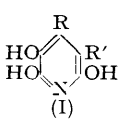
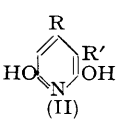
597. *Synthesis of Some Methyl-substituted* 2 : 3 : 6-*Trihydroxypyridines.*

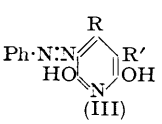
By D. E. Ames, R. E. Bowman, and T. F. Grey.

The dihydroxypyridines (II; R = Me, R′ = H or Me) have been converted, *via* the phenylazo- (III) and diacetylamino-compounds (IV), into the corresponding trihydroxypyridines (I). Methylation of (II) with diazomethane has been investigated, various *O*- and *N*-methyl derivatives being isolated. The infra-red and ultra-violet spectra of these products are discussed.

Two of the six possible trihydroxypyridines have been known for many years but, as far as we are aware, none of the remaining isomers or any corresponding nuclear-alkylated compounds have been described. 2 : 3 : 4-Trihydroxypyridine and analogous alkyl derivatives have been prepared by Ost (*J. pr. Chem.*, 1883, **27**, 257), Lapworth and Collie (*J.*, 1897, **71**, 838) and others; the other known isomer is the 2 : 4 : 6-compound (*inter al.*, Baron, Remfry, and Thorpe, *J.*, 1904, **85**, 1742; Schroeter, Seidler, Sulzbacher, and Kanitz, *Ber.*, 1932, **65**, 432; and Jacini, *Gazzetta*, 1938, **68**, 592). The two methyl-substituted trihydroxypyridines (I; R = Me, R′ = H or Me) have now been synthesised for examination as possible antibacterial agents.


(I)

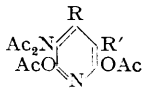

(II)

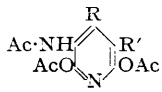

(III)

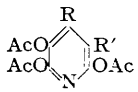
The dihydroxy-base (II; R = Me, R′ = H), prepared from ethyl α-cyano-β-methylglutaconate essentially by the method of Rogerson and Thorpe (*J.*, 1905, **87**, 1685), was coupled with benzenediazonium chloride to give the azo-compound (III; R = Me, R′ = H). Reduction of the latter with zinc–acetic acid–acetic anhydride, followed by prolonged boiling of the insoluble products with acetic anhydride, furnished

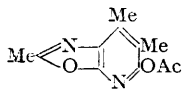
the tetra-acetyl derivative (IV; R = Me, R′ = H); when acetylation was incomplete the triacetyl compound (V; R = Me, R′ = H) could be isolated, though only in poor yield.

When (IV) was hydrolysed with hydrochloric acid, the β-amino-group was replaced by hydroxyl; similar displacement of the β-amino-group in a related dihydroxypyridine derivative was described by Lapworth and Collie (*loc. cit.*). Separation of the rather unstable, amphoteric trihydroxy-base from the ammonium chloride also formed proved


(IV)

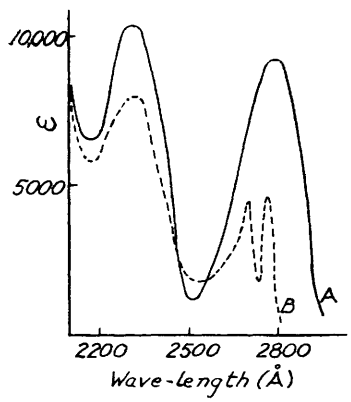

(V)


(VI)


(VII)

difficult and the product was therefore converted into the triacetate (VI; R = Me, R′ = H) which was purified by distillation. Hydrolysis with hydrochloric acid then gave the hydrochloride of (I; R = Me, R′ = H), the hydroxy-base itself being obtained by reaction with one equivalent of diazomethane. This method was used as the compound was susceptible to autoxidation in alkaline solution.

The synthesis of (I; R = R′ = Me) was effected similarly. Acetyl compounds of



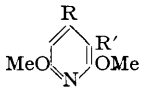
A, 6-*Acetoxy*-4 : 5 : 2′-*trimethyloxazolo*(5′ : 4′-2 : 3)*pyridine*.
B, 2-*Methylbenzoxazole*.

types (IV) and (V) were obtained in this case also and were similarly converted into the hydrochloride (I; R = R′ = Me).

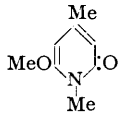
During preliminary experiments on the reductive acetylation of (III), non-crystalline products were encountered, probably owing to incomplete acetylation. When one of these mixtures (from III; R = R′ = Me) or the triacetyl derivative (V; R = R′ = Me) was distilled, a crystalline substance, $C_{11}H_{12}O_3N_2$, m. p. 119—120°, was obtained which gave two mols. of acetic acid on hydrolysis and contained no active hydrogen (Zerewitinov). The infra-red spectrum showed that amide and hydroxyl groups were absent but bands at 1748 (ester C=O) and 1193 cm.$^{-1}$ (C–O) showed the presence of one or more acetoxy-groups. This evidence, together with the mode of formation, suggests that this material is 6-acetoxy-4 : 5 : 2′-trimethyloxazolo(5′ : 4′-2 : 3)pyridine (VII). The ultra-violet absorption curves of this material and of 2-methylbenzoxazole are similar (see Fig.), and the chief differences are in accord with the observations by Badger, Pearce, and Pettit (*J.*, 1951, 3199) that replacement of CH by N in aromatic systems causes a considerable loss of fine structure and increases the intensity of absorption bands at longer wave-lengths. It is shown below that the presence of the methyl and acetoxy-groups in the pyridine ring causes only slight change in the spectrum.

