REACTION OF PYRIDINES WITH EPICHLOROHYDRIN

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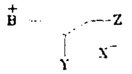
The reaction of pyridines with epichlorohydrin can occur by three routes depending upon the conditions used. Two of these lead to stable 1-cycloimmonium-2-chloro-2-propanol and 1,3-biscycloimmonium-2-propanol salts whereas the third gives unstable colored compounds.

As an oxirane, epichlorohydrin reacts with pyridines or analogous bases to form colored materials [1-3]. Lohmann [2] quotes around 35 such dyes but this number may readily be increased. Their structure has not been established up to this time. That given in [1] for a quinoline dye is incorrect since it does not correspond in composition or properties. Data for the stable, aromatic N-glycidylcycloimmonium salts VIIa-d has not been reported but the related ammonium salts VIIe are stable and well known [3].

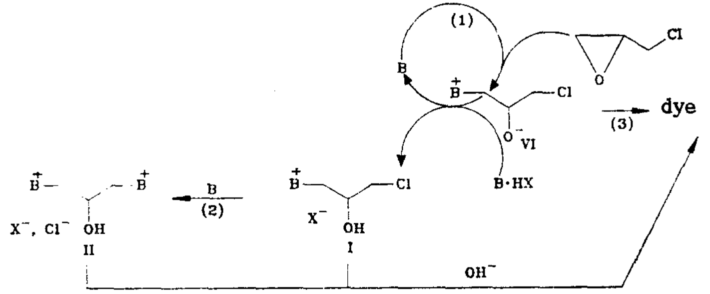
By treating epichlorohydrin with pyrdines we have obtained and identified a series of colorless, stable cycloimmonium and biscycloimmonium derivatives I-V. These substances are evidently precursors of dyes into which they are converted in alkaline media.



I-VII

a B = pyridine, b B = γ-picoline, c B = quinoline, d B = isoquinoline, e B = trialkylamine
Ia-d $X=ClO_4$, $Y=OH$, $Z=Cl$; IIa,b $X^-=2ClO_4^-$, $Y=OH$, $Z=B^+$; IIIa $X=ClO_4$, $Y=Z=Cl$; IVa $X^-=2ClO_4^-$, $Y=Cl$, $Z=B^+$; Va,b $X=ClO_4$, $Y=Z=OH$; VIa,d X^- absent, $Y=O^-$, $Z=Cl$; VIIa,d $(YZ)=O$

Compounds Ia-d are readily formed by treating epichlorohydrin with pyridine perchlorates or fluoroborates containing a small amount of the free base B (but not with chlorides or bromides with high nucleophilicity anions). It is significant that with very pure or mildly acidic perchlorates the reaction only occurs with difficulty or not at all. The bases themselves, as indicated above, give only colored compounds. This suggests that the reaction takes place via a cyclic mechanism, the first step of which is nucleophilic opening of the oxirane ring by a catalytic amount of base B:



If in a medium where it cannot be stabilized by protonation, the formed betaine VI is converted to a dye either directly or via the intermediate oxirane VII (route 3). In the presence of the salt B·HX the betaine VI is stabilized in the form of the chlorohydrin salt I. In its absence base B, (which in excess of epichlorohydrin continues the process (route 1) up to full conversion of epichlorohydrin and salt B·HX to chlorhydrin I) in the absence of epichlorohydrin is quaternized by chlorohydrin I to biscycloimmonium salts II

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(route 2). Evidently the most rapid process (excluding protonation, of course) is the reaction B + epichlorohydrin → VI and it is this fact which allows practically quantitative direction along the chosen one of the three routes by change in medium and stoichiometry.

