509. *Preparation of Some 3,4,5-Trialkylpyridines.*

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The synthetic route, involving cyclization of trisubstituted cyanoglutaconic esters, which is efficient for 3,4,5-trimethylpyridine, is increasingly difficult with 3-ethyl-4,5-dimethylpyridine and 3,5-diethyl-4-methylpyridine.

3,4,5-Trialkylpyridines are not readily accessible. 3,4,5-Trimethylpyridine was prepared from diethyl γ-cyano-αβγ-trimethylglutaconate to facilitate identification of the constituents of coal-tar, shale oil, etc.; Tsuda, Mishima, and Maruyama [1] ascribed somewhat different properties for this compound from those which we found. Discrepant physical data on such hygroscopic bases are common in the literature, so Arnall's isolation of this base from coal tar [2] was opportune. The method, which appears generally impracticable for higher members of the series, was applied with increasing difficulty to 3-ethyl-4,5-dimethylpyridine and 3,5-diethyl-4-methylpyridine: our best overall yields were below 4%, compared with 28% of the collidine. As alkylpyridines may be difficult to characterize by analysis, each homologue was converted into several salts (see Table 1).

The diethyl αβγ-trialkyl-γ-cyanoglutaconates (I) were prepared by a modification of Rogerson and Thorpe's method [3,4] in which the crude potassium derivative, formed by condensing ethyl cyanoacetate and ethyl acetoacetate with alcoholic potassium ethoxide,

[1] Tsuda, Mishima, and Maruyama, *Pharm. Bull.* (*Japan*), 1953, **1**, 283; *Chem. Abs.*, 1955, **49**, 8277.
[2] Arnall, *J.*, 1958, 1702.
[3] Rogerson and Thorpe, *J.*, 1905, **87**, 1685.

was alkylated twice. An attempt to obtain the potassium derivative of the α-ethyl-β-methyl ester (I; R = Et, R′ = H) by condensing ethyl α-acetobutyrate with ethyl cyanoacetate was unsuccessful,[3] although similar preparations of the αβ-dimethyl analogue (I; R = Me, R′ = H) have been described.[4,5] Ethyl propionylacetate failed to condense

TABLE 1. *Salts of* 3,4,5-*trimethylpyridine* (*A*), 3-*ethyl*-4,5-*dimethylpyridine* (*B*), *and* 3,5-*diethyl*-4-*methylpyridine* (*C*).

			Found (%)				Required (%)			
Salt	M. p.[a]	Formula	C	H	N	X	C	H	N	X
A picrate	174—175° [b]	—	—	—	—	—				
B ,, ...	133	$C_{15}H_{16}O_7N_4$	49·7	4·4	15·5		49·5	4·4	15·4	
C ,, ...	105	$C_{16}H_{18}O_7N_4$	50·9	4·6	15·2		50·8	4·8	14·8	
A styphnate	d > 225 [c]		—	—	—	—				
B ,, ...	149 (d)	$C_{15}H_{16}O_8N_4$	47·4	4·3	14·8		47·4	4·2	14·7	
C ,, ...	131	$C_{16}H_{18}O_8N_4$	48·8	4·6	14·2		48·7	4·6	14·2	
A picrolonate ...	228 (d) [d]		—	—	—	—				
B ,, ...	167 (d)	$C_{19}H_{21}O_5N_5$	57·5	5·3	17·2		57·1	5·3	17·5	
C ,, ...	184 (d)	$C_{20}H_{23}O_5N_5$	57·9	5·7	16·7		58·1	5·6	16·9	
A chloroplatinate	s > 235 [e]	$C_{16}H_{24}N_2Cl_6Pt$	29·4	3·7	4·2	30·1 [f]	29·5	3·7	4·3	29·9
B ,,	208 (d)	$C_{18}H_{28}N_2Cl_6Pt$	31·8	4·2	4·0	28·7 [f]	31·8	4·1	4·1	28·7
C ,,	s 217	$C_{20}H_{32}N_2Cl_6Pt$	34·0	4·5	3·8	27·8 [f]	33·9	4·6	4·0	27·6
A chloroaurate ...	161—162 (d)	$C_8H_{12}NCl_4Au$	21·1	2·7	3·0	42·6 [g]	20·8	2·6	3·0	42·7
B ,, ...	135	$C_9H_{14}NCl_4Au$	23·1	2·9	3·0	41·5 [g]	22·7	3·0	2·9	41·5
C ,, ...	119	$C_{10}H_{16}NCl_4Au$	24·7	3·3	3·0	40·0 [g]	24·6	3·3	2·9	40·3
A methiodide ...	149—150	$C_9H_{14}NI$	40·6	5·5	5·0	48·1 [h]	41·1	5·4	5·3	48·2
B ,, ...	132 (d)	$C_{10}H_{16}NI$	43·5	6·0	5·3	46·2 [h]	43·3	5·8	5·1	45·8
A hydrochloride	d > 220 [i]	$C_8H_{12}NCl$	61·2	7·6	9·1		61·0	7·7	8·9	

