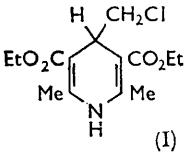
321. *The Nitrous Acid Rearrangement of a 4-Cyano-4,5-dihydroazepine.*

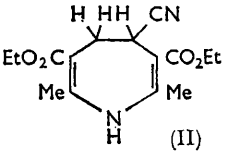
By E. Bullock, B. Gregory, and A. W. Johnson.

The claim that the action of nitrous acid on the 4-cyano-4,5-dihydroazepine (II) yields a derivative of 4-azatropone is shown to be incorrect and the product is now formulated as a derivative (IV; R = CO_2Et) of furo[2,3-*b*]pyridine. The same rearrangement is caused by the action of silver nitrate, except that the product is accompanied by some of the 1,7-diazaindene (VII). Some properties and reactions of the products are described.

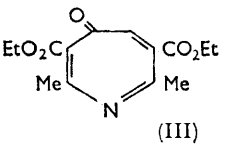
In a recent Paper,[1] we described the ring expansion of the 4-chloromethyl-1,4-dihydro-2,6-lutidine (I) to the 4,5-dihydro-azepine (II) caused by the action of potassium cyanide. In an attempted dehydrogenation, the azepine (II) was treated with sodium nitrite in glacial acetic acid and yielded a solid, m. p. 119—120°, which originally [2] we regarded as a derivative (III) of 4-azatropone. This structure has now been proved to be incorrect and in the present Paper it will be shown that the product obtained from the action of nitrous acid on (II) is the furo[2,3-*b*]pyridine (IV; R = CO_2Et).



(I)



(II)



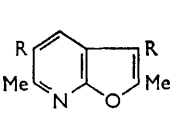
(III)

The molecular formula, $C_{14}H_{17}NO_5$, previously quoted for the nitrous acid product should therefore be amended to $C_{15}H_{17}NO_5$, and it will be apparent that the main evidence in favour of (III) derived from the interpretation of the nuclear magnetic resonance spectrum, applies equally well to structure (IV; R = CO_2Et). The spectrum of the product (chloroform–trifluoroacetic acid) contained two ethyl (ester) groups [triplets at τ 8·51 and 8·52 (J = 7·2 c./sec.) and a quartet at τ 5·52 (J = 7·2 c./sec.)], two methyl groups (τ 7·04 and 7·14) and one other single proton (τ 1·25). These signals were all shifted to low field relative to the spectrum of (II), and in particular the position of absorption of the single proton suggested a ring current and hence aromaticity [3] of the product. It has also been found that a low yield of compound (IV; R = CO_2Et) can be produced directly from (I) by the prolonged action of aqueous ethanolic potassium cyanide. The diester failed to form a picrate although it was soluble in cold concentrated sulphuric acid and could be recovered unchanged from the solution by cautious basification. Reaction of the ester (IV; R = CO_2Et) with hydrazine yielded a monohydrazide. The nuclear methyl groups were resistant to oxidation and the ester was recovered unchanged after treatment with permanganate in aqueous pyridine or with selenium dioxide in aqueous dioxan under reflux conditions. Alkaline hydrolysis of the ester (IV; R = CO_2Et) gave a dicarboxylic acid which could be decarboxylated with copper bronze at 320° and gave a good yield of a liquid, formerly believed to be 2,7-dimethyl-4-azatropone (III; H for CO_2Et), C_8H_9NO but now amended to C_9H_9NO and formulated as 2,6-dimethylfuro[2,3-*b*]pyridine (IV; R = H). We have experienced difficulty in obtaining consistent analytical figures for these furopyridine derivatives. Like the parent diester, (IV; R = H) showed no NH stretching band in the infrared spectrum and the strong band at 1613 cm.$^{-1}$,

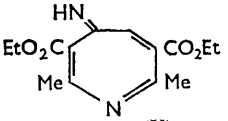
[1] Brignell, Bullock, Eisner, Gregory, Johnson, and Williams, *Proc. Chem. Soc.*, 1962, 122; *J.*, 1963, 4819.
[2] Bullock, Gregory, and Johnson, *J. Amer. Chem. Soc.*, 1962, **84**, 2260.
[3] Pople, *J. Chem. Phys.*, 1956, **24**, 1111.

