765. *Ring Contractions of Alloxan with Alicyclic Secondary Amines: Formation of Amine Salts of Alloxanic Acid.*

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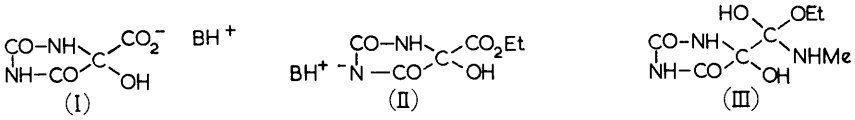
The so-called alloxanic acid amide hydrates formed from alloxan and secondary amines are shown to be amine salts of alloxanic acid. The adducts formed from anhydrous alloxan and morpholine or piperidine in ethanol are shown to be salts of the amine with the acidic imide group of ethyl alloxanate.

Fisher and Day [1] reported that alloxan reacts with secondary amines (morpholine, piperidine, pyrrolidine, and dimethylamine) to give amides of alloxanic acid, and that the same products were formed from ethyl alloxanate and the secondary amines in aqueous solution. The " amides " all retained an additional molecule of water and the obvious inference that the compounds are salts (I; B = base) and not amides has now been confirmed by preparation of morpholine and piperidine alloxanate by neutralising the acid with the amines. The products were identical with those prepared by Fisher and Day's methods, as judged by general physical properties, infrared spectra, and mixed melting-point determinations, and piperidine alloxanate in water showed the high equivalent conductance ($\Lambda = 51$) expected for such a salt. The reported [1] thermal decomposition of the morpholine compound into 5-hydroxyhydantoin, carbon dioxide, and morpholine is no longer surprising with the revised constitution, and both the morpholine and the piperidine salt gave an immediate and quantitative precipitate of barium alloxanate on addition of aqueous barium hydroxide.



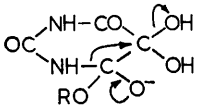
(I) (II) (III)

When piperidine was added to a solution of anhydrous alloxan in dry ethanol a compound $C_{11}H_{19}N_3O_5$ was obtained which formally is an adduct of alloxan, piperidine, and ethanol, and the same product was obtained from ethyl alloxanate and piperidine in dry ethanol (or dry acetone). Morpholine gave a similar product and these compounds we formulate as salts (II) of ethyl alloxanate. The equivalent conductance of the piperidine compound (II) in methanol was high ($\Lambda = 26$) as expected for a salt. A compound obtained from ethyl alloxanate and methylamine is evidently an analogous salt (although it was described by Biltz and Lachmann [2] as an " ethanolate " (III) of the methylamide. The structures (II) were established by warming the piperidine salt with water on a steam-bath for 15 minutes, which converted it into piperidine alloxanate (I; B = piperidine), and by precipitating the sodium salt of ethyl alloxanate from the piperidine salt with methanolic sodium methoxide and then liberating the ethyl ester from the precipitate with dry hydrogen chloride in tetrahydrofuran. Infrared measurements support the assigned structures as the salts (II; B = piperidine, morpholine) retained a band at 5·7 μ (ester-carbonyl) but lacked the absorption at 5·6—5·65 μ typical of the un-ionised alloxanate ring, and showed one instead of two peaks in the N–H stretching region. It was stated [2] that the methylamine salt of ethyl alloxanate (II; B = NH_2Me) (Biltz and Lachmann's " ethanolate," III), when warmed with water, yielded the hydrated amide which, like Fisher and Day's compounds, could not be dehydrated without decomposition, so that this " amide " is clearly the methylamine analogue (II; B = $NHMe_2$) of the piperidine and morpholine salts.

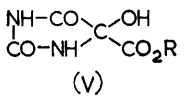
The revised constitution of the products from alloxan and secondary amines necessitates

[1] Fisher and Day, *J. Amer. Chem. Soc.*, 1955, **77**, 4894.
[2] Biltz and Lachmann, *J. prakt. Chem.*, 1926, **113**, 309.

modification of the mechanism proposed by Fisher and Day for the ring contraction. Nucleophilic attack by solvent anions, or by solvent molecules followed by proton transfer to the amine, would give the intermediate (IV; R = H or Et) from which the products (V; R = H or Et) would arise by migration of nitrogen from C-4 to C-5. This migration is in agreement with radiotracer studies,[3] which established that formation of alloxanic acid from alloxan does not occur by C⟶C migration, as in rearrangements of the



(IV)



(V)

benzilic acid type. Ring contraction of alloxan under the influence of hydroxyl ions or amines (morpholine, piperidine, pyrrolidine, methylamine, and dimethylamine) in aqueous solution thus leads to the alloxanate anion. Alkoxides in dry alcohols give rise to the metal salts of alloxanate esters (*e.g.*, salt of V; R = Me),[1] and the amines in dry ethanol yield corresponding amine salts (II).

Experimental

Infrared spectra (2—15 μ) of Nujol mulls were recorded on an Infracord spectrometer, and positions of absorption in the region 5·5—6·5 μ were accurately measured (by Dr. R. A. Jones) with a Grubb–Parsons S4 spectrometer (calcium fluoride prism).

Ethyl alloxanate [2] gave carbonyl absorption bands at 5·55, 5·68, 5·76, and 5·82 μ.

Morpholine Alloxanate (I; B = C_4H_9NO).—(*a*) Morpholine (1·1 g.) was added to a solution of alloxanic acid (2 g.) in dry methanol (7 c.c.), and ether was added to produce a faint turbidity. After storage at 0° the *morpholine alloxanate* (2·8 g., 90%) was collected; it crystallised from aqueous ethanol (addition of ethanol to an aqueous solution) in prisms, m. p. 120° (lit.,[1] 119·8—120·8°) (Found: C, 36·4; H, 5·9; N, 15·8. $C_8H_{13}N_3O_6,H_2O$ requires C, 36·2; H, 5·7; N, 15·8%), $\nu_{max.}$ 5·66, 5·77, 6·07, and 6·23 μ.