[a] d = decomp., s = sinters. [b] Lit.,[1,2] m. p. 174° and 178°. [c] Lit.,[2] m. p. 180°. [d] Lit.,[1,2] m. p. 188° and 232° (decomp.). [e] Lit.,[1] m. p. 197—198° (no analysis). [f] X = Pt. [g] X = Au. [h] X = I. [i] Sublimed at 120° (bath)/0·5 mm.

in the same manner with ethyl cyanoacetate when treated with potassium t-butoxide, so this preparative approach may be applicable to the 4-methyl homologues only. However, the reaction mixtures were not examined for amounts of the required products which would be too small to be of value.

Significant quantities of the more volatile substituted crotonic esters were obtained only in the preparations of the higher trialkylcyanoglutaconic esters, when more than one such by-product occurs [3,6] (see Table 2). Thus, the action of potassium ethoxide and ethyl iodide on diethyl γ-cyano-α-ethyl-β-methylglutaconate gave, together with the required product (I; R = R′ = Et), an approximately equivalent amount of the monoester (II; R = Et, R′ = H), formed from the starting material, but much less of the expected trialkyl analogue (II; R = R′ = Et).

Because the hydrolysis of the ester (II; R = R′ = Me) with hydrochloric acid affords a mixture of the dihydroxy-compound (III; R = R′ = Me) and the trimethylglutaconic acid,[3] the crude ethyl γ-cyano-α-ethyl-β-methylcrotonate fractions were alkylated in the same manner to obtain the αβγ-trialkyl-substituted esters (II; R = Et, R′ = Et or Me). These furnished low yields of hydroxypyridones on cyclization, but no evidence was found, in the infrared absorption or elsewhere, that either ester contained other by-products, *e.g.*, the ααβ-trialkyl isomers. The infrared spectra of the trialkylcyanocrotonic esters exhibit strong bands near 5·78 μ (carbonyl stretching vibrations of unsaturated esters) at wavelengths generally about 0·04 μ higher than the corresponding bands of the substituted cyanoglutaconic esters. A similar relation was observed between the nitrile bands, at 4·52—4·54 and 4·47—4·52 μ, respectively, which in the glutaconic esters are subject to the " quenching " effect of the α-ethoxycarbonyl group.

On hydrolysis with hydrochloric acid, the ethyl-substituted glutaconic esters afforded

[4] Kon and Nanji, *J.*, 1931, 560.
[5] Hope, *J.*, 1922, **121**, 2216.
[6] Hope and Sheldon, *J.*, 1922, **121**, 2233.

lower yields of dihydroxypyridines than did the trimethyl analogue (I; R = R′ = Me), but attempts to isolate the by-products, the corresponding αβγ-trialkylglutaconic acids, were unsuccessful.[7] Cyclizations with methanolic potassium hydroxide also gave mixtures which were difficult to separate,[8] including two unstable, viscous distillates, which were

TABLE 2. *Preparation of αβγ-trialkyl-γ-cyanoglutaconic and corresponding crotonic esters.*