originally attributed to " carbonyl " frequency (cf. ref. 4) is probably associated with the Δ^2-double bond of (IV; R = H) although it may be a ring vibration. The nuclear magnetic resonance spectrum formally interpreted on the basis of structure (III; H for CO_2Et), can equally well be interpreted on the basis of structure (IV; R = H). It showed the presence of two methyl groups (τ 7·41, 7·53) and three other protons [2·36, 3·02 (doublet, J = 7·9 c./sec.), and τ 3·69]. The signal at τ 3·69 was a close quartet (J = 0·8 c./sec.) due to interaction of the proton with the higher field methyl group (a doublet, J = 0·8 c./sec.). The furopyridine (IV; R = H) gave a styphnate and an unstable picrate.

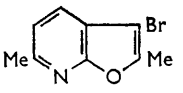
The best yield of the ester (IV; R = CO_2Et) from the dihydroazepine (II) has been obtained by the action of hot aqueous ethanolic silver nitrate. The main product (53%) was (IV; R = CO_2Et) but a minor product was shown to contain an imino-group in place of one oxygen atom in (IV; R = CO_2Et). This compound was originally believed to be the 4-azaiminotropone (V) but it could not be hydrolysed to the ester (III) by the action of acid. This observation, together with new analytical data, led us to abandon the azatropone (III) and (V) formulations. Furthermore, treatment of the lutidine (I) with ^{14}C-labelled potassium cyanide gave labelled nitrile (II) which was reacted with silver nitrate to give ester (IV; R = CO_2Et) and the by-product mentioned above, both of which retained more than 85% of the original radioactivity, showing that the cyanide carbon had not been eliminated. Bromination of the furo[2,3-*b*]pyridine (IV; R = H) gave a monobromo-derivative (VI) in which the bromine was very stable; for example, it could not be hydrolysed by hydrogen bromide in acetic acid at 160° for 6 hours or by aqueous formic acid at 100° for 40 hours. Furthermore, the bromine could not be replaced in the Finkelstein reaction or by the action of silver acetate in acetic acid at 100° for 4 days and the bromo-compound was recovered unchanged after reaction with methanolic ammonia at 100—115° for 6 hours. Substitution reactions carried out under these conditions are well recognised in the bromotropone series.[5–7]



(IV)



(V)



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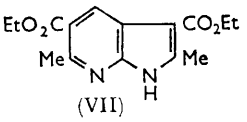


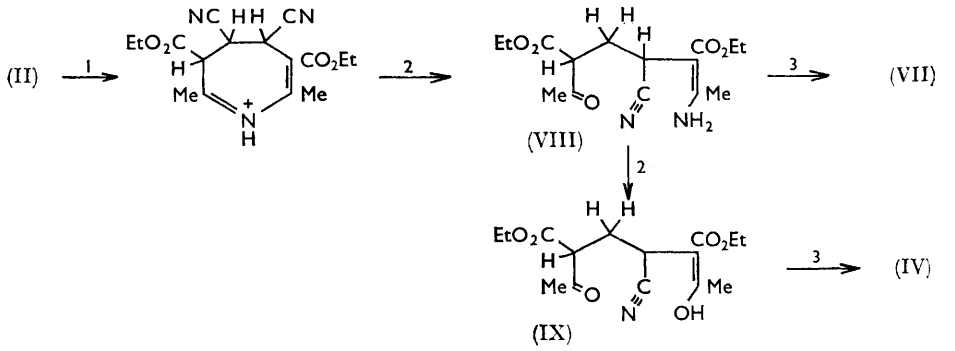
(VII)

On the new formulation, the minor product of the silver nitrate reaction is the pyrrolo-[2,3-*b*]pyridine or 1,7-diazaindene (VII), which would not be expected to be converted into the furopyridine (IV; R = CO_2Et) under hydrolytic conditions. 1,7-Diazaindene itself occurs in coal tar,[8] but several good methods are available for the synthesis of its derivatives.[9] On the other hand the furo[2,3-*b*]pyridines are not well known [10] although the furo[2,3-*b*]quinoline system is contained in a well-known group of alkaloids.[11]

