The Alleged Pyridone Tautomer of 2,3-Dihydro-4-methylfuro[2,3-*b*]-pyridin-6-ol

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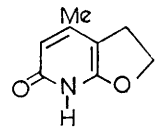
The alleged isolable pyridone tautomer of the title compound is shown to be 4-methylpyridine-3-spirocyclopropane-2(3*H*),6(1*H*)-dione.

In connection with a study of the tautomerism of isoquinolin-3-ols we prepared 4-methyldihydrofuro[2,3-*b*]-pyridin-6-ol, which, like isoquinolin-3-ol exists predominantly in the pyridinol form in non-polar solvents but as a mixture of tautomers [(I) ⇌ (II)] in ethanol.

Stevens and his co-workers [1] obtained a mixture of two isomeric compounds by treatment of the glutaconimide (III) or the cyanopyridone (IV) with hydrochloric acid. They regarded the isomers as the isolable pyridone (I) and pyridinol (II) tautomers, and their claim has been favourably reviewed.[2,3] The claim could not be substantiated by Ritchie,[4] who obtained only one isomer, which he and others [5] have shown is tautomeric [(I) ⇌ (II)] in ethanol solution. The structure of the second isomer obtained by Stevens has remained unknown.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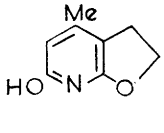
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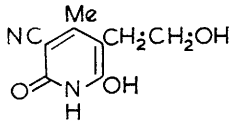
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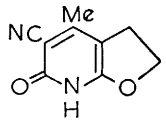
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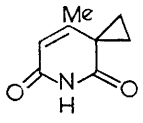
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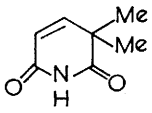
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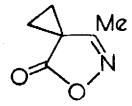
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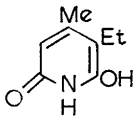
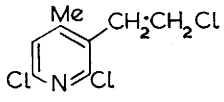

(VIII)


(IX)


(X)

We find that the pyridone [(I) ⇌ (II)] is accompanied by an isomer when the glutaconimide (III) or its ammonium salt is treated with hydrochloric acid and the reaction is worked up by addition of ammonia.

The second isomer has properties similar to those originally assigned to the pyridone tautomer (I).[1] It is readily soluble in hot ethyl acetate, gives no ferric reaction, and shows $\lambda_{max.}$ 252 mμ (log ε 4·07). We assign the constitution (V) to this compound in view of the following evidence. Analysis and molecular weight determination (mass spectrum) establish the molecular formula $C_8H_9NO_2$. The i.r. spectrum shows N–H (3100 and 3200 cm.$^{-1}$) and carbonyl absorption (1680 and 1700 cm.$^{-1}$) similar to the bands shown by compound (VI). The spirocyclopropane (V) absorbs at longer wavelength ($\lambda_{max.}$ 252 mμ) than the model compound (VI) ($\lambda_{max.}$ 230 mμ). This agrees with the ability of a cyclopropane ring to extend a conjugated system.[6] The n.m.r. spectrum ($CDCl_3$) shows a broad band (1H) at τ 0·5 (imide) a quartet (1H, *J* 1 c./sec.) at τ 3·85 (olefinic H allylically coupled to Me), and overlapping signals at τ 8·2 consisting of a doublet (3H, *J* 1 c./sec.) and a typical AA'BB' pattern. Although at lower field than is normally associated with protons of the cyclopropane ring the AA'BB' system corresponds to that measured for the similar spirocyclopropane (VII) in both position [τ (CCl_4) 8·2] and appearance.[7] In trifluoroacetic acid the high-field signals are clearly resolved into a doublet (3H, *J* 1 c./sec.) at τ 8·0 and an AA'BB' system (τ 7·95—7·6).

The chemical properties of (V) agree with the assigned structure. Reaction with diazomethane gives an *N*-methyl derivative, and hydrogenation over platinum the hydroxy-pyridone (VIII).

Reaction of (V) with phosphoryl chloride at 180° affords the trichloro-compound (IX). Originally cited as evidence for the constitution (I) [1] this reaction is equally compatible with the revised structure (V). Opening of the cyclopropane ring of (V) followed by replacement of the ring-bound oxygen atoms by chlorine would give (IX).

