# 637. *Cyclic Quaternary Ammonium Salts. Part I. The Oxidation of 6,12-Dihydrodipyrido*[1,2-a:1′,2′-d]*pyrazidiinium Salts.*

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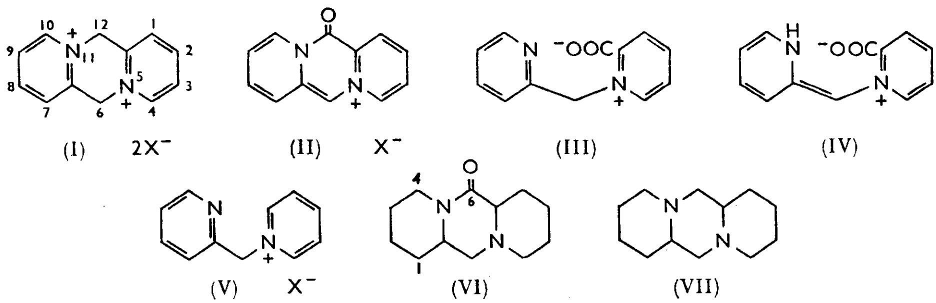
The oxidation of 6,12-dihydrodipyrido[1,2-*a*:1′,2′-*d*]pyrazidiinium salts to 12-oxo-9*H*-dipyrido[1,2-*a*:1′,2′-*d*]pyrazin-5-ium salts (II) is reported. Hydrolysis of the monosalt (II) gave the betaine (III) and hydrogenation of both (II) and (III) gave a lactam (VI). The last was converted by lithium aluminium hydride into a mixture of isomeric perhydrodipyrido[1,2-*a*:1′,2′-*d*]pyrazines (VII).

We are interested in the effects of oxidising agents and dehydrogenation catalysts on some diquaternary derivatives of 2,5-dihydropyrazine.

The action of phosphorus tribromide on 2-pyridylmethanol gave the diquaternary salt [1,2] (I; X = Br) in good yield. Attempts to dehydrogenate this system by heating intimate mixtures of the dibromide or the dipicrate with palladium–charcoal failed. Since the dehydrogenation of the dibromide (I; X = Br) in solution was not possible due to insolubility, a solution of the dipicrate (I; X = picrate) in nitromethane containing




suspended palladium–charcoal was boiled under reflux, giving the monoquaternary salt (II; X = picrate). This was converted into the corresponding bromide (II; X = Br) by ion exchange. The bromide is an orange solid, very soluble in water to give solutions that are yellow with a strong green fluorescence; but the colour and fluorescence are irreversibly destroyed by aqueous alkali or very slowly on storage.

No organic material could be extracted from an alkaline solution of the bromide (II; X = Br) and evaporation of the solution gave no identifiable residue. Hydrolysis of the bromide (II; X = Br) on an ion-exchange column gave a betaine, assigned structure (III) in preference to (IV) since its ultraviolet (u.v.) absorption spectrum was very similar to that of α-picoline and of homarine. In addition, the absorption spectrum of the betaine, on change of solution from alkaline to acid, showed loss of fine structure together with a large increase in the molecular extinction coefficient, characteristic of alkylpyridines [3] (see Figure).

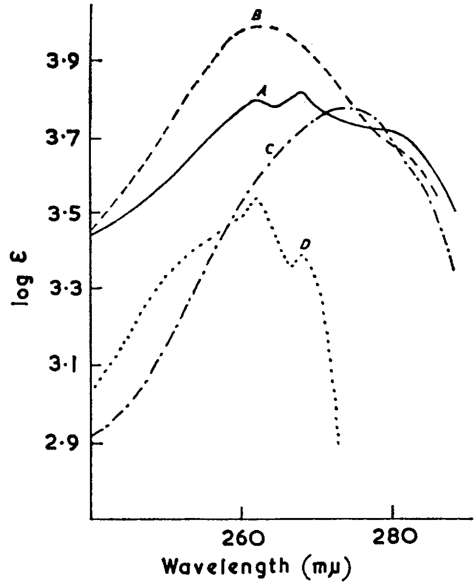
Treatment of the betaine (III) with alcoholic picric acid gave, instead of the expected betaine picrate, the picrate (V; X = $C_6H_2N_3O_7$), m. p. 172°. Since melting points of 158° [4] and 168—169° [5] have been previously recorded, the identity of our dipicrate was established by its preparation from 1-2′-pyridylmethylpyridinium bromide (V; X = Br), obtained by a modification of Brown and Humphreys' method.[4]

[1] Sŏrm and Šedivý, *Coll. Czech. Chem. Comm.*, 1948, **13**, 289.
[2] Tetsuzo Kato, *J. Pharm. Soc. Japan*, 1955, **75**, 1239.
[3] Brown and Mihm, *J. Amer. Chem. Soc.*, 1955, **77**, 1723.
[4] Brown and Humphreys, *J.*, 1959, 2040.
[5] Bunsuke Umezawa, *Chem. Pharm. Bull.* (*Tokyo*), 1960, **8**, 918.