The rearrangement of (II) to (IV) clearly involves a number of steps. A possible interpretation of the action of nitrous acid on (II) is an initial protonation of the vinylamine system, followed by hydrolysis to the acyclic intermediate (VIII), which could be converted into (IX) by acid. A double cyclisation and oxidation then leads to the furopyridine. When silver nitrate is substituted for nitrous acid the tendency to hydrolyse

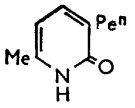
[4] Proctor, *Chem. and Ind.*, 1960, 408.
[5] Doering and Mayer, *J. Amer. Chem. Soc.*, 1953, **75**, 2387.
[6] Ter Borg, van Helden, and Bickel, *Rec. Trav. chim.*, 1962, **81**, 177.
[7] Seto, *Sci. Rep. Tôhoku Univ.*, 1953, **37**, 275.
[8] Kruber, *Chem. Ber.*, 1943, **76**, 130.
[9] *E.g.*, Koenigs and Fulde, *Ber.*, 1927, **60**, 2106; Clemo and Swan, *J.*, 1945, 603; Robison and Robison, *J. Amer. Chem. Soc.*, 1955, **77**, 457, and later papers.
[10] *E.g.*, Robinson and Watt, *J.*, 1934, 1536.
[11] Openshaw, " The Alkaloids," Ed. Manske, Academic Press, New York and London, 1960, vol. 7, p. 233.

the acylic vinylamine (VIII) before cyclisation is apparently reduced and some of the pyrrolopyridine is obtained.



Reagents: 1, H^+; 2, H_2O; 3, $-H_2O$, O_2.

Further support for the existence of the furo[2,3-*b*]pyridine system in the rearrangement product (IV) came from studies of its ozonolysis and hydrogenolysis. When 2,6-dimethylfuropyridine (IV; R = H) was hydrogenated in the presence of platinum, two equivalents of hydrogen were absorbed and a crystalline product, $C_9H_{13}NO$, was obtained. This was formulated as 6-methyl-3-n-propyl-2-pyridone (XI) on the basis of the similarity of its spectra with those of the known 3-ethyl-6-methyl-2-pyridone.[12] Hydrogenolysis of the furan rings of furoquinoline alkaloids have been reported several times.[13]



(XI)

Experimental

Ultraviolet spectra were determined on ethanolic solutions and infrared spectra were measured for chloroform solutions (except where otherwise stated). Most of the nuclear magnetic resonance spectra were measured on an AEI RS2 instrument operating at 60 Mc./sec.

Diethyl 2,6-Dimethylfuro[2,3-b]*pyridine-3,5-dicarboxylate.*—(i) Sodium nitrite (0·48 g.) was added in small portions to a solution of diethyl 4-cyano-4,5-dihydro-2,7-dimethylazepine-3,6-dicarboxylate [1] (II; 2 g.) in glacial acetic acid (9 c.c.). The mixture was kept for 1½ hr., and then neutralised with saturated aqueous sodium carbonate solution, and the aqueous layer decanted from the brown gum which was washed with water and dissolved in benzene–chloroform (1 : 1) and dried. The products of 13 such experiments were combined and chromatographed on alumina (Spence type H), more benzene–chloroform being used for elution. The first pale yellow fraction was collected and, after removal of the solvent, the oily residue slowly crystallised. Crystallisation from aqueous ethanol gave the *product* as hair-like needles (2 g.; 8%), m. p. 119—120°, which could be sublimed at 80—90°/0·1 mm. [Found: C, 61·6, 61·7; H, 5·9, 5·9; N, 4·7, 4·9%; *M* (Rast), 294. $C_{15}H_{17}NO_5$ requires C, 61·85; H, 5·9; N, 4·8%; *M*, 291]; $\lambda_{max.}$ 219 and 296 mμ (ε 37,200 and 9800), shoulder at 249 mμ (ε 11,900); $\nu_{max.}$ 1620 (C=C) and 1720 (ester carbonyl) cm.$^{-1}$.