Methylation of the dihydroxypyridines of type (II) was also investigated. Diazomethane and (II; R = Me, R′ = H) gave a mixture from which three products were isolated. The first, m. p. 33—33·5°, was evidently the dimethoxy-compound (VIII; R = Me, R′ = H) as it could be separated by distillation whereas the other two compounds

were much less volatile. A second dimethylation product, m. p. 92°, isolated by fractional crystallisation, must be 6-methoxy-1 : 4-dimethylpyrid-2-one (IX). The third substance was a monomethylation product, presumably (X*a*) or the tautomeric form (X*b*),



(VIII)



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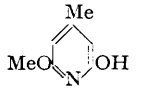
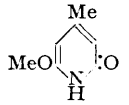
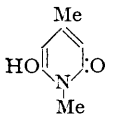


(X*a*)

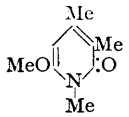


(X*b*)

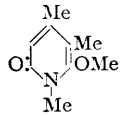
or possibly (XI). The structures assigned to these three compounds accord with the spectroscopic data (see below).



(XI)



(XII)



(XIII)

In the case of (II; R = R′ = Me), no monomethylation product was isolated after treatment with diazomethane; a dimethoxy-compound and an isomer, m. p. 119—120°, were obtained, however, and, in one experiment, a third dimethylation product, m. p. 85—87°. The two isomers had infra-red spectra similar to that of (IX) and they are evidently the two possible methoxy-1-methylpyridones (XII and XIII). Since steric effects would be expected to lead to the formation of (XII) rather than (XIII), the compounds, m. p. 119—120° and 85—87°, are formulated as (XII) and (XIII) respectively, the yield of the latter being very small. Methylation of (II; R = R′ = Me) with methyl sulphate also furnished the dimethoxy-compound and the product, m. p. 119—120°.

Comparison of the ultra-violet absorption spectra (see Table) of the series derived from

	Ethanol		0·1N-HCl		Alkali (pH 8·9)	
	$\lambda_{max.}$ (Å)	ε	$\lambda_{max.}$ (Å)	ε	$\lambda_{max.}$ (Å)	ε
(II; R = Me, R′ = H)	2400	7,600	2085	7,600	2375	8,000
	3220	13,100	2910	6,900	3170	14,600
(II; R = R′ = Me)	2380	6,400	2100 *	9,900	2370	7,700
	3230	7,800	2510	3,900	3250	14,800
			2970	4,000		
(I; R = Me, R′ = H)	2505	9,400	2530	9,900	—	—
(I; R = R′ = Me)	—	—	2550	11,900	—	—
			3050	1,800		
(VIII; R = Me, R′ = H)	2270	7,400	2140	3,300	2215	5,100
	2765	6,600	2890	11,500	2760	6,800
(VIII; R = R′ = Me)	2275	8,200	2230	4,700	2230	6,500
	2810	7,100	2920	7,800	2805	7,000
2 : 6-Diacetoxy-4-methylpyridine	2600	3,600	2590	3,700	—	—
2 : 6-Diacetoxy-3 : 4-dimethylpyridine	2630	4,200	2625	4,100	—	—
2 : 5 : 6-Triacetoxy-4-methylpyridine	2630	3,900	2625	3,800	—	—
	3290	450				
2 : 5 : 6-Triacetoxy-3 : 4-dimethylpyridine	2665	4,700	—	—	—	—
(IV; R = Me, R′ = H)	2640	3,900	2630	4,000	—	—
(IV; R = R′ = Me)	2675	3,800	2675	3,900	—	—
(IX)	2320	5,600	—	—	—	—
	3035	9,100				
(X) or (XI)	2280	6,400	—	—	—	—
	2880	5,400				
	3020	6,800				
(XII)	2330	4,900	2310	3,700	2310	4,500
	3070	9,500	3050	9,900	3060	10,000
1-Methylpyrid-2-one †	2300	6,000	—	—	—	—
	3050	5,000				

* Inflection. † Cunningham, Newbold, Spring, and Stark, *J.*, 1949, 2092.

(II) and (I) shows that introduction of the second methyl group causes a slight bathochromic shift, usually of 30—50 Å, as with toluene and *o*-xylene (Doub and Vandenbelt, *J. Amer. Chem. Soc.*, 1947, **69**, 2714; 1949, **71**, 2414).

