetrahydro-1,3-oxazine, the nitrosation of which gave 2-ethyl-3-nitrosotetrahydro-1,3-oxazine. Conclusive evidence for the tetrahydro-1,3-oxazine structure was obtained by NMR spectroscopy.

DURING the preparation of 3,3′-oxybispropylamine from 3,3′-oxydipropionitrile considerable amounts of 3-amino-1-propanol were obtained. In an attempt to utilize this by-product, it was condensed with propion aldehyde. The condensation products of γ-amino alcohols with carbonyl compounds are tetrahydro-1,3-oxazines (I) or Schiff bases (II), or mixtures of the two isomeric forms, depending on the structure of the reagents used. The structures I and II exist in equilibrium in cases where R^1 is H. The choice between these structures has previously been made on the basis of chemical and physical properties, but uncertainties remain particularly in those compounds in which both an open and a cyclic structure are possible. The IR spectrum has given much information about the Schiff base structure,[1a],[2] but has been less satisfactory for positive identification of the tetrahydro-1,3-oxazine structure.[3]

The present paper is concerned with the structure of condensation products of 3-amino-1-propanol with propionaldehyde.





RESULTS AND DISCUSSION

The condensation product of 3-amino-1-propanol with an excess of propionaldehyde was separated into two fractions: a low-boiling (III; b.p. 60–61°/40 mm, 60% yield) and a high-boiling fraction (IV; b.p. 92–94°/3 mm).† VPC analysis revealed that III was homogeneous, but IV was a mixture of four compounds with relative areas in the ratio of about 5:1:12:1. Elemental analysis of III agreed with the formula $C_6H_{13}NO$. It was readily hydrolysed by dilute mineral acids to regenerate propionaldehyde and 3-amino-1-propanol. The nitrosation of III gave a nitroso derivative, a yellow liquid of b.p. 88–89°/4 mm, with the formula $C_6H_{12}N_2O_2$ (V). Acid hydrolysis of V regenerated propionaldehyde and 3-amino-1-propanol, accompanied by the

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† Sixteen grams of IV from 0·5 mole of 3-amino-1-propanol.

evolution of a gas. The NH group of the —NH—CHEt—O— part of I is not that of a secondary amine but the whole group may be regarded as an "acetal in the ammonia system" or an "ammono acetal".[4] The NH bond, however, does provide for nitrosation. Structure II has no such bond. Hence, the nitrosation to V is chemical evidence in support of I rather than II.