(ii) Diethyl 4-chloromethyl-1,4-dihydro-2,6-dimethylpyridine-2,5-dicarboxylate [1] (I; 1 g.) was dissolved in hot ethanol (50 c.c.) and then cooled. Potassium cyanide (0·1 g.) and water (10 c.c.) was then added and the mixture shaken for 6 days. The solution was then evaporated *in vacuo*, and the residual gum was crystallised from ethanol and then sublimed at 80—90°/0·1 mm. The sublimate had m. p. 115—119°, not depressed on admixture with the sample from the previous experiment. The infrared absorption was also identical with that of the preceding product.

[12] Tschitschibabin and Widonowa, *J. Russ. Phys. Chem. Ges.*, 1921, **54**, 402 (*Chem. Zentr.*, 1923, III, 1025).

[13] Ohta and Miyazaki, *Pharm. Bull.* (*Japan*), 1953, **1**, 184; Gell, Hughes, and Ritchie, *Austral. J. Chem.*, 1955, **8**, 114, 422; Cooke and Haynes, *ibid.*, 1954, **7**, 273.

(iii) Diethyl 4-cyano-4,5-dihydro-2,7-dimethylazepine-3,6-dicarboxylate (20 g.; 1 mol.) in ethanol (400 c.c.) was mixed with a solution of silver nitrate (12 g.; 1·03 mol.) in water (200 c.c.), and the solution heated under reflux on the water-bath. After 45 min. a silver mirror had formed on the flask; after 1½ hr. the mirror started to break up and 30 min. later the solution was clear and the silver formed a residue at the bottom of the flask. The residue was separated, and on cooling needles separated from the filtrate. These were separated and dried, and the product (12·1 g.) dissolved in benzene–chloroform (1 : 1) and chromatographed on alumina (Spence type H). Two fractions were thus obtained and the solvent was evaporated from each and the residues crystallised to constant m. p. from aqueous ethanol. The first fraction gave diethyl 2,6-dimethylfuro[2,3-*b*]pyridine-3,5-dicarboxylate (10·7 g.; 53%), m. p. 119—120°, which was identical in all respects with the material prepared by the above methods. The second fraction gave *diethyl 2,6-dimethylpyrrolo*[2,3-*b*]*pyridine-3,5-dicarboxylate* (1·4 g.; 7%) as hair-like crystals, m. p. 211—211·5° [Found: C, 62·1; H, 6·1; N, 9·9%; *M* (thermistor drop; $CHCl_3$), 310. $C_{15}H_{18}N_2O_4$ requires C, 62·05; H, 6·25; N, 9·65%; *M*, 290]; $\lambda_{max.}$ 235 and 299 mμ (ε 40,000 and 7700), $\lambda_{infl.}$ 253 mμ (ε 18,200); in ethanol acidified with 0·01N-hydrochloric acid, $\lambda_{max.}$ 235 and 301 mμ (ε 34,500 and 8700), $\lambda_{infl.}$ 253 mμ (ε 20,500); in ethanol basified with 0·01N-sodium hydroxide, $\lambda_{max.}$ 241, 248, 274, and 311 mμ (ε 26,100, 26,100, 23,300, and 9800, respectively); $\nu_{max.}$ 1620 (C=C), 1704 (ester carbonyl), and 3443 (NH) cm.$^{-1}$. The nuclear magnetic resonance spectrum determined in chloroform–trifluoroacetic acid showed a singlet at τ 0·82 (aromatic proton), two singlets at τ 6·96 and 7·17 (two methyl groups), a triplet at τ 8·53 (J = 7·7 c./sec.), and a quartet at τ 5·55 (J = 7·7 c./sec.) associated with the ethyl groups of the esters.

(iv) Potassium [^{14}C]cyanide (15·1 mg.; 0·1 mc.) was dissolved in dimethyl sulphoxide (30 c.c.). A mixture of diethyl 4-chloromethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (3 g.) and unlabelled potassium cyanide (1·28 g.) was added to the solution, and the suspension stirred at room temperature for 24 hr. Addition of water yielded plates of diethyl 4-cyano-4,5-dihydro-2,7-dimethylazepine-3,6-dicarboxylate (2·3 g.), m. p. 107—108·5°, which was crystallised from aqueous ethanol to constant count. A solution of the cyano-compound (2·1 g.) in ethanol (42 c.c.) was mixed with a solution of silver nitrate (1·26 g.) in water (21 c.c.), and the mixture heated under reflux for 2 hr. The precipitated silver was separated and the filtrate treated as in the previous experiment to yield the furopyridine (1·1 g.), m. p. 118·5—119°, and the pyrrolopyridine (0·15 g.), m. p. 211·5—212°. The counts (c.p.m./mg.) obtained were: cyano-compound (mean of 5), 614; furopyridine (mean of 6), 532; pyrrolopyridine (mean of 5), 527.