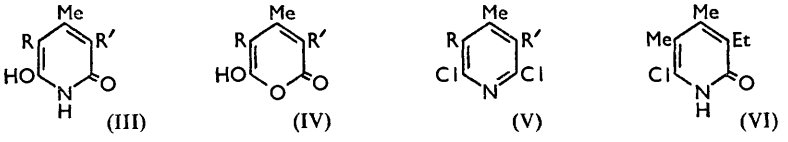
	Product	Reactant	Yield (%)	B. p./mm.	n_D^{20} [a]	d_4^{20}
1.	I; R = R′ = Me	I; R = Me, R′ = H	78	120—125°/2 [c]	1·4623	
2.	I; R = Et, R′ = Me	I; R = Et, R′ = H	39	107—108°/0·2	1·4567	1·0439
3.	I; R = R′ = Et	I; R = Et, R′ = H	43	125°/0·2	1·4544	1·0266
4.	II; R = Et, R′ = H	I; R = Et, R′ = H	30 [d]	132°/15 [f]	1·4594 (18°)	0·9714
		I; R = Et, R′ = H	38 [e]			
5.	II; R = Et, R′ = Me	II; R = Et, R′ = H [h]	54	136°/24	1·4595 (15·5°)	0·9743
6.	II; R = R′ = Et	II; R = Et R′ = H [h]	47	136°/12	1·4591	0·9595
		I; R = Et, R′ = H	2 [i]			
7.	I; R = Me, R′ = Et	I; R = Me, R′ = H	39	114—116°/0·12	1·4556	1·0387
8.	II; R = Me, R′ = Et	I; R = Me, R′ = H	11 [j]	121°/12	1·4595 (15·5°)	0·9778

	Formula	Found (%) C	H	N	Required (%) C	H	N	Infrared bands (μ) [b] (C⋮N)	(C:O)
1.		(known compound)						4·52 w	5·77 s
2.	$C_{14}H_{21}O_4N$	62·7	7·7	5·5	62·9	7·9	5·2	4·47 vw	5·73 s
3.	$C_{15}H_{23}O_4N$	64·3	8·2	5·3	64·0	8·2	5·0	4·50 vw	5·77 s
4.		—	—	—	—	—	—	4·52 m	5·76 s [g]
5.	$C_{11}H_{17}O_2N$	67·6	8·7	7·4	67·7	8·8	7·2	4·54 m	5·77 vs
6.	$C_{12}H_{19}O_2N$	68·9	9·1	6·7	68·9	9·1	6·7	4·54 m	5·80 s
		68·6	8·9	6·8					
7.	$C_{14}H_{21}O_4N$	63·1	7·8	5·6	62·9	7·9	5·2	4·47 vw	5·75 s
8.	$C_{11}H_{17}O_2N$	67·4	8·7	7·4	67·7	8·8	7·2	4·54 m	5·79 s

[a] At other temperatures in parentheses. [b] s = strong, m = medium, w = weak, v = very. [c] Lit.,[7] b. p. 133—140°/3 mm. [d] By-product with 2nd compound, other by-product (II; R = Et, R′ = Me) not isolated. [e] By-product with 3rd compound. [f] Lit.,[17] b. p. 141°/20 mm. [g] Ester (I; R = Et, R′ = H) had bands at 4·51 (w) and 5·76 μ (s). [h] Crude $C_{10}H_{15}O_2N$ fraction contaminated with required ester. [i] By-product with 3rd compound, identical (infrared spectrum) with ethylation product from (II; R = Et, R′ = H). [j] By-product with previous compound.

essentially the trialkylglutaconic anhydrides (IV; R = Et, R′ = Me) and (IV; R = R′ = Et).[9] Although purification of the hydroxypyridones (III; R = Et, R′ = Me; and R = R′ = Et) involves great losses, crude cyclization products may be converted into dichloropyridines.

(I) $EtO_2C\cdot CR{:}CMe\cdot CR'(CN)\cdot CO_2Et$ $EtO_2C\cdot CR{:}CMe\cdot CHR'\cdot CN$ (II)



(III) (IV) (V) (VI)

The preparation of the trimethyl derivative (V; R = R′ = Me) and especially the ethyl-substituted dichloro-compounds (V; R = Et, R′ = Me; and R = R′ = Et) involved exceptionally vigorous reactions with phosphorus oxychloride, a chloropyridone (VI) being isolated from one experiment under relatively mild conditions (see Table 3). Because of initial difficulties in replacing the α-hydroxyl groups by chlorine, their reduction with phosphorus and iodine [10] was investigated in the pyridine series: poor yields of 2,3,4- and

[7] Adams, Van Duuren, and Braun, *J. Amer. Chem. Soc.*, 1952, **74**, 5608.
[8] Thorpe, *J.*, 1905, **87**, 1682.
[9] Montagne, *Bull. Soc. chim.*, 1946, 67.
[10] Hammick and Thewlis, *J.*, 1948, 1457.