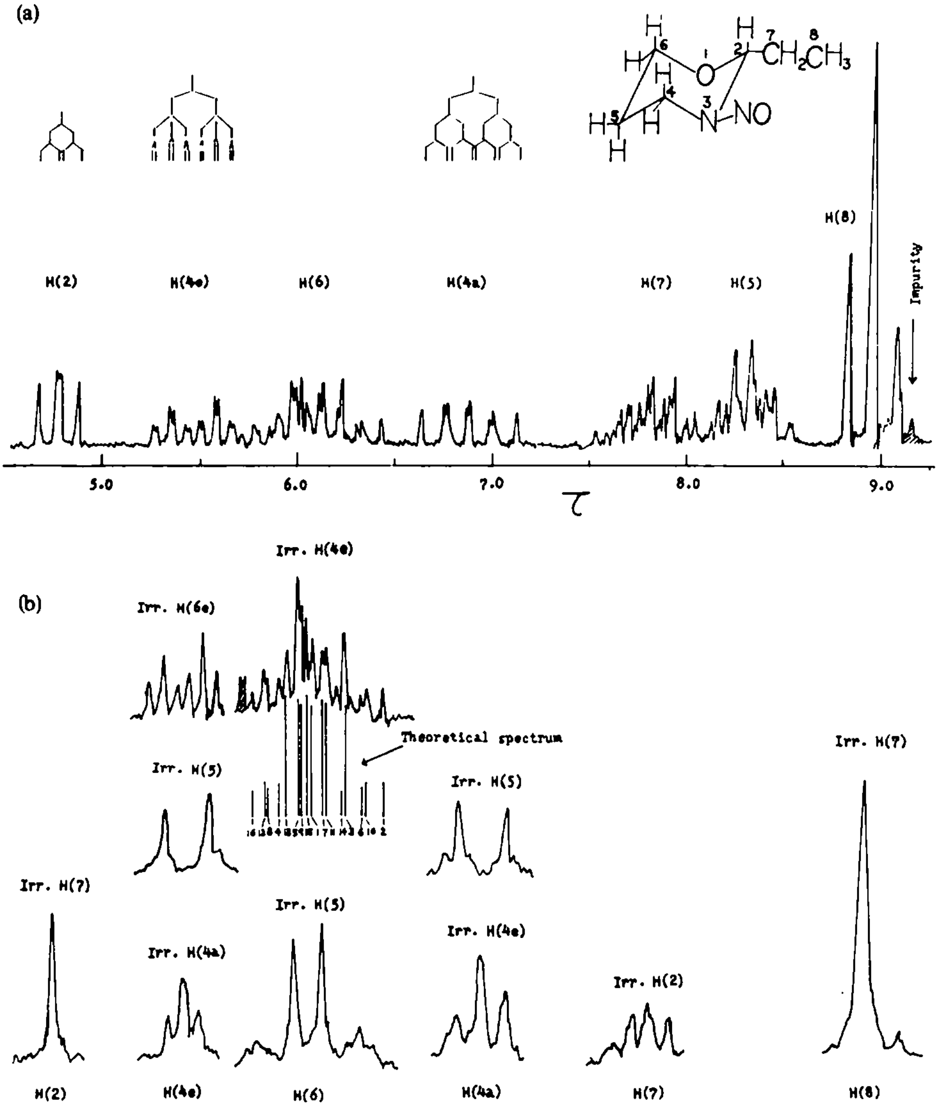


FIG. 1 NMR spectrum of 2-ethyl-3-nitrosotetrahydro-1,3-oxazine in CCl_4 at 60 Mc/s at 20°:

(a) single resonance spectrum

(b) double resonance spectrum.

The structure of V was demonstrated to be 2-ethyl-3-nitrosotetrahydro-1,3-oxazine through NMR spectroscopy. The NMR spectrum of V in CCl_4 at 60 Mc/s at 20° exhibits seven distinct signals with relative intensities in the ratio of 1:1:2:1:2:2:3 in the order of increasing τ-value (Fig. 1a). The highest field signal (triplet, τ 8·97, $J = 7{\cdot}2$ c/s), corresponding to three protons was assigned to the C(8) Me protons. The methine proton on the carbon, to which both the N and O atoms are attached, has the lowest chemical shift (τ 4·78, four lines). The two proton multiplet at τ 7·78 was assigned to the C(7) methylene protons by double irradiation experiments as follows (Fig. 1b). Irradiation of 2H(7) results in collapse of the 3H(8) triplet to a sharp singlet. On irradiation of H(2) the 2H(7) multiplet becomes a quartet, and conversely, irradiation of 2H(7) results in collapse of the H(2) signal to a sharp singlet. The four line signal for H(2) ($J_{2,7} = 6{\cdot}4$ and 5·6 c/s) suggests that rotation about the C(2)—C(7) bond may be restricted at room temperature by steric interference between the N(3) nitroso and the C(2) ethyl group. This argument is supported by the fact that the four line signal approaches a triplet ($J_{2,7} = \sim 6$ c/s) when the spectrum of V is measured at 100° (Fig. 2). The Et group is probably in an equatorial position on steric grounds. It is also expected that this steric interference would restrict ring-flip of the tetrahydro-1,3-oxazine ring in V. Validity of this argument will be shown later.