Reaction of Diethyl 2,6-Dimethylfuro[2,3-b]*pyridine-3,5-dicarboxylate with Hydrazine.*—The ester (1 g.) in ethanol (5 c.c.) was treated with hydrazine hydrate (99%; 2·5 c.c.) and warmed on the water-bath for 10 min., a solid then began to separate. The product was kept overnight in the refrigerator and the needles (0·986 g.), m. p. 300·5—305°, of the *monohydrazide* were separated and washed (Found: C, 56·4; H, 5·3; N, 15·2. $C_{13}H_{15}N_3O_4$ requires C, 56·3; H, 5·45; N, 15·15%); $\nu_{max.}$ 1635 (hydrazide carbonyl), 1715 (ester carbonyl), and 3390 (NH) cm.$^{-1}$.

2,6-Dimethylfuro[2,3-b]*pyridine-3,5-dicarboxylic Acid.*—The diethyl ester (536 mg.) was added to a solution of potassium hydroxide (536 mg.) in water (12 c.c.), and the suspension heated on the water-bath. Ethanol was added dropwise until a clear solution was obtained which was then heated on the water-bath for 4½ hr. The solution was cooled and extracted with ether and the aqueous layer was acidified with 5N-hydrochloric acid. The precipitated *acid* (429 mg.) was separated and dried; it had m. p. >350°. It was sparingly soluble in water and most organic solvents but crystallised from aqueous acetic acid as needles. It could be sublimed at 160—190°/0·1 mm. (Found: C, 56·2; H, 3·85; N, 5·8. $C_{11}H_9NO_5$ requires C, 56·2; H, 3·85; N, 5·95%); $\lambda_{max.}$ 218 and 293 mμ (ε 30,100 and 7200), $\lambda_{infl.}$ 249 mμ (ε 7700); $\nu_{max.}$ 1622, 1654, 1680, 1699, and 1722 cm.$^{-1}$.

2,6-Dimethylfuro[2,3-b]*pyridine.*—The foregoing acid (500 mg.) and copper bronze (5 g.) were well mixed and then heated at 350° *in vacuo* in a bulb tube. The *furopyridine* was distilled, the oil was dissolved in ether, the solution dried, and the solvent removed to give the product (232 mg.) which was purified by repeated distillation, b. p. 114—115°/13 mm.; n_D^{22} 1·5550 (Found: C, 73·6; H, 6·25; N, 9·5. C_9H_9NO requires C, 73·45; H, 6·15; N, 9·5%); $\lambda_{max.}$ 217, 250, and 290 mμ (ε 15,000, 7000, and 9550), $\lambda_{infl.}$ 257 mμ (ε 6450); $\nu_{max.}$ 837, 927, 963, 997, 1023, 1054, 1097, 1124, 1144, 1165, 1274, 1300, 1338, 1405, 1452, 1473, 1596, 1614, 1652, 1724, 1759, 1909, 2740, 2752, 2862, 2881, 2932, 3120, and 3329 cm.$^{-1}$. The picrate, m. p. 128°

(decomp.), was unstable but the *styphnate*, m. p. 143—146°, formed yellow plates (Found: C, 45·8; H, 3·3; N, 14·0. $C_{15}H_{12}N_4O_9$ requires C, 45·9; H, 3·1; N, 14·3%).