The proposed scheme of nucleophilic opening of the oxirane ring does not fundamentally demand the electrophilic assistance of protonation of the oxirane (without protonation route 3 is readily achieved). Moreover, as indicated above, with the B·HX salt and in excess acid the given reaction does not occur. This is in contradiction to the mechanism proposed by Hayes, King, and Peterson [4] for the reaction of pyridine salts with cyclohexene oxide. The authors [4], however, carried out the reaction of the oxirane with the pyridinyl salts in the medium of the bases themselves such that the catalytic mechanism proposed by us can also apply. In the case of the reaction with epichlorohydrin a large excess of the base B cannot be used both because of quaternization by route 2. These synthetic circumstances force a revision of the mechanism of the reaction of pyridines with oxiranes.

The stable salts I can be considered as a particular case of stabilization of the betaines VI by salt formation: I = VI·HX. The unusal stability of the perchlorates $VI \cdot HClO_4$ alternates with the limited stability of the acetates $VI \cdot CH_3COOH$. The hydroxides $VI \cdot H_2O$, as with the betaine VI anhydrobases, are rapidly converted to colored materials. The simplest dyes have the composition VI, i.e., B + epichlorohydrin. There are also formed substances of composition 2B + epichlorohydrin and more complex colored products by condensation, dehydrochlorination, dehydration, and oxidation. Acetates $VI \cdot CH_3COOH$ are readily formed in acetic acid from the perchlorates $VI \cdot HClO_4$ by an exchange reaction with potassium acetate. They are formed as colorless liquids or low melting crystalline substances although extremely hygroscopic, thus hindering their analysis. Upon heating the acetates above 100°C they lose acetic acid and are converted to dyes. The hydroxides $VI \cdot H_2O$ are formed in aqueous solutions from the perchlorates by exchange with potassium carboante. The solutions stay colorless for several hours and then become colored. Attempts to concentrate the solutions, even without heating, lead to rapid dye formation. Both the acetates and the hydroxides have PMR spectra analogous to the spectra of the perchlorates and are converted to the latter simply by using perchloric acid. The dyes, however, do not show this reversibility. The cycloimmonium I and biscycloimmonium II analogs behave similarly in these reactions.

Treatment of I and II with thionyl chloride readily converts them to the chlorides III and VI.

Perchlorates I and II are characterized by unusually low melting points. Thus Ia melts at 68-70°C and can be held in the molten state at near 100°C indefinitely without any kind of change. In particular, the corresponding synthesized glycol Va could generally not be crystallized. Exchange of OH for Cl in these compounds leads to a sharp increase in melting points. An optical anisotropy of fusion was noted for the perchlorates Ia, and Va,b.

EXPERIMENTAL

IR Spectra were measured on a UR-20 spectrometer and PMR spectra on a Tesla BS-467 (60 MHz) instrument using CF_3COOH solvent and TMS internal standard. The elemental composition of all perchlorates (C, H, N, and Cl) corresponded to those calculated. Compounds with other anions and perchlorate Vb were not analyzed.

1-(2-Hydroxy-3-chloropropyl)pyridinium perchlorate (Ia, $C_8H_{11}Cl_2NO_5$). A solution of pyridinium perchlorate (18 g, 0.1 mole), epichlorohydrin (8 ml, 9.4 g, 0.102 mole), and pyridine (3-5 drops) in alcohol (150 ml) was refluxed for 3 h. The mixture was cooled overnight at −15°C and about 23 g (85%) of colorless material separated. The mother liquor was evaporated *in vacuo* to give an additional, less pure batch. The overall yield was close to quantitative. The colorless crystals had mp 68-70°C (from alcohol). In the melt, the substance did not change upon heating at least up to 150°C and could be held without change at 100°C for 2 days . Sudden heating above 200°C causes it to explode. The product is extremely prone to supercooling and is very soluble in water and hot ethanol, and insoluble in ether and benzene. IR Spectrum (supercooled liquid film): 3460 s br (ν O–H); 3145 m, 3095 s, 3070 s, 3020 vw, 2970 w (ν C–H); 1630 s (ν C=N); 1585 vw, 1495 s (ν C=C); 1450 w, 1420 w, 1320 w, 1290 m (δ C–H); 1100 vs br (νClO_4); 780 s (νC–Cl); 690 s (δ C–Cl, trans); 630 cm^{-1} s (δ C–Cl, gauche). PMR Spectrum: 3.81 (2H, d, J = 4 Hz, $3\text{-}CH_2$); 4.78 (3H, m, $1\text{-}CH_2$+CH); 8.0 ppm (5H, m, Ar).