Solution of (V) in concentrated hydrochloric acid followed by dilution with water gives the chloro-compound (X; R = H), which is also obtained by reaction of the furopyridine [(I) ⇌ (II)] with phosphoryl chloride at 145°.[8] Brief reaction of (X; R = H) with ammonium hydroxide regenerates the isomer (V). These changes are conveniently followed spectrophoto-

[1] J. R. Stevens, R. H. Beutel, and E. Chamberlin, *J. Amer. Chem. Soc.*, 1942, **64**, 1093.
[2] H. S. Mosher in 'Heterocyclic Compounds,' ed. R. C. Elderfield, Wiley, New York, 1959, vol. 1, p. 397.
[3] H. Meislich in 'Chemistry of Heterocyclic Compounds,' ed. E. Klingsberg, Interscience, New York, 1962, vol. 14, part 3, p. 624.
[4] M. Ritchie, *Austral. J. Chem.*, 1956, **9**, 244.
[5] E. Spinner and G. B. Yeon, *Tetrahedron Letters*, 1968, 5691, and cited references.
[6] M. J. Jorgenson and T. Leung, *J. Amer. Chem. Soc.*, 1968, **90**, 3769.
[7] H. Wamhoff and F. Korte, *Chem. Ber.*, 1966, **99**, 2962.
[8] M. V. Rubtsov and L. N. Yakhontov, *J. Gen. Chem. U.S.S.R.*, 1955, **25**, 1034.

metrically. An ethanolic solution of the chloro-compound (X; R = H) shows $\lambda_{max.}$ 312 mμ. Addition of ammonium hydroxide shifts $\lambda_{max.}$ to 332 mμ, but this absorption, attributed to the anion of (X; R = H) is rapidly replaced by $\lambda_{max.}$ 252 mμ, characteristic of the cyclopropane (V). The *N*-methyl derivative of (V) undergoes an analogous cycle of reactions involving the chloro-compound (X; R = Me).

Formation of (V) by reaction of glutaconimide (III) with hydrochloric acid involves slow reaction of the furopyridine [(I) ⇌ (II)] with hydrochloric acid to give the chloro-compound (X; R = H), which undergoes ring closure [7] to (V) during alkaline work-up. This interpretation is confirmed by isolation of the chloro-compound (X; R = H) from the reaction of (III) with hydrochloric acid when alkaline work-up is avoided.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. Unless specified, i.r. spectra were determined for Nujol mulls, and u.v. spectra for solutions in ethanol. N.m.r. spectra were taken with a Varian A60 spectrometer, and mass spectral measurements were made with an A.E.I. MS902 instrument at the University of Hull.

Reaction of the Ammonium Salt of 2,6-Dihydroxy-5-hydroxyethyl-4-methylpyridine-3-carbonitrile (III) [4] *with Hydrochloric Acid.*—(a) *With alkaline work-up.* The ammonium salt (320 mg.) and concentrated hydrochloric acid (1·5 ml.) in a sealed tube were heated at 150—160° for 8 hr. The cooled tube was opened (pressure) and the product was diluted with water (1·5 ml.), made slightly alkaline with ammonium hydroxide, and neutralised with acetic acid. After cooling in ice the crystalline product (80 mg.) was filtered off. The n.m.r. spectrum of the product indicated a 1 : 1 mixture of compounds (I) and (V). The crude product was separated into fractions soluble and insoluble in ethyl acetate. Crystallisation of the latter from methanol gave compound (I), m.p. 245—248°, τ (CF_3CO_2H) 3·5 (1H, s), 4·9 (2H, t, *J* 8 c./sec.), 6·65 (2H, t, *J* 8 c./sec.), and 7·6 (3H, s), $\nu_{max.}$ 1600, 1640, 2650, and 3100 cm.$^{-1}$. The mass spectrum included strong molecular ion and *M* − 1 peaks, together with *m/e* 123·0684 (C_7H_9NO), 122·0607 (C_7H_8NO), 94·0659 (C_6H_8N), and 79·0548 (C_6H_7).

After repeated crystallisation from ethyl acetate the ethyl acetate-soluble product had m.p. 175—177° (rapid heating) (Found: C, 63·35; H, 5·85; N, 9·25. Calc. for $C_8H_9NO_2$: C, 63·6; H, 6·0; N, 9·3%). The mass spectrum was almost identical with that recorded for compound (I).