The spectra of the acetylation products of (I) and (II) are similar to those of pyridine and the picolines (Daeniker, *Helv. Chim. Acta*, 1952, **35**, 1955); replacement of a hydrogen atom by an acetoxy-group in an aromatic system usually results in only a slight change in the spectrum (see, *e.g.*, Braude, *J.*, 1949, 1906). Closely similar spectra are also shown by the tetra-acetyl derivatives in accordance with the assigned structures (IV); the facility with which the amino-group is diacetylated is rather surprising in view of the highly substituted ring system present. The formation of diacetyl derivatives of various substituted 3-aminopyridines has been reported by Schickh, Binz, and Schulz (*Ber.*, 1936, **69**, 2593), Clemo and Swan (*J.*, 1948, 198), and den Hertog, Kolder, and Combé (*Rec. Trav. chim.*, 1951, **70**, 591). Structures (V) appear to be probable for the corresponding triacetyl compounds but the absorption spectra are complicated by interaction with the solvent (ethanol). This instability seems difficult to explain in comparison with the relatively stable nature of the tetra-acetyl compounds; alternative structures, such as 1-acylpyridones appear to be unlikely, however, because conversion into (IV) can be effected by boiling acetic anhydride. Furthermore, the infra-red spectra provide evidence favouring the structures (V): first, a strong band in the range 1600—1613 cm.$^{-1}$ indicates the presence of a true pyridine ring (see below); and, secondly, intense bands at about 3270 (N–H), 1650 and 1520 cm.$^{-1}$ are characteristic of an amide group.

The dimethoxypyridines (VIII) show the expected ultra-violet light absorption properties (cf. den Hertog, Wibaut, Schepman, and van der Wal, *Rec. Trav. chim.*, 1950, **69**, 700). Since aromatic methoxy- and hydroxy-compounds generally possess very similar absorption spectra (Jones, *J. Amer. Chem. Soc.*, 1945, **67**, 2127; Burawoy and Chamberlain, *J.*, 1952, 2310), the great differences in the case of (II) and (VIII) must indicate that the former exist largely in hydroxypyridone forms as in the case of pyrid-2-one (cf. Mosher, " Heterocyclic Compounds," Vol. I, Ed. Elderfield, Wiley, 1950, p. 436). The spectra of the other methylation products are almost identical with that of 1-methylpyrid-2-one (see Table) in accordance with the assigned structures. This evidence indicates that the monomethylation product exists as (X*b*) rather than (X*a*), though the alternative structure (XI) cannot be excluded.

In contrast with those of dihydroxypyridines, the spectra of the trihydroxypyridines (I) are almost the same in ethanol and in dilute acid (oxidative decomposition occurred in alkaline solution), a situation which may be due to the formation of a zwitterion in both media.

All the compounds of the diacetoxy-, triacetoxy-, and dimethoxy-pyridine series already described and those of types (IV) and (V) show an intense infra-red absorption band in the range 1600—1613 cm.$^{-1}$ corresponding to the ring vibration band at 1597 cm.$^{-1}$ in pyridine itself. In the oxazolopyridine (VII) this band occurs at 1620 cm.$^{-1}$. In the di- and trihydroxypyridines, the phenylazo-compounds of type (III), and the *N*-methylation products, however, this band is either weak, occurs as a side-band, or is absent, thus providing further evidence that these compounds exist mainly in pyridone forms. Additional support for this conclusion is that all these compounds possess strong bands at 1626—1669 and 1506—1558 cm.$^{-1}$, characteristic of amide groups (Randall, Fowler, Fuson, and Dangl, " Infra-red Determination of Organic Structures," Van Nostrand, 1949, p. 20).

All the di- and tri-hydroxypyridines described above have been tested against a range of Gram-positive and Gram-negative organisms by Dr. A. S. Schlingman (Parke, Davis & Co., Detroit). At a concentration of 0·1 mg./c.c. these compounds were inactive with the exception of (I; R = R′ = Me) which partially inhibited the growth of *Neisseria catarrhalis*, *Micrococcus pyogenes* var. *aureus*, *Brucella suis*, and *Salmonella typhosa*.

Experimental

2 : 6-*Dihydroxy*-4-*methylpyridine Hydrochloride*.—Ethyl α-cyano-β-methylglutaconate (63 g.; Rogerson and Thorpe, *J.*, 1905, **87**, 1687) was refluxed with concentrated hydrochloric acid (250 c.c.) for 4 hr. The solution was concentrated and, on cooling, the product crystallised. Recrystallisation from hydrochloric acid (100 c.c.; 5N) furnished needles (27 g.) of 2 : 6-*dihydroxy*-4-*methylpyridine hydrochloride dihydrate*, m. p. 222—224° with dehydration (preheated bath) (Found: C, 38·8; H, 6·4; N, 7·4; Cl, 18·3. $C_6H_8O_2NCl,2H_2O$ requires C, 39·2; H, 6·5;

N, 7·6; Cl, 19·3%). Infra-red spectrum (Nujol mull): max. at 3413, 2688, 1634, 1524, 1344, 1263, 1236, 1171, 1003, 903, and 824 cm.$^{-1}$.