(*b*) A solution of alloxan monohydrate (2 g.) and morpholine (1·1 g.) in water (15 c.c.) was boiled under reflux until it became yellow (5 min.). Ethanol (220 c.c.) was added and, after storage at 0° overnight, the salt (1·9 g., 62%) was collected. It crystallised from aqueous ethanol in prisms, m. p. 120° alone and when mixed with that described under (*a*).

(*c*) A solution of morpholine (1·1 g.) and ethyl alloxanate (2·3 g.) in water (15 c.c.) was heated on a steam-bath for 15 min. before addition of ethanol (220 c.c.) and cooling to 0°. Next day the salt (2·7 g., 90%) was collected; it crystallised from aqueous ethanol in prisms, m. p. and mixed m. p. 120°.

Piperidine Alloxanate (I; B = $C_5H_{11}N$).—The *salt* was prepared in the same way as the morpholine analogue by methods (*a*) (90%), (*b*) (68%), and (*c*) (86%) with piperidine in place of morpholine. It crystallised from aqueous ethanol in prisms, m. p. 153° (lit.,[1] 133°) (Found: C, 43·9; H, 6·4; N, 17·3. $C_9H_{15}O_5N_3$ requires C, 44·1; H, 6·2; N, 17·1%), $\nu_{max.}$ 5·62, 5·67, 5·78, 6·09, and 6·27 μ.

Morpholine Salt of Ethyl Alloxanate (II; B = C_4H_9NO).—(*a*) Morpholine (1·1 g.) was added to a solution of anhydrous alloxan (1·7 g.) in dry ethanol (10 c.c.), and the resulting suspension was cooled for 2 hr. The *morpholine salt* of ethyl alloxanate (1·9 g., 58%) was collected; it crystallised from ethanol in prisms, m. p. 126° (Found: C, 43·2; H, 6·1; N, 15·5. $C_{10}H_{17}N_3O_6$ requires C, 43·6; H, 6·2; N, 15·3%), $\nu_{max.}$ 5·77, 6·14, and 6·29 μ.

(*b*) Morpholine (1·1 g.) was added to a solution of ethyl alloxanate (2·3 g.) in dry ethanol (10 c.c.). The mixture was stored at 0° for 1 hr. and filtration then gave the morpholine salt (2·4 g., 71%). The salt was obtained almost quantitatively from ethyl alloxanate and morpholine in dry acetone.

Piperidine Salt of Ethyl Alloxanate (II; B = $C_5H_{11}N$).—(*a*) Piperidine (1·06 g.) was added to a solution of alloxan monohydrate (1·7 g.) in dry ethanol (10 c.c.), and the resulting suspension was cooled for 2 hr. before collection of the *piperidine salt* of ethyl alloxanate (2·1 g., 72%), which crystallised from dry ethanol in needles, m. p. 125—126° (Found: C, 48·3; H, 7·0; N, 15·4. $C_{11}H_{19}N_3O_5$ requires C, 48·3; H, 7·0; N, 15·4%), $\nu_{max.}$ 5·75s, 5·94w, 6·14, and 6·32 μ.

[3] Kwart, Spayd, and Collins, *J. Amer. Chem. Soc.*, 1961, **83**, 2579.

(*b*) Piperidine (1·06 g.) was added to a solution of ethyl alloxanate (2·3 g.) in dry ethanol (10 c.c.), and the solution was stored at 0° for 1 hr. before collection of the salt (2·7 g., 80%), which crystallised from ethanol in needles, m. p. and mixed m. p. 125—126°. A solution of the salt (2·7 g.) in water (5 c.c.) was heated on a steam-bath for 15 min. and then diluted with ethanol (75 c.c.) and stored at 0°. Next day piperidine alloxanate (1·4 g., 58%), m. p. and mixed m. p. 153°, was collected; its infrared absorption was indistinguishable from that of the sample described above

Liberation of Ethyl Alloxanate from its Piperidine Salt.—Sodium methoxide (0·54 g.) in methanol was added to a solution of the piperidine salt (2·7 g.) in the minimum of dry methanol. The immediate gelatinous precipitate of the sodium salt of ethyl alloxanate was collected and dried (2·0 g., 96%); its infrared absorption was indistinguishable from that of the sodium salt prepared from ethyl alloxanate and sodium ethoxide (absorption at 5·83 and 6·18 μ). The sodium salt was suspended in dry tetrahydrofuran in a flask protected from moisture, dry hydrogen chloride was passed in for 30 sec., and the mixture was shaken for 1½ hr. before filtration from sodium chloride. The filtrate was evaporated under reduced pressure, and re-evaporated after the addition of dry methanol. The residue was dissolved in a little warm, dry acetone, and the solution was diluted to incipient turbidity with dry chloroform. Ethyl alloxanate (1·4 g., 75%) crystallised in long plates pointed at both ends, m. p. 115—116° alone and when mixed with an authentic specimen.[2]

Electrical Conductivities.—0·1M-Solutions of the salts were measured at 20° with a Philips conductivity bridge, model GM 4249, and a dipping-electrode conductivity cell. We thank Dr. B. J. Steel for these measurements.

Microanalyses were performed under the supervision of Dr. W. Zimmermann, C.S.I.R.O. Microanalytical Laboratory, Melbourne. We thank Dr. R. A. Jones for infrared measurements.

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