(b) *Without alkaline work-up.* The ammonium salt (660 mg.) and concentrated hydrochloric acid (3 ml.) were heated at 160° for 20 hr. (sealed tube). The product was diluted with hydrochloric acid (3 ml.), concentrated to small bulk under reduced pressure on a water-bath, and filtered. The solid obtained (240 mg.) gave the *chloro-compound* (X; R = H), m.p. 148—150° (from acetone–water) (Found: C, 50·75; H, 5·05; Cl, 18·75. $C_8H_{10}ClNO_2$ requires C, 51·2; H, 5·3; Cl, 18·9%), τ * (CF_3CO_2H) 3·35 (1H, s), 6·2 (2H, t, *J* 6 c./sec.), 6·8 (2H, t, *J* 6 c./sec.), and 7·45 (3H, s), $\nu_{max.}$ 1645, 1615, 2150, and 3450 cm.$^{-1}$, $\lambda_{max.}$ 312 mμ (log ε 3·7).

Reaction of 2,3-Dihydro-4-methylfuro[2,3-b]*pyridine-6-ol* (I) *with Phosphoryl Chloride.*—The title compound (800 mg.) and phosphoryl chloride (2·5 ml.) were heated at 145° for 5 hr. (sealed tube). The product was poured on ice, and the precipitate (820 mg.) was filtered off. Recrystallisation from acetone–water gave the product (550 mg.), m.p. 148—150°, identical (mixed m.p. and i.r. spectrum) with the compound (X; R = H) prepared previously.†

Reaction of the Furopyridine (I) *with Hydrochloric Acid.*—The title compound (100 mg.) in concentrated hydrochloric acid (2 ml.) was heated at 160° for 15 hr. The product was diluted with water (4 ml.), made alkaline with ammonium hydroxide, and neutralised with acetic acid. The resulting solid (50 mg.) was a 1 : 1 mixture of compounds (I) and (V) (i.r. analysis). The ethyl acetate-soluble portion gave 4-methylpyridine-3-spirocyclopropane-2(3*H*),6(1*H*)-dione, m.p. 175—177°, identical with material already described (mixed m.p. and i.r. spectrum).

Reaction of the Spiro-compound (V) *with Hydrochloric Acid.*—The title compound (100 mg.) and concentrated hydrochloric acid (2 ml.) were set aside for 1 hr. Evaporation of the acid under reduced pressure on a water-bath followed by addition of water gave the chloro-compound (X; R = H) (115 mg.), identical (mixed m.p. and i.r. spectrum) with the samples already prepared.

Reduction of (V).—The spirocyclopropane (500 mg.) in glacial acetic acid (50 ml.) was shaken with Adams catalyst (200 mg.) and hydrogen at 4·5 atmos. for 6 hr. The product was filtered off and the solvent was evaporated under reduced pressure on a water-bath. The product gave *3-ethyl-4-methylpyridine-2,6-diol* (280 mg.), m.p. 172—173° (from ethanol), $\lambda_{max.}$ 314 mμ (log ε 3·63), $\nu_{max.}$ 1630, 2550, and 2750 cm.$^{-1}$ (Found: C, 62·65; H, 7·1; N, 9·35. $C_8H_{11}NO_2$ requires C, 62·7; H, 7·2; N, 9·1%), τ (CF_3CO_2H) 3·36 (1H, s), 7·25 (2H, q, *J* 8 c./sec.), 7·5 (3H, s), and 8·8 (3H, t, *J* 8 c./sec.).

Reaction of (V) *with Diazomethane.*—The spirocyclopropane (110 mg.) in methanol (8 ml.) was treated with excess of ethereal diazomethane for 12 hr. at room temperature. The pure product (80 mg.) was isolated by silica chromatography, with benzene–methanol (9 : 1) as eluant. Crystallisation from light petroleum (b.p. 60—80°) afforded the *N-methyl derivative*, m.p. 89—90° (Found: C, 65·2; H, 6·6; N, 8·75. $C_9H_{11}NO_2$ requires C, 65·4; H, 6·7; N, 8·5%), τ ($CDCl_3$) 8·2 (AA′BB′ system, 4H) overlapping 8·25 (3H, d, *J ca.* 1 c./sec.), 6·8 (3H, s), and 3·8br ($W_{\frac{1}{2}}$ 4·5 c./sec., *J ca.* 1 c./sec.), $\lambda_{max.}$ 255 mμ (log ε 3·86).