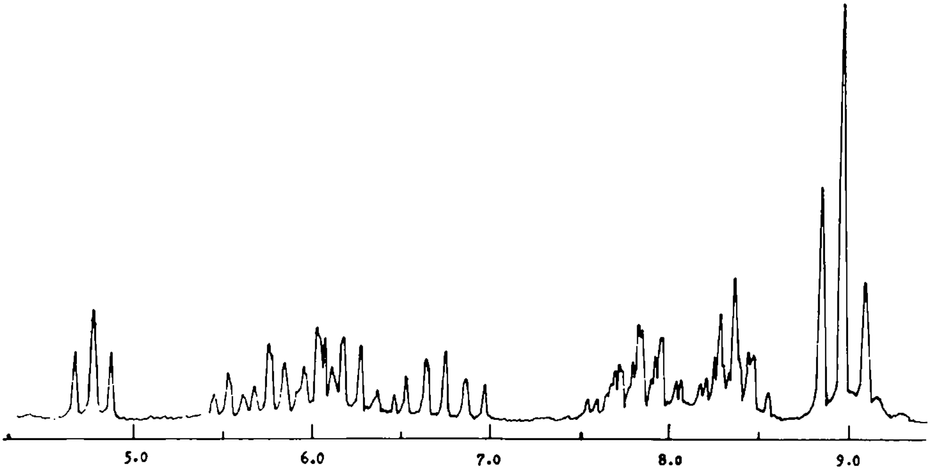
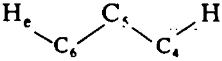


FIG. 2 NMR spectrum of 2-ethyl-3-nitrosotetrahydro-1,3-oxazine in CCl_4 60 Mc/s at 100°.

The two proton multiplet at τ 8·32 was assigned to the C(5) methylene protons. This assignment is supported by double irradiation experiments of the C(4) and C(6) protons. Irradiation of the one proton signal (five lines) at τ 6·87 results in collapse of the one proton signal (two triplets) at τ 5·49 to a triplet. Conversely, irradiation of the latter results in collapse of the former to a triplet. Both the above two signals change into doublets with the coupling constant of 13·8 c/s when 2H(5) is irradiated. These observations apparently indicate that the two protons corresponding to these two signals should be located on the same carbon, namely, either C(4) or C(6). The chemical shift difference between these two signals is 1·35 ppm. It is known[5] that in saturated cyclic nitrogen compounds having a rigid chair conformation the chemical shift difference between the equatorial and the axial proton on the carbon, to which the N atom is attached, is substantially larger than that observed in cyclohexane and sugar acetate derivatives ($\delta_{a,e} = 0{\cdot}1$–$0{\cdot}68$ ppm),[6] as has neen observed in quinolizidine ($\delta_{a,e} = 0{\cdot}93$ ppm)[5] and piperidazine derivatives ($\delta_{a,e} = 1{\cdot}35$–$1{\cdot}81$ ppm).[7] On the basis of the double irradiation and the chemical shift difference, it may be concluded that the signal at τ 6·87 corresponds to H(4a)* and that at τ 5·49 to H(4e).*

The remaining two proton multiplet at τ 6·05 was assigned to 2H(6). The multiplet changes into a quartet ($J_{a,e} = 11{\cdot}8$ c/s, $\delta_{a,e} = 0{\cdot}30$ ppm) when 2H(5) is irradiated. Irradiation of H(4e) causes simplification of the H(6e) part* of the H(6) multiplet, and conversely, irradiation of H(6e) results in disappearance of the small splitting of 1 c/s from the H(5e) signal, indicating that the observed small splitting is assigned as a long range spin–spin coupling. The long range coupling through four σ-bonds such as this has been also observed in 2,3,4-tri-O-benzoyl-α-D-ribopyranosyl halides.[8] The 2H(6) multiplet was analysed following the method established by Fujiwara and Fujiwara (the KL part of the ABKL spectrum),[9] neglecting the long range spin–spin coupling of H(4e) and H(6e). The theoretical spectrum is in agreement with the experimental spectrum (Fig. 1b).

The rigidity of the tetrahydro-1,3-oxazine ring in V at room temperature is demonstrated by (1) the long range spin-spin coupling[10] of H(4e) and H(6e) through four σ-bonds and (2) the large chemical shift difference[6] between H(4a) and H(4e). The above long range coupling indicates that the  system lies in or near a common plane;[10] in other words, the tetrahydro-1,3-oxazine ring in V is rigid. When the NMR spectrum of V was recorded in a series of increasing temperature it was found that the above chemical shift difference becomes smaller as the temperature is raised ($\delta_{a,e} = 1{\cdot}35$, $1{\cdot}25$, $1{\cdot}15$ and $1{\cdot}09$ ppm at 20, 50, 80 and 100°, respectively), and that the above long-range coupling also becomes indistinct at high temperatures. The observed spectral change can only be attributed to hindered ring-flip. The value of 1·09 ppm for $\delta_{a,e}$ at 100° indicates that the tetrahydro-1,3-oxazine ring in V is still rigid at this temperature. The N(3) nitroso group may probably be in an equatorial position.†