Hydrogenation of the bromide (II; X = Br) and the betaine (III) gave the lactam (VI) which showed intense infrared absorption in the 1640 $cm.^{-1}$ region, characteristic of six-membered lactams.[6]

Oxidation of the dihydro-dibromide (I; X = Br) with selenium dioxide [7] in boiling glacial acetic acid gave either the bromide (II; X = Br) after 5 minutes or 1-2′-pyridylmethyl pyridinium bromide hydrobromide (as V; X = Br) after 16 hours.

Reduction of the lactam (VI) by lithium aluminium hydride gave a base, m. p. 40—42°, the analytical data for which agreed with those expected for the perhydro-compound (VII). Hydrogenation of the dihydro-dibromide (I; X = Br) gave a base m. p. 95—96°, the analyses for which again agreed with those calculated for the perhydro-compound (VII). Melting points of 81,[1] 92—95,[2] and 95—96° [8] have been recorded for (VII) respectively, and Winterfeld and Rath [9] reported the isolation of a pair of isomeric perhydrodipyridopyrazines (VII), suggesting that the higher-melting isomer contained two *trans*-ring fusions and the lower-melting isomer contained one *cis*- and one *trans*-ring fusion. We conclude, therefore, that our low-melting base is a mixture of isomers, the principal




Spectra of: *A*, the betaine (III) in 0·1N-sodium hydroxide; *B*, the betaine (III) in 0·1N-hydrochloric acid; *C*, homarine sulphate and *D*, α-picoline, both in 0·1N-sodium hydroxide.

component being the isomer containing a *cis*- and a *trans*-ring fusion. However, crystallisation and chromatography failed to raise the melting point above 52°. Similarly, the basic material, m. p. 74—76°, obtained from the dihydro-dibromide (I; X = Br) is clearly a mixture of isomers containing a preponderance of the isomer having both ring fusions *trans*.

The m. p.s of the monomethiodides of our isomeric perhyro-compounds (VII) show a marked difference from those recorded by Winterfeld and Rath; [9] they are also in the reverse order; the higher-melting base giving the lower-melting methiodide. We have prepared the higher-melting base (VII) by Winterfeld and Rath's method [9] and the melting point of its methiodide was the same as that of the methiodide of our base obtained from the dihydro-dibromide (I; X = Br). Recently, Winterfeld [10] has recorded m. p. 310° (decomp.) for the methiodide of the low-melting base and this is in good agreement with the melting point recorded by us.

[6] Edwards and Tara Singh, *Canad. J. Chem.*, 1954, **32**, 683.
[7] Jerchel, Heider, and Wagner, *Annalen*, 1958, **613**, 153.
[8] Winterfeld and Will, *Naturwiss.*, 1955, **42**, 178.
[9] Winterfeld and Rath, *Arch. Pharm.*, 1960, **293**, 141.
[10] Personal communication from Professor Winterfeld.

That the low-melting base (VII) has one *cis*- and one *trans*-ring fusion is supported by the much faster formation of the methiodide than occurs with the isomer having both ring fusions *trans*; this is expected from the greater accessibility of the nitrogen lone pair in the isomer having a *cis*-ring fusion. The formation of the higher-melting methiodide from the lower-melting base (VII) is consistent with the melting points of the isomeric methiodides of the 2-methyl- and of the 3-methylquinolzidines recorded by Moynehan, Schofield, Jones, and Katritzky.[11] In both series of salts the isomer having a *cis*-ring fusion and an equatorial methyl group is higher-melting than the isomer having a *trans*-ring fusion and an equatorial methyl group.

The stereochemistry of the perhydro-bases (VII) is being further studied and the possible existence of the isomer having two *cis*-ring fusions investigated. The separation of the isomeric lactams (VI) is also being attempted.

## EXPERIMENTAL

Melting points were determined on a Kofler block.

*6,12-Dihydrodipyrido*[1,2-a:1′,2′-d]*pyrazidiinium Dipicrate* (I; X = picrate).—Treatment of the dibromide [1] (I; X = Br) with aqueous sodium picrate gave the *dipicrate* which crystallised from water as yellow prisms, m. p. 195—196° (decomp.) (Found: C, 45·2; H, 2·5. $C_{24}H_{16}N_8O_{14}$ requires C, 45·0; H, 2·5%).