1-(2-Hydroxy-3-chloropropyl)-4-methylpyridinium perchlorate (Ib, $C_9H_{13}Cl_2NO_5$) was obtained either as above or by the following method: γ-picolne perchlorate (2 g, 10.3 mmole), γ-picoline (1 drop), and epichlorohydrin (10 ml) were refluxed for 1 h and then distilled *in vacuo* to dryness to remove excess epichlorohydrin. The semi-solid residue was triturated with ether and decanted three times with ether. Drying *in vacuo* gave a practically quantitative yield of colorless material with mp 78-81°C (from ethanol). IR Spectrum (in vaseline mull): 3450 br (ν O–H); 1630 s (ν C=N); 1500 s (ν C =C); 1100 vs br (ν ClO_4); 780 s (ν C–Cl); 685 s (δ C–Cl, trans); 625 cm^{-1} s (δ C–Cl, gauche). PMR spectrum: 2.67 (3H, s, CH_3); 3.80 (2H, d, J = 4 Hz, 3-CH_2); 4.75 (3H, m, 1-CH_2 + CH); 7.87 (2H, d, J = 7 Hz, β-H); 8.68 ppm (2H, d, J = 7 Hz, α-H).

1-(2-Hydroxy-3-chloropropyl)quinolinium perchlorate (Ic, $C_{12}H_{13}Cl_2NO_5$) was prepared from pyridinium perchorate and epichlorohydrin as described for synthesis of the pyridine analog to give colorless crystals (85%) with mp 133-135°C (from ethanol). PMR Spectrum: 3.87-5.87 (5H, m, Alk); 7.9-9.3 ppm (7H, m, Ar).

2-(2-Hydroxy-3-chloropropyl)isoquinolinium perchlorate (Id, $C_{12}H_{13}Cl_2NO_5$) was obtained from isoquinolinium perchlorate and epichlorohydrin similarly to the above in 92% yield with mp 110-112°C (from alcohol). PMR Spectrum: 3.83 (2H, d, J = 4 Hz, 3-CH_2); 4.92 (3H, m, 1-Ch_2+ CH); 7.87-8.67 (6H, m, Ar); 9.63 ppm (1H, c, Ar).

2-Hydroxy-1,3-bis(1-pyridinium)propanebisperchlorate (IIa, $C_{13}H_{16}Cl_2N_2O_9$). A solution of pyridinium perchlorate (1.8 g, 10 mmole), pyridine (0.8 ml, 10 mmole), and epichlorohydrin (0.8 ml, 10 mmole) in ethanol (80 ml) was refluxed for 5 h, cooled, and $HClO_4$ (57%, 1 ml) added. After standing overnight at –15°C the precipitate was separated, washed with cold alcohol, and dried at 100°C to give 3 g (72%). The mother liquor contained a further 0.5 g of colored material. The colorless crystals had mp 158-160°C (from ethanol). PMR Spectrum: 4.67-5.67 (5H, m, Alk); 7.2-9.2 ppm (10H, m, Ar). The same material could be obtained in quantitative yield by refluxing the salt Ia and pyridine for 2-3 h in ethanol.

2-Hydroxy-1,3-bis(4-methyl-1-pyridinium)propanebisperchlorate (IIb, $C_{15}H_{20}Cl_2N_2O_9$) was obtained similarly from γ-picoline perchlorate, γ-picoline, and epichlorohydrin to give a 74% yield with mp 208-210°C (from ethanol). PMR Spectrum: 2.67 (6H, s, CH_3); 4.4-5.2 (5H, m, Alk); 7.79 (4H, d, J = 7 Hz, β-H); 8.61 ppm (4H, d, J = 7 Hz, α-H).