The IR spectrum of compounds with structure II may be expected to show a strong absorption in the 1640–1690 cm^{-1} region due to the aliphatic C=N group,[2e] whilst structure I should have no corresponding absorption. Structure I may also show a characteristic NH absorption in the 3300–3500 cm^{-1} region,[2e] but no OH absorption. Compound III, immediately after purification by fractional distillation (homogeneous by VPC analysis), exhibits no absorption at all in the double-bond region, but it shows

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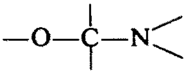
* Axial protons are known to absorb at higher field compared with the corresponding equatorial protons. See Ref. 6.

† On the basis of the argument by Hamlow, Okuda and Nakagawa[5] about the large chemical shift difference observed in quinolizidine, it may similarly be supposed that the unusually large chemical shift difference observed in V would be attributed to partial participation of the nitrogen (N3) lone pair in an antibonding σ-orbital between C(4) and H(4a). If this is valid, both the nitrogen lone pair and the σ^*-orbital may be expected to lie in or near a common plane; in other words, the N(3) nitroso group would be in an equatorial position.

an NH absorption at 3330 cm^{-1}. This NH assignment was confirmed by examining the spectrum of a dilute solution in CCl_4. Several groups of workers characterized the  $-O-\overset{|}{\underset{|}{C}}-N<$ system in cyclic compounds by a triplet or in some cases by a quintet of bands in the 1080–1200 cm^{-1} region.[1a, 10] The spectrum of III shows three bands at 1087, 1107 and 1152 (with two shoulders at 1145, 1160) cm^{-1}. Whether this represents the  $-O-\overset{|}{\underset{|}{C}}-N<$ system as has been suggested[1a,11] but questioned by others[3] cannot be stated. Nitroso compound V shows no absorption characteristic of the C=N, OH and NH groups, but it shows four bands at 1090, 1118, 1135, and 1185 cm^{-1}.

On the basis of analysis, acid hydrolysis, nitrosation of III to 2-ethyl-3-nitrosotetrahydro-1,3-oxazine, and IR spectrum, it seems reasonable to assume that III is 2-ethyltetrahydro-1,3-oxazine. The complete absence of a C=N absorption in III and its homogeneity by VPC analysis suggest that III, immediately after purification by fractional distillation, is free from a Schiff base within the limits of detectability by IR and VPC analyses. After standing for a couple of days at room temperature or short heating (20–30 min.) at 100° III exhibits a weak but sharp bend at 1647 cm^{-1}, which may be attributed to the C=N group in structure II. This spectral change is interpreted in terms of a well known equilibrium between structures I (R^1=H) and II.

The NMR spectrum of freshly distilled III is too complicated to analyse, because of overlapping of the lower field signals. On the basis of IR and VPC analyses it is unlikely that this complexity of the spectrum would be due to an equilibrium between structures I and II. It may partially be attributed to a conformational change owing to ring-flip of the tetrahydro-1,3-oxazine ring in III. The difference in electronegativities between H (with III) and —NO (with V) at N(3) may also be responsible for the difference in spectrum between III and V.

The high-boiling fraction IV shows a sharp b.p. (93–94°/3 mm) on repeated distillation, but VPC analysis revealed that it was still a mixture of four compounds. The high-boiling fraction thus remains unidentified.