*12-Oxo-12*H-*dipyrido*[1,2-a:1′,2′-d]*pyrazin-5-ium Bromide* (II; X = Br).—(i) The dipicrate (I; X = picrate) (1 g.) in nitromethane (100 ml.) and 10% palladium–charcoal were boiled under reflux for 4 hr. The catalyst was filtered off and the filtrate concentrated under reduced pressure to half volume. The solution was cooled; the *picrate* (0·3 g., 45%) crystallising. Recrystallisation from water or nitromethane gave golden needles, m. p. 221—223° (decomp.) (Found: C, 50·8; H, 2·6. $C_{18}H_{11}N_5O_8$ requires C, 50·8; H, 2·6%). The *bromide* (II; X = Br) was obtained by passing a solution of the picrate (1 g.) in water (2 l.) through Amberlite I.R.A.-400(Br) and evaporating the eluate under reduced pressure. The brown residue crystallised from methanol–ether as orange prisms, m. p. >350° (0·54 g.; 83%) (Found: C, 51·8; H, 3·2. $C_{12}H_9BrN_2O$ requires C, 52·0; H, 3·3%); $\lambda_{max.}$ in water 2130, 2610, 3080, 3180, and 4580 Å ($\log_{10} \varepsilon$ 4·42, 3·94, 3·07, 3·03, and 4·44).

(ii) Resublimed selenium dioxide (0·193 g.) was added to a solution of the bromide (I; X = Br) (0·4 g.) in glacial acetic acid (32 ml.), and the solution was boiled under reflux for 5 min. Acetone (2 ml.) was added and the solution boiled for a further 5 min. The solution was cooled and selenium filtered off. Addition of ether precipitated the *bromide* which crystallised from methanol as orange prisms (0·16 g., 50%).

*1-2′-Pyridylmethylpyridine-2-carboxylate Betaine* (III).—A solution of the bromide (II; X = Br) (0·5 g.) in water (7 ml.) was passed through Amberlite I.R.A.-400(OH) (20 cm. × 1 cm.). The column was eluted with water (25 ml.), and the eluate evaporated to dryness. The *betaine* crystallised from methylene chloride as off-white prisms, m. p. 145—146° (decomp.) (Found: C, 66·9; H, 4·7; N, 13·9. $C_{12}H_{10}N_2O_2$ requires C, 67·3; H, 4·7; N, 13·1%); $\lambda_{max.}$ in 0·1N-sodium hydroxide 2620, 2680, and 2750—2800sh Å ($\log_{10} \varepsilon$ 3·8, 3·83, and 3·75); $\lambda_{max.}$ in 0·1N-hydrochloric acid 2620 Å ($\log_{10} \varepsilon$ 4·0).

*1-2′-Pyridylmethylpyridinium Bromide Hydrobromide* (*as* V; X = Br).—(i) Resublimed selenium dioxide (0·193 g.) was added to a solution of the bromide (I; X = Br) (0·4 g.) in glacial acetic acid (32 ml.). The solution was boiled under reflux for 16 hr. and then cooled and selenium filtered off. Evaporation of the filtrate gave a black residue which crystallised from alcohol–di-isopropyl ether as a brown solid, m. p. 200—203° (0·125 g., 31%). Recrystallisation from alcohol gave the *bromide hydrobromide* as buff prisms, m. p. 204—206° (Found: C, 37·7; H, 4·1; N, 8·1. $C_{11}H_{11}BrN_2,HBr,H_2O$ requires C, 37·7; H, 4·0; N, 8·0%).

(ii) A solution of phosphorus tribromide (1·65 g.) in dry benzene (125 ml.) was added to a solution of 2-pyridylmethanol (2 g.) and dry pyridine (20 g.) in dry benzene (125 ml.). A white solid separated and the suspension was boiled under reflux for 24 hr.; then cooled and benzene decanted. The residue was washed with ether and then dissolved in 50% hydrobromic acid–acetic acid. Addition of ether and trituration with alcohol gave a solid,

[11] Moynehan, Schofield, Jones, and Katritzky, *J.*, 1962, 2637.

recrystallisation of which from alcohol gave the *bromide hydrobromide* (3·84 g., 60%) as buff prisms, m. p. 204—206° (Found: C, 38·1; H, 4·1%).

The bromide [4] was obtained by passing an aqueous solution of the bromide hydrobromide through Amberlite IR-4B (OH). Evaporation of the eluate and drying of the residue *in vacuo* gave a hygroscopic solid, m. p. 128—129°. The *monopicrate* obtained by the addition of aqueous sodium picrate to the bromide, crystallised from alcohol as yellow needles, m. p. 125—126° (Found: C, 50·6; H, 3·3; N, 17·0. $C_{17}H_{13}N_5O_7$ requires C, 51·1; H, 3·3; N, 17·5%).