Bromination of 2,6-Dimethylfuro[2,3-b]*pyridine.*—A solution of bromine (1·1 g.) in carbon tetrachloride (15 c.c.) was added to a solution of the furopyridine (232 mg.) in carbon tetrachloride (10 c.c.) at room temperature. After 14 hr., the mixture was evaporated at room temperature leaving an unstable red solid which lost hydrogen bromide. The solid was boiled with acetone to remove excess of bromine, the acetone removed at room temperature *in vacuo*, and the hydrobromide, m. p. >350°, washed with ether. The salt was dissolved in 10% ammonium hydroxide, and the free base extracted into ether. The ethereal extract was washed once with water, dried, and evaporated; the pale yellow oil (258 mg.; 72%) soon partially crystallised. It was purified by repeated sublimation at 60—70°/0·1 mm., an external copper tube being used over the glass tube to produce an extended temperature gradient. A small quantity of unchanged 2,6-dimethylfuro[2,3-*b*]pyridine was obtained as an oil, but the main product formed granular crystals (152 mg.; 42%), m. p. 82—83° [Found: C, 47·6; H, 3·5; N, 5·75; Br, 34·6%; *M* (Rast), 219, C_9H_8BrNO requires C, 47·8; H, 3·6; N, 6·2; Br, 35·35%; *M*, 226]; $\lambda_{max.}$ 221, 261, and 288 mμ (ε 15,750, 5410, and 10,180), $\lambda_{infl.}$ 254 mμ (ε 5270); $\nu_{max.}$ 902, 934, 979, 1017, 1053, 1121, 1164, 1271, 1293, 1336, 1389, 1446, 1471, 1596, 1608, 2927, and 3380 cm.$^{-1}$.

6-*Methyl*-3-*n*-*propyl*-2-*pyridone.*—2,6-Dimethylfuro[2,3-*b*]pyridine (492 mg.) was dissolved in ethanol (30 c.c.) and hydrogenated in presence of Adams' platinum catalyst (80 mg.) at room temperature for 2 days. After the absorption of 2·03 mol. of hydrogen, the hydrogenation was discontinued, the catalyst removed, and the solvent evaporated to give an oil which rapidly crystallised. It was purified by repeated sublimation at 70°/0·01 mm. and the product was thus obtained as needles, m. p. 80·5—81·5° (Found: C, 71·2; H, 8·6; N, 9·6. $C_9H_{13}NO$ requires C, 71·5; H, 8·7; N, 9·25%); $\lambda_{max.}$ 233 and 307 mμ (ε 6800 and 8340); $\nu_{max.}$ 893, 947, 975, 1093, 1125, 1166, 1284, 1388, 1399, 1435, 1473, 1556, 1579, 1622, 1632, 1644, 2874, 2936, 2966, 3129, 3198, 3278, and 3387 cm.$^{-1}$; n.m.r. spectrum ($CHCl_3$ solution), two doublets at τ 2·92 and 4·12 (J = 7·0 c./sec.) (aromatic nuclear protons), a distorted triplet at τ 7·42 (J = 6·5 c./sec.) (α-CH_2 of n-propyl side-chain), a singlet at τ 7·64 (the 6-methyl group), a multiplet (8 lines) at approx. τ 8·36 (J ~7·0 c./sec.) (β-CH_2 of n-propyl side-chain), and a triplet at τ 9·03 (J = 7·0 c./sec.) (CH_3 of n-propyl side-chain).

The molecular weight, determined either by the thermistor drop or Rast method gave high values, probably due to intermolecular hydrogen bonding.

A sample of 3-ethyl-6-methyl-2-pyridone,[12] prepared for comparison purposes, had m. p. 102—103° (lit.,[12] 100—101°); $\lambda_{max.}$ 232·5 and 306 mμ (ε 6670 and 7920); $\nu_{max.}$ 949, 980, 1024, 1095, 1125, 1159, 1326, 1349, 1370, 1388, 1401, 1464, 1476, 1559, 1580, 1622, 1624, 1645, 2612, 2759, 2878, 2939, 3127, 3189, 3280, and 3387 cm.$^{-1}$; n.m.r. spectrum ($CHCl_3$ solution), two doublets at τ 2·86 and 4·03 (J = 6·8 c./sec.) (aromatic nuclear protons), a quartet at τ 7·46 (J = 7·5 c./sec.) (CH_2 of ethyl side-chain), a singlet at τ 7·6 (the 6-methyl group), and a triplet at τ 8·8 (J = 7·5 c./sec.) (CH_3 of ethyl side-chain).

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