A solution of the hydrochloride (1·0 g.) in water (5 c.c.) was just basified with dilute aqueous ammonia, a deep blue colour rapidly developing. A slight excess of glacial acetic acid was added and the product slowly separated. After 1 hr., the pale blue solid (0·4 g.), m. p. 194—196°, was filtered off (cf. Rogerson and Thorpe, *loc. cit.*, who give m. p. 194°). Recrystallisation from absolute ethanol containing acetic acid gave the pyridine as plates, m. p. 194—196°. Infra-red spectrum (Nujol mull): max. at 1650, 1597, 1539, 1520, 1299, *ca.* 1205 (broad), 1160, and 997 cm.$^{-1}$. Alternatively, aniline (2·5 g.) was added to a solution of the hydrochloride (5·0 g.) in the minimum volume of hot ethanol. After acidification with glacial acetic acid, the solution was cooled and the free base crystallised, (m. p. 191—193°; 3·0 g.). This procedure proved the more convenient, especially for larger-scale experiments, and readily gave a colourless product.

2 : 6-*Diacetoxy*-4-*methylpyridine*.—The foregoing hydrated hydrochloride (20 g.) was refluxed with acetic anhydride (200 c.c.) for 1·5 hr. Distillation of the solution furnished the *diacetate* (18·8 g.), b. p. 120—122°/0·5 mm., n_D^{20} 1·4971, m. p. 62—62·5°. It separated from ether–light petroleum (b. p. 40—60°) in cubes, m. p. 62—62·5° (Found: C, 58·4; H, 5·4; N, 6·7. $C_{10}H_{11}O_4N$ requires C, 57·9; H, 5·3; N, 6·7%). Infra-red spectrum (film of super-cooled liquid): max. at 1770, 1613, 1563, 1433, 1407, 1368, 1319, 1208, 1172, 1144, 1047, 1018, 999, 973, 890, 842, 751, and 730 cm.$^{-1}$.

2 : 6-*Dihydroxy*-4-*methyl*-3-*phenylazopyridine*.—A solution of the foregoing hydrated hydrochloride (15 g.) in water (70 c.c.) was mixed with sodium acetate (70 g.) in water (100 c.c.), then treated with benzenediazonium chloride solution (from aniline, 7 g.). The crude azo-compound was separated, washed with water and methanol, and dried *in vacuo* (yield 17 g., 90%; m. p. 242—246°). The pure *azo*-compound, m. p. 251—252°, was obtained as fine, red needles by recrystallisation from methanol (Found: C, 62·7; H, 5·0; N, 17·9. $C_{12}H_{11}O_2N_3$ requires C, 62·9; H, 4·8; N, 18·3%). Ultra-violet absorption spectrum (in ethanol): max. at 2590, 4130, and 4150 Å (ε 13,700, 34,000, and 33,000 respectively) and inflections at 2550 and 4110 Å (ε 13,200 and 33,700 respectively). Infra-red spectum (Nujol mull): max. at 3356, 1656, 1585, 1515, 1451, 1405, 1256, 1214, 895, 870, 809, and 757 cm.$^{-1}$.

2 : 6-*Diacetoxy*-3-*diacetylamino*-4-*methylpyridine*.—The foregoing azo-compound (13 g.) was added during 50 min. to a stirred mixture of zinc (24 g.), acetic acid (40 c.c.), and acetic anhydride (20 c.c.) at 10—15°; more zinc (6 g.), acetic acid (30 c.c.), and acetic anhydride (30 c.c.) were then added to accelerate the reduction. The mixture was shaken for 30 min. and filtered, the solids being washed with acetic acid (60 c.c.) followed by acetic anhydride (60 c.c.) to remove acetanilide. Extraction of the residue with boiling acetic anhydride (150 c.c.; 3 × 80 c.c.) and evaporation *in vacuo* furnished a gum which crystallised on trituration with ethyl methyl ketone. Repeated recrystallisation from the same solvent gave 2·0 g. of material, m. p. 145—155°.

The combined mother-liquors were evaporated and the residue refluxed for 3 hr. with acetic anhydride (150 c.c.). Evaporation and crystallisation of the residue from light petroleum (b. p. 60—80°)–ethyl methyl ketone (1 : 1) gave rectangular plates of 2 : 6-*diacetoxy*-3-*diacetylamino*-4-*methylpyridine* (6·6 g.; 42% allowing for the 2·0 g. of material removed), m. p. 142—143° (Found: C, 54·3, 54·6; H, 5·2, 5·2; N, 8·9, 8·9%; acetyl val., 52·2; *C*-Me, 22·0. $C_{14}H_{16}O_6N_2$ requires C, 54·5; H, 5·2; N, 9·1%; acetyl val. for 4 groups, 55·8; 5*C*-Me 24·4%). Infra-red spectrum (Nujol mull): max. at 1767, 1724, 1608, 1563, 1370, 1333, 1279, 1244, 1191, 1149, 1053, 1014, 986, 956, 908, 877, 862, 778, and 766 cm.$^{-1}$.