The dipicrate obtained by the addition of alcoholic picric acid to the bromide, crystallised from alcohol as yellow needles, m. p. 172° (lit., m. p. 158°,[4] 168—169° [5]) (Found: C, 43·5; H, 2·4. Calc. for $C_{17}H_{13}N_5O_7,C_6H_3N_3O_7$: C, 43·9; H, 2·6; N, 17·8%). The same dipicrate, m. p. and mixed m. p. 172° (Found: C, 43·7; H, 2·7; N, 17·3%) was obtained by action of alcoholic picric acid on the betaine (III).

*Perhydro*-6-*oxodipyrido*[1,2-a:1′,2′-d]*pyrazine* (VI).—(i) A solution of the bromide (II; X = Br) (0·5 g.) in methanol (50 ml.) was hydrogenated to completion over Adams catalyst at atmospheric temperature and pressure; the hydrogen uptake was 240 ml. (6 double bonds require 243 ml.). The catalyst was filtered off, the solvent evaporated, and the residue made alkaline with aqueous sodium hydroxide. An ethereal extract of the alkaline solution was dried ($Na_2SO_4$) and distilled, giving the *lactam*, b. p. 145—155°/7·5 mm. (bath temp.) (0·25 g., 67%) (Found: C, 69·6; H, 10·15; N, 13·1. $C_{12}H_{20}N_2O$ requires C, 69·2; H, 9·7; N, 13·45%). The *monomethiodide* crystallised from methylated spirits as prisms, m. p. 149—152° (Found: C, 44·7; H, 6·8; N, 8·0. $C_{13}H_{23}IN_2O$ requires C, 44·6; H, 6·6; N, 8·0%). The *monomethopicrate* crystallised as yellow needles, m. p. 190—191° (Found: C, 50·55; H, 5·5; N, 15·7. $C_{19}H_{25}N_5O_8$ requires C, 50·55; H, 5·6; N, 15·5%).

(ii) A solution of the betaine (III) (0·25 g.) in water (50 ml.) was hydrogenated to completion over Adams catalyst at atmospheric temperature and pressure; the hydrogen uptake was 177 ml. (6 double bonds require 176 ml.). The catalyst was filtered off and the filtrate evaporated. The residue had b. p. 126—128°/0·5 mm. (bath temp.) (Found: C, 69·5; H, 9·4; N, 13·0%). The i.r. spectrum of the lactam was identical with that of the sample obtained as in (i).

cis,trans-*Perhydrodipyrido*[1,2-a:1′,2′-d]*pyrazine* (VII).—The saturated lactam (VI) (0·54 g.) in dry ether (30 ml.) was added slowly to a stirred solution of lithium aluminium hydride (1 g.) in dry ether (30 ml.), and the resulting solution boiled under reflux for 2 hr. The mixture was set aside overnight and the excess of hydride then decomposed with water. The ether layer was separated and dried, and the ether evaporated. The base had b. p. 125—130°/3 mm. (bath temp.) and distilled material, m. p. 41—42° (Found: C, 74·4; H, 11·0; N, 14·5. Calc. for $C_{12}H_{22}N_2$: C, 74·2; H, 11·4; N, 14·4%). Crystallisation of the base from acetone raised the m. p. to 52°. The *monomethiodide* crystallised from methylated spirits as needles, m. p. 315—316° (decomp.) [lit. m. p. 171—172°,[9] 310° (decomp.) [10] (Found: C, 46·5; H, 7·5; N, 8·2. $C_{13}H_{25}IN_2$ requires C, 46·4; H, 7·5; N, 8·3%).

trans,trans-*Perhydrodipyrido*[1,2-a:1′,2′-d]*pyrazine* (VII).—The dibromide (I; X = Br) was hydrogenated to completion at atmospheric pressure.[1,2] Recrystallisation of the base (VII) from acetone gave plates, m. p. 95—96° (lit., m. p. 81°,[1] 92—95°,[2] 95—96° [9]) (Found: C, 74·4; H, 11·3; N, 13·8. Calc. for $C_{12}H_{22}N_2$: C, 74·2; H, 11·4; N, 14·4%).

The *monomethiodide* crystallised from methylated spirits as needles, m. p. 268° (decomp.) (lit.,[9] m. p. 209—210°) (Found: C, 46·4; H, 7·3; N, 8·2. $C_{13}H_{25}IN_2$ requires C, 46·4; H, 7·5; N, 8·3%).

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