1-(2,3-Dichloropropyl)pyridinium perchlorate (IIIa, $C_8H_{10}Cl_3NO_4$). A mixture of 1-(2-hydroxy-3-chloropropyl)pyridinium perchlorate (1 g, 3.68 mmole) and thionyl chloride (5 ml) was refluxed for 2 h and evaporated to dryness. The residue was triturated with chloroform and was washed with chloroform and ether to give an approximately 1 g yield (94%) of large colorless, transparent, crystals with mp 113-115°C (from alcohol). PMR Spectrum: 2.7-4.7 (5H, m, Alk); 7.1-8.2 ppm (5H, m, Ar).

2-Chloro-1,3-bis(1-pyridinium)propanebisperchlorate (IVa, $C_{13}H_{15}Cl_3N_2O_8$). IIa (2 g, 4.82 mmole) and $SOCl_2$ (40 ml) were refluxed for 5 h and evaporated to dryness. The residue was washed twice with ether and crystallized from ethanol to give 2 g (96%) of colorless crystals with mp 260°C (decomp.). PMR Spectrum: 3.9-5.0 (5H, m, Alk); 7.1-8.3 ppm (10H, m, Ar).

2-Hydroxy-1,3-bis(1-piperidinium)propanediacetate and bistrifluoroacete (VIa·CH_3·COOH, VIa·2CF_3COOH). A solution of the corresponding bisperchlorate IIa (3 g, 7.2 mmole) and anhydrous potassium acetate (1.4 g, 14.2 mmole) in glacial acetic acid (50 ml) was refluxed for 5 min, cooled, the precipitate of potassium perchlorate separated, and the solution evaporated *in vacuo* at a temperature no greater than 50°C. The viscous liquid was triturated with dry ether (20 ml), washed twice on the filter with ether (with the exclusion of air), and dried *in vacuo* over fused KOH to give 2.3 g (80%) of colorless, strongly hygroscopic material with mp 75-90°C. Melting at 100-120°C caused decomposition with evolution of acetic acid and formation of a dark solid. Upon treatment with perchloric acid the diacetate is quantitatively converted to the starting diperchlorate (mp 158-160°C) which did not depress the melting point of an authentic sample. Treatment of the diacetate with trifluoroacetic acid led to quantitative formation of the bistrifluoroacetate with mp 157-160°C. A sample mixed with the bis perchlorate (which had the same melting point) gave a depression of melting point of 20°C. The PMR spectra of both diacetate and bistrifluoroacetate were similar to that of the bis perchlorate.

1-(2,3-Dihydroxypropyl)-4-methylpyridinium perchlorate (Vb, $C_8H_{12}ClO_6$). A mixture of γ-picoline perchlorate (8 g, 41 mmole), γ-picoline (3 drops), and glycidol (3 ml, 45 mmole) was refluxed in alcohol (100 ml) for 5 h. The product was diluted with a five fold excess of ether and the alcohol/ether layer separated from the viscous oil. The oily material was twice reprecipitated from alcohol solution and dried at 110°C for 2 h at atmospheric pressure and then *in vacuo*. Upon prolonged standing the colorless, hygroscopic, highly viscous oil crystallized to product (8 g, 78%) with mp 82-85°C. From concentrated alcoholic solutions this solid substance again precipitated as an oil. IR Spectrum (liquid film): 3550-3250 vs (ν O–H); 3160 m, 3100 s, 3060 s, 3030 w, 2980-2850 vs (ν C–H); 1635 s (ν C=N); 1605 m, 1570 vw, 1510 s (ν C=C); 1470 m, 1380 m, 1310 m, 1250 m, 1240 w (δ C–H and δ O–H); 1210 m, 1185 m (ν C–O); 1100 cm^{-1} vs br (ν ClO_4). PMR Spectrum: 2.71 (3H, s, CH_3); 3.9 (3H, m, CH+3-CH_2); 4.5 (2H, d, J = 9 Hz, 1-CH_2); 7.87 (2H, d, J = 6 Hz, β-H); 8.63 ppm (2H, d, J = 6 Hz, α-H).

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