The material, m. p. 145—155°, was recrystallised repeatedly from ethyl methyl ketone, to give needles of 3-*acetamido*-2 : 6-*diacetoxy*-4-*methylpyridine*, m. p. 177—178° (Found: C, 53·6; H, 5·4; N, 10·1, 10·3. $C_{12}H_{14}O_5N_2$ requires C, 54·1; H, 5·3; N, 10·5%). The ultra-violet absorption spectrum of this compound in ethanol changed with time and, as preparation of the solution required a considerable time, owing to the slow dissolution in cold ethanol, extensive interaction may have occurred before the spectrum could be determined. The results on this solution were as follows: max. at 2675 and 3240 Å (ε 3100 and 6000); the values of ε after 6 hr. were 2900 and 6700, and after 24 hr. 2600 and 7100 respectively. Attempts to effect these changes on a preparative scale were unsuccessful as the substance could be recovered unchanged from cold ethanol and boiling with ethanol gave a purple gum. The infra-red spectrum of this compound (Nujol mull) had the following max.: 3268, 1773, 1656, 1608, 1518, 1370, 1284, 1192, 1149, 1057, 1018, 903, and 887 cm.$^{-1}$.

2 : 3 : 6 *Triacetoxy*-4-*methylpyridine*.—The diacetylamino-compound (15 g.) was refluxed for

1 hr. with concentrated hydrochloric acid (150 c.c.), and the solution evaporated to dryness *in vacuo*. The residue was warmed with acetic anhydride (150 c.c.) until the gum dissolved and the ammonium chloride was then removed by filtration. After refluxing for 1 hr., the filtrate was distilled to give the *triacetoxy*-compound (11·0 g., 85%) as a very viscous, almost colourless oil, b. p. 170—174°/0·9 mm., n_D^{20} 1·4960 (Found: C, 53·7; H, 4·9; N, 4·7. $C_{12}H_{13}O_6N$ requires C, 53·9; H, 4·9; N, 5·2%). Infra-red spectrum (liquid film): max. at 1767, 1608, 1567, 1456, 1427, 1395, 1366, 1339, *ca.* 1220—1175, 1146, 1057, 1017, 988, 904, 877, 826, and 765 cm.$^{-1}$.

2 : 3 : 6-*Trihydroxy*-4-*methylpyridine Hydrochloride*.—The foregoing triacetate was hydrolysed for 1 hr. with boiling concentrated hydrochloric acid (100 c.c.). Evaporation under reduced pressure and recrystallisation from hydrochloric acid (8N) furnished colourless needles of 2 : 3 : 6-*trihydroxy*-4-*methylpyridine hydrochloride dihydrate*, m. p. 82—83° (Found: C, 34·2; H, 5·5; N, 6·6; Cl, 16·5. $C_6H_8O_3NCl,2H_2O$ requires C, 33·7; H, 5·7; N, 6·6; Cl, 16·6%). Infra-red spectrum (Nujol mull): max. at *ca.* 3200 (broad), 1645, 1553, 1435, 1377, 1302, 1241, 1009, 855, 807, and 741 cm.$^{-1}$.

Treatment of an aqueous solution with ferric chloride solution gave a deep purple colour which rapidly faded to yellow and then changed to dark red; excess of ferric chloride produced only a yellow colour. When an aqueous solution of the hydrochloride was shaken with sodium hydrogen carbonate solution a green colour developed on the surface, and when shaken in air the solution became dark blue. Ammoniacal silver nitrate solution gave an immediate black precipitate.

2 : 3 : 6-*Trihydroxy*-4-*methylpyridine*.—An ethereal diazomethane solution, prepared from methylnitrosourea (1·5 g.), potassium hydroxide solution (5 c.c., 50%), and ether (30 c.c.), was added to the hydrochloride (1·0 g.) dissolved in methanol (2 c.c.). The clear solution was immediately treated with acetic acid (1 c.c.) and, on cooling at 0°, the crude product slowly separated. Recrystallisation from ethanol furnished yellow prismatic needles of 2 : 3 : 6-*trihydroxy*-4-*methylpyridine* which sintered at 200—205° and decomposed without melting at higher temperatures (Found: C, 50·6; H, 4·8; N, 10·0. $C_6H_7O_3N$ requires C, 51·1; H, 5·0; N, 9·9%). It became brown after a few hr. at room temperature.

2 : 6-*Diacetoxy*-3 : 4-*dimethylpyridine*.—Ethyl γ-cyano-αβ-dimethylglutaconate (Rogerson and Thorpe, *loc. cit.*; 125 g.) was refluxed with concentrated hydrochloric acid (450 c.c.) for 5 hr. and the solution evaporated almost to dryness. After addition of excess of aqueous ammonia, the mixture was distilled until the dihydroxypyridine began to sublime. The residue and sublimate were thoroughly washed with water containing a little acetic acid. Attempts to purify the resulting crude dihydroxypyridine by sublimation and recrystallisation failed. This material was therefore refluxed with acetic anhydride (300 c.c.) for 30 min. and then distilled, to give 2 : 6-*diacetoxy*-3 : 4-*dimethylpyridine* (82 g., 70%), oil, b. p. 136—140°/1 mm., n_D^{20} 1·5033, m. p. 64—65°. Recrystallisation from water containing a little ethanol gave thin plates, m. p. 64—65° (Found: C, 58·8; H, 5·8; N, 6·8. $C_{11}H_{13}O_4N$ requires C, 59·2; H, 5·9; N, 6·3%). Infra-red spectrum (Nujol mull): max. at 1761, 1613, 1590, 1374, *ca.* 1200 (broad), 1147, 1083, 1027, and 885 cm.$^{-1}$.