TABLE 1. COUPLING CONSTANTS OF THE PROTONS IN 2-ETHYL-3-NITROSOTETRAHYDRO-1,3-OXAZINE

Coupling constant (c/s)		
$J_{8,7} = 7\cdot2$	$J_{6a,6e} = 11\cdot8$	$J_{4a,4e} = 13\cdot8$
$J_{2,7} = 6\cdot4$	$J_{6a,5} = 7\cdot7$	$J_{4a,5} = 7\cdot8$
$J_{2,7} = 5\cdot6$	$J_{6a,5} = 5\cdot9$	$J_{4a,5} = 6\cdot8$
	$J_{6e,5} = 4\cdot4$	$J_{4e,5} = \cdot0$
	$J_{6e,5} = 4\cdot3$	$J_{4e,6e} = 1\cdot0$

EXPERIMENTAL

B.ps. are uncorrected. IR spectra were measured with a rocksalt prism. NMR spectra were measured to various temps in CCl_4 (5–10%) on a Varian Associates Model V-4311 high resolution spectrometer operating at 60 Mc/s, using TMS (τ 10·00) as an internal standard. VPC analysis was carried out using 500 × 0·35 cm (A), 300 × 0·35 cm (B) and 100 × 0·35 cm (C) columns packed with 80–100 mesh

Celite, which was coated with 30% by weight of diethyl phthalate (A) or 30% by weight of high vacuum silicane grease (B and C). Column A was used for propionaldehyde at 40°, and columns B and C for 3-amino-1-propanol, III, IV, and V at 90–150°. Helium outlet flow rates were 50–60 cc/min. The peak areas were obtained by half-width and peak-height measurements. Microanalysis was performed by Dr. Yamadera.

2-*Ethyltetrahydro*-1,3-*oxazine* (III). A mixture of 3-amino-1-propanol (37·6 g), propionaldehyde (58 g) and benzene (100 ml) was heated for 3 hr under reflux. The benzene and unused propionaldehyde were removed by distillation from the reaction mixture, and the residue was distilled through a 40-cm Vigreux column to yield 2-ethyltetrahydro-1,3-oxazine in 60% yield (b.p. 59–61°/40 mm), a high-boiling fraction (b.p. 92–94°/3 mm, 16 g), and a tarry residue (3 g). Redistillation of the tetrahydro-1,3-oxazine gave a sharp b.p. of 60–61°/40 mm. In several runs the yield of the tetrahydro-1,3-oxazine ranged between 55–60%. (Found: C, 62·62; H, 11·42; N, 12·26. $C_6H_{13}NO$ requires: C, 62·56; H, 11·37; N, 12·16%).

2-Ethyltetrahydro-1,3-oxazine (2·3 g) was treated with 30 ml 10% HClaq for 30 min at room temp. The mixture was neutralized with a KOHaq and then extracted with ether. VPC analysis of the ether extract (after being dried) indicated the presence of propionaldehyde. To the aqueous layer residue were added 5 g of KOH pellets and 50 ml ether. The mixture was allowed to stand for 1 hr with chilling and occasional shaking. The ether layer was decanted, and the residue was extracted twice with ether. VPC analysis of the combined ether extracts (after being dried) showed the presence of 3-amino-1-propanol.

2-*Ethyl*-3-*nitrosotetrahydro*-1,3-*oxazine* (V). To a cold soln (0—5°) of conc. HCl (7·8 ml) and water (30 ml) 2-ethyltetrahydro-1,3-oxazine (8·5 g) was added with stirring. A cold coln of $NaNO_2$ (5·5 g) in 30 ml water was added dropwise to the cold mixture with stirring. The mixture was stirred for 1 hr at 0–5°, and then allowed to stand overnight at this temp. The mixture was neutralized with a dil NaOHaq, saturated with NaCl, and then extracted with ether 5 times. The combined ether extracts were dried and then the ether was removed by distillation. The residue was distilled to yield 2-ethyl-3-nitrosotetrahydro-1,3-oxazine in 52% yield (b.p. 86–89°/4 mm). Redistillation gave a sharp b.p. of 88–89°/4 mm. (Found: C, 49·74; H, 8·35; N, 19·79. $C_6H_{12}N_2O_2$ requires: C, 49·98; H, 8·38; N, 19·43%).

2-Ethyl-3-nitrosotetrahydro-1,3-oxazine was hydrolyzed with a dilute hydrochloric acid solution, in the same manner described for 2-ethyltetrahydro-1,3-oxazine, to yield propionaldehyde, 3-amino-1-propanol and a gas.

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