Reaction of 1,4-Dimethylpyridine-3-spirocyclopropane-2(3H),6(1H)dione with Hydrochloric Acid.—The *N*-methyl derivative (40 mg.) was treated with concentrated hydrochloric acid (2 ml.). The precipitate (41 mg.) which formed rapidly was filtered off after addition of water (5 ml.). Crystallisation from light petroleum (b.p. 60—80°) gave the *chloro-compound* (X; R = Me), m.p. 82—83° (Found for the molecular ions: *m/e* 201·0559 and 203·0533. $C_9H_{12}{}^{35}ClNO_2$ requires 201·0556; $C_9H_{12}{}^{37}ClNO$ requires 203·0537), τ ($CDCl_3$) 6·3 (2H, t, *J* 6·5 c./sec., CH_2Cl) and 7·1 (2H, t, *J* 6·5 c./sec., CH_2 adjacent to ring). Each component of the second triplet is broadened, probably by homoallylic coupling to the *C*-methyl and ring methylene protons. These appear as a broad singlet (3H) at τ 7·95 and a broad signal showing fine splitting (*J ca.* 1 c./sec.) at 6·6; $\nu_{max.}$ 1645 and 2500 cm.$^{-1}$.

* This compound clearly exists in the enol form in trifluoroacetic acid.

† Other workers (ref. 8) give m.p. 133·5—134° for a hydrate of the chloro-compound prepared in a similar manner.

Reaction of the Chloro-compounds (X; R = H) *and* (X; R = Me) *with Ammonium Hydroxide.*—A suspension of the chloro-compound (X; R = H) (60 mg.) in water (1 ml.) was cooled in ice and ammonium hydroxide (*d* 0·88; 2 drops) was added. The solid dissolved but was rapidly replaced by an oil which crystallised when scratched. The product was acidified with glacial acetic acid, and after 30 min. in ice the crystalline precipitate (40 mg.) was filtered off. Recrystallisation from ethyl acetate gave the spirocyclopropane (V), identical with material already prepared (mixed m.p. and i.r. spectrum). The chloro-compound (X; R = Me) was similarly converted into 1,4-dimethylpyridine-3-spirocyclopropane-2(3*H*),6(1*H*)-dione.

Reaction of 3-*Hydroxyethyl*-4-*methylpyridine*-2,6-*diol with Thionyl Chloride.*—The trihydroxy-compound [4] (30 mg.) in ether (2 ml.) was stirred with thionyl chloride (1 ml.) at room temperature for 30 min., and then the mixture was boiled under reflux for 1 hr. Evaporation under reduced pressure and addition of water gave the chloro-compound (X; R = H) (31 mg.).

Reaction of the Chloro-compound (X; R = H) *with Triethylamine.*—A solution of the foregoing chloro-compound (50 mg.) in dry ether (5 ml.) and triethylamine (150 mg.) was boiled under reflux (2 hr.). Extraction with ether, washing, drying, and evaporation gave the crude spirocyclopropane (V), m.p. 168—170° (15 mg.). Crystallisation from ethyl acetate gave pure material, m.p. 174—177°.

Reaction of the Chloro-compound (X; R = H) *with Diazomethane.*—The title compound (100 mg.) in methanol (6 ml.) was cooled in ice and ethereal diazomethane was added dropwise until the yellow colour was not immediately discharged. The crude oily product obtained by evaporation of solvents was crystallised from benzene (× 3), giving an O-*methyl derivative*, m.p. 168—169° (Found: C, 53·9; H, 5·95; N, 7·5. $C_9H_{12}ClNO_2$ requires C, 53·6; H, 5·95; N, 6·9%), τ (CF_3CO_2H) 3·45 (1H, s), 5·9 (3H, s), 6·2 (2H, t, *J* 7 c./sec.), 6·8 (2H, t, *J* 7 c./sec.), and 7·4 (3H, s).

U.v. Spectra of 2,3-*Dihydro*-6-*hydroxy*-4-*methylfuro*[2,3-b]-*pyridine*-5-*carbonitrile.*[4] The poor solubility of this compound (especially in dioxan) renders the ε values only approximate: $\lambda_{max.}$ (EtOH) 305 and 343 mμ (log ε 3·98 and 3·78); $\lambda_{max.}$ (dioxan) 301 and 350 mμ (log ε 4·08 and 2·72).

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