On addition of ammonia to the original hydrolysis mixture and during the subsequent distillation a vivid blue colour developed, this effect being minimised by the use of acetic acid during the working up, as described. Similar blue or green colours have been observed during the preparation of di- and tri-hydroxypyridines by Rogerson and Thorpe and by Lapworth and Collie (*locc. cit.*). The hydrochlorides of compounds of type (II) are stable and can be kept for several months without change, but the corresponding free bases gradually become blue or brown, especially in soda-glass containers. These compounds give colourless solutions in aqueous sodium hydroxide, but ammoniacal solutions rapidly become blue.

2 : 6-*Dihydroxy*-3 : 4-*dimethylpyridine*.—The foregoing diacetate (82 g.) was refluxed for 1·5 hr. with concentrated hydrochloric acid (300 c.c.). On cooling, 2 : 6-*dihydroxy*-3 : 4-*dimethylpyridine hydrochloride hydrate* crystallised in plates, m. p. 93—94°, unchanged by recrystallisation from hydrochloric acid (5N) (Found: C, 42·6; H, 6·6; N, 6·9. $C_7H_{10}O_2NCl,H_2O$ requires C, 43·4; H, 6·2; N, 7·2%). Infra-red spectrum (Nujol mull): max. at 3448, 1639 (inflection at 1610), 1534, 1344, 1323, 1316, 1229, 1188, 1116, and 1003 cm.$^{-1}$.

When this material was heated at 50°/0·5 mm. for several hours it furnished 2 : 6-dihydroxy-3 : 4-dimethylpyridine, m. p. 188—190° (Found: C, 60·7; H, 6·7; N, 9·7. Calc. for $C_7H_9O_2N$: C, 60·4; H, 6·5; N, 10·1%). Rogerson and Thorpe (*loc. cit.*) give m. p. 189°. Infra-red spectrum (Nujol mull): max. at 1626, 1600 (side-band), 1580, 1539, 1490, 1372, 1306, 1205, 1183, and 996 cm.$^{-1}$.

2 : 6-*Dihydroxy*-3 : 4-*dimethyl*-5-*phenylazopyridine*.—By the method used for the preparation

of the monomethyl analogue, this compound was obtained in 64% yield. Recrystallisation from a large volume of methanol furnished red needles of the *azo*-compound, m. p. 255—256° (Found: C, 63·8; H, 5·3; N, 16·8. $C_{13}H_{13}O_2N_3$ requires C, 64·2; H, 5·4; N, 17·3%). Infra-red spectrum (Nujol mull): max. at 1650, 1587, 1506, 1456, 1372, 1247, 1199, 1171, 1157, 904, and 756 cm.$^{-1}$. Ultra-violet absorption spectrum (in ethanol): max. at 2550, 2600, 4140, and 4170 Å (ε, 14,500, 14,800, 35,500, and 35,600 respectively).

2 : 6-*Diacetoxy*-5-*diacetylamino*-3 : 4-*dimethylpyridine*.—The foregoing azo-compound (12·2 g.) was reduced with zinc (20 g.), acetic acid (60 c.c.), and acetic anhydride (40 c.c.) as in the previous case. The mixture was filtered and the solid washed with acetic acid (3 × 100 c.c.); evaporation of the combined filtrates gave a solid residue (23 g.) which was washed with boiling ether (3 × 100 c.c.). Part of the remaining fine powder (14 g.; m. p. 170—174°) was recrystallised repeatedly from ethyl methyl ketone. 2 : 6-*Diacetoxy*-5-*acetamido*-3 : 4-*dimethylpyridine* separated in threads, m. p. 197—198° (Found: C, 55·8; H, 5·8; N, 10·2. $C_{13}H_{16}O_5N_2$ requires C, 55·7; H, 5·8; N, 10·0%). Infra-red spectrum (Nujol mull): max. at 3268, 1758, 1650, 1603, 1527, 1372, 1272, 1218, 1202, 1119, 1092, 1047, 1015, 928, 854, 795, and 717 cm.$^{-1}$. Like the lower homologue this compound interacted with ethanol during the measurement of the ultra-violet spectrum. The values obtained were: max. at 2700 and 3350 Å (ε 3200 and 3800 respectively); after 6 hr. the maximum at the lower wave-length had disappeared and a single maximum 3340 Å (ε 10,100) was found.

The remaining material (12 g.) was refluxed for 7 hr. with acetic anhydride (120 c.c.), and the excess of anhydride then removed *in vacuo*. Crystallisation of the residue from ether (50 c.c.) gave the product, m. p. 92—94° (8·8 g., 63% allowing for the portion removed). 2 : 6-*Diacetoxy*-5-*diacetylamino*-3 : 4-*dimethylpyridine* separated from ether in rectangular plates, m. p. 96—97° (Found: C, 55·6; H, 5·8; N, 8·8. $C_{15}H_{18}O_6N_2$ requires C, 55·9; H, 5·6; N, 8·7%). Infra-red spectrum (Nujol mull): max. at 1767, 1718, 1600, 1433, 1416, 1333, 1282, 1247, *ca.* 1190 (broad), 1131, 1091, 1055, 1037, 1016, 954, 922, and 877 cm.$^{-1}$.

The triacetyl compound, m. p. 197—198°, (0·5 g.), was refluxed with acetic anhydride (10 c.c.) for 7 hr. Isolated as before and crystallised from ether, the tetra-acetyl compound (0·5 g.) melted at 94—95°.

2 : 5 : 6-*Trihydroxy*-3 : 4-*dimethylpyridine Hydrochloride*.—Hydrolysis of the foregoing tetra-acetyl derivative (8·8 g.) and acetylation of the resulting triol, as in the case of the lower homologue, furnished 2 : 5 : 6-*triacetoxy*-3 : 4-*dimethylpyridine* (6·8 g., 88%) which distilled as a pale yellow, extremely viscous syrup, b. p. 175—177°/0·9 mm., n_D^{20} 1·4988 (Found: C, 55·9; H, 5·5; N, 4·5. $C_{13}H_{15}O_6N$ requires C, 55·5; H, 5·4; N, 5·0%). Infra-red spectrum (liquid film): max. at 1770, 1605, 1435, 1410, 1370, *ca.* 1190 (broad), 1088, 1042, 1013, 952, 925, 876, 756, and 713 cm.$^{-1}$.

The triacetate (6·6 g.) was hydrolysed as in the previous case and the product crystallised from aqueous "AnalaR" hydrochloric acid (1 : 1). The *hydrochloride hydrate* separated as needles, m. p. 98—100° (with dehydration; preheated bath) (Found: C, 40·5; H, 5·9; N, 7·3; Cl, 15·4. $C_7H_{12}O_4NCl$ requires C, 40·1; H, 5·8; N, 6·7; Cl, 16·9%). Infra-red spectrum (Nujol mull): max. at 3356, 3205, 1736, 1669, 1623, 1543, 1381, 1289, 1259, 1174, 1095, 1046, and 894 cm.$^{-1}$. The acid solution gave an intense red colour with a trace of ferric chloride.

6-*Acetoxy*-4 : 5 : 2′-*trimethyloxazolo*(5′ : 4′-2 : 3)*pyridine*.—The azo-compound (III; R = R′ = Me) (20 g.) was reduced with zinc (40 g.), acetic acid (150 c.c.) and acetic anhydride (25 c.c.), the almost colourless solution being filtered after 1 hr. The residue obtained by evaporation of the filtrate *in vacuo* was refluxed with acetic anhydride (150 c.c.) for 30 min. Removal of the excess of anhydride furnished a gum which partly crystallised, trituration with ether giving small amounts of the crude tri- and tetra-acetyl compounds. The viscous residual gum was then distilled to give an oil, b. p. 160—180°/2 mm., which solidified on trituration with ether. After several recrystallisations from ether and ethyl methyl ketone–light petroleum (b. p. 60—80°), 6-*acetoxy*-4 : 5 : 2′-*trimethyloxazolo*(5′ : 4′-2 : 3)*pyridine* was obtained as prismatic needles, m. p. 119—120° [Found: C, 59·9; H, 5·6; N, 13·0%; acetyl val., 36·6. $C_{11}H_{12}O_3N_2$ requires C, 60·0; H, 5·5; N, 12·7%; acetyl val. (2 groups), 39·1]. Infra-red spectrum (Nujol mull): max. at 1748, 1621, 1567, 1362, 1258, 1208, 1110, 1087, 1063, 1012, 924, 912, and 868 cm.$^{-1}$. Ultra-violet absorption spectrum (in EtOH): max. at 2320 and 2790 Å (ε 8600 and 9700 respectively).

Pyrolytic Distillation of 5-*Acetamido*-2 : 6-*diacetoxy*-3 : 4-*dimethylpyridine*.—When the triacetyl compound was heated at 200—220°/*ca.* 5 mm. the oxazolopyridine sublimed in needles, m. p. 115—117° undepressed by admixture with the sample already described.

Reaction of 2 : 6-*Dihydroxy*-4-*methylpyridine with Diazomethane*.—Ethereal diazomethane,

prepared from methylnitrosourea (90 g.) by the method of Arndt (*Org. Synth.*, Coll. Vol. II, p. 166), was added gradually to an ice-cold suspension of the dihydroxypyridine (22·5 g.) in methanol (150 c.c.). After 21 hr. at room temperature, the dark green solution was evaporated and volatile product distilled under reduced pressure. Redistillation furnished 2 : 6-*dimethoxy*-4-*methylpyridine* (9·9 g., 36%), b. p. 57°/2 mm., n_D^{20} 1·5007, needles, m. p. 33—33·5° (Found : C, 62·9; H, 7·5; N, 9·3, OCH_3, 40·4. $C_8H_{11}O_2N$ requires C, 62·7; H, 7·2; N, 9·1; OCH_3, 40·5%). Infra-red spectrum (liquid film) : max. at 2959, 1608, 1563, 1447, 1383, 1346, 1284, 1217, 1198, 1142, 1104, 1057, 991, 957, 925, and 821 cm.$^{-1}$.

Fractional crystallisation of the distillation residue furnished 6-*methoxy*-1 : 4-*dimethylpyrid*-2-*one* (IX) as prismatic needles [from ethyl methyl ketone–light petroleum (b. p. 60—80°)], m. p. 92° (Found : C, 62·5; H, 7·4; N, 9·4; OCH_3, 18·8. $C_8H_{11}O_2N$ requires C, 62·7; H, 7·2; N, 9·1; OCH_3, 20·3%) [infra-red spectrum (Nujol mull) : max. at 1656, 1580, 1531, 1401, 1263, 1242, 1189, 1171, 1131, 1037, 1027, 988, 923, 836, and 769 cm.$^{-1}$], and (?) 6-*methoxy*-4-*methylpyrid*-2-*one* (X), plates (from ethyl methyl ketone), m. p. 170—171° (Found : C, 59·9; H, 6·2; N, 10·3; OCH_3, 20·2. $C_7H_9O_2N$ requires C, 60·4; H, 6·5; N, 10·1; OCH_3, 22·1%) [infra-red spectrum (Nujol mull) : max. at 2688, 1650, 1605, 1558, 1427, 1357, 1248, 1155, 1094, 1034, 994, 966, 936, 839, and 775 cm.$^{-1}$].

Demethylation of 2 : 6-*Dimethoxy*-4-*methylpyridine*.—The dimethoxy-compound (0·7 g.) was refluxed for 5 hr. with concentrated hydrochloric acid (10 c.c.). On cooling, 2 : 6-dihydroxy-4-methylpyridine hydrochloride hydrate crystallised, m. p. 217—219° (with dehydration; pre-heated bath), undepressed by admixture with authentic material.

Methylation of 2 : 6-*Dihydroxy*-3 : 4-*dimethylpyridine*.—(a) *With diazomethane.* The amine hydrochloride hydrate (12 g.) in methanol (40 c.c.) was left with ethereal diazomethane (from 60 g. of methylnitrosourea) at room temperature for 21 hr. After removal of the solvent, the volatile product was distilled, giving 2 : 6-*dimethoxy*-3 : 4-*dimethylpyridine* (2·5 g.; 24%), b. p. 61—62°/0·9 mm., n_D^{20} 1·5080, plates, m. p. 26—27° (Found : C, 64·7; H, 8·0; N, 8·4; OCH_3, 35·0. $C_9H_{13}O_2N$ requires C, 64·7; H, 7·8; N, 8·4; OCH_3, 37·2%). Infra-red spectrum (liquid film) : max. at 2967, 1608, 1575, *ca.* 1450 (broad), 1370, 1341, 1282, 1193, 1160, 1111, 1062, 1017, 963, 905, 829, 781, and 754 cm.$^{-1}$.

Repeated recrystallisation of the distillation residue from carbon tetrachloride and ethyl methyl ketone furnished (?) 6-*methoxy*-1 : 3 : 4-*trimethylpyrid*-2-*one* (XII), rectangular plates (1·0 g.), m. p. 119—120° (Found : C, 64·3; H, 7·8; N, 8·3). $C_9H_{13}O_2N$ requires C, 64·7; H, 7·8; N, 8·4%). Infra-red spectrum (Nujol mull) : max. at 1647, 1582, 1550, 1217, 1205, 1103, 1049, 1004, 938, 808, and 766 cm.$^{-1}$.

In one experiment a very small amount of (?) 6-*methoxy*-1 : 4 : 5-*trimethylpyrid*-2-*one* (XIII), m. p. 85—87°, was also obtained by fractional crystallisation of the distillation residue (Found : C, 64·3; H, 7·4; N, 8·7%). Infra-red spectrum (Nujol mull): max. at 3125, 1639, 1603, 1585, 1546, 1266, 1208, 1183, 1168, 1104, 1004, 838, 774, and 765 cm.$^{-1}$.

(b) *With methyl sulphate.* To a boiling solution of the hydrochloride hydrate (20 g.) and sodium hydroxide (46 g.) in water (200 c.c.), methyl sulphate (140 g.) was added during 3 hr. with occasional additions of sodium hydroxide solution (10N) to keep the mixture alkaline. The solution was then refluxed for a further 30 min., cooled, and poured into ice-water (1 l.), the mixture being extracted four times with ether. After being washed with very dilute aqueous ammonia and water, the combined extracts were dried (Na_2SO_4) and evaporated. Crystallisation of the residue from benzene–light petroleum (b. p. 60—80°) yielded the methoxypyridone (0·9 g.), m. p. 118—120°, undepressed by admixture with the sample obtained in (*a*). The mother-liquors were distilled, to give the dimethoxy-compound (1·4 g.), b. p. 68°/1·5 mm., n_D^{20} 1·5094.

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