3,4,5-trimethylpyridine resulted. As alternative to catalytic hydrogenation, removal of the α-chlorine atoms through the formation and decomposition of the hydrazide [11] converted the compound (V; R = R′ = Me) into a mixture of products, apparently including 2-hydroxy-3,4,5-trimethylpyridine.

TABLE 3. *Preparation of substituted 2,6-dichloropyridines from the corresponding 2,6-dihydroxy-compounds.*

Product	Reaction time (hr.)	Yield (%)	M. p.	Formula	Found (%) C	H	N	Cl	Required (%) C	H	N	Cl
V; R = R′ = Me [1] ...	6 [a]	85	99° [b]		—	—	—	—	—	—	—	—
V; R = Et, R′ = Me [2]	24	78	66	$C_9H_{11}NCl_2$	52·8	5·4	6·7	34·7	53·0	5·4	6·9	34·7
By-product (VI) [c] [3] ...	3	3 [c]	198	$C_9H_{12}ONCl$	58·4	6·8	7·9	18·8	58·2	6·5	7·5	19·1
V; R = R′ = Et [4] ...	18 [d]	27	19—20 [e]	$C_{10}H_{13}NCl_2$	54·9	5·8	6·4	32·3	55·1	6·0	6·4	32·5

[a] Heating under reflux (ref. 1) or for 12 hr. at 180° gave mixed products. [b] Lit., m. p. 96—96·3°. [c] With 19% of (V; R = Et, R′ = Me). [d] Longer treatment (24 hr.) was less effective, and under milder conditions only starting material was recovered. A mixed product of high chlorine content resulted when PCl_5 was added (12 hr.). [e] B. p. 109°/0·05 mm., $n_D^{21·5}$ 1·5470.

[1] $\lambda_{max.}$ 225 (ε 3220) and 275 mμ (ε 3600); $\nu_{max.}$ 14·18 μ (C–Cl). [2] $\lambda_{max.}$ 220 (7140) and 275 mμ (ε 4430); $\nu_{max.}$ 14·34 cm.$^{-1}$ (C–Cl). [3] $\nu_{max.}$ 14·85 (C–Cl), also 6·12 m and 6·36 s μ (amide). [4] $\lambda_{max.}$ 221 (ε 7950) and 276 mμ (ε 4060); $\nu_{max.}$ 14·21 μ (C–Cl).

The bases and derivatives containing a pyridine nucleus showed no peaks in the ultraviolet spectrum above 300 mμ, and the dominant hydroxypyridone character of the dihydroxypyridines was indicated by their absorption maxima near 322 mμ.[12] In the comparison of some lower pyridine homologues, the lengthening of an alkyl side-chain had been found to cause no appreciable change in the ultraviolet absorption,[13] and there was a barely perceptible bathochromic shift in both maxima on passing from 3,4,5-trimethyl- to 3-ethyl-4,5-dimethyl- and 3,5-diethyl-4-methyl-pyridine. A similar displacement with increasing size of the substituent alkyl groups, which was shown by the hydroxypyridones, is not typical of pyridine compounds.

The infrared spectra of 3,4,5-trimethyl-, 3-ethyl-4,5-dimethyl-, and 3,5-diethyl-4-methyl-pyridine each had three bands in the specific 10—15 μ range,[14] which moved to shorter wavelength with lower intensity with increasing molecular weight.[15] These were at 11·42, 12·19, and 13·84 μ, at 11·34, 12·15, and 13·56 μ, and at 11·24, 12·12, and 13·42 μ respectively. The three peaks of longest wavelength lay outside the range of 13·66—13·81 μ (724—732 cm.$^{-1}$) suggested by Cook and Church [16] for out-of-plane deformation vibrations of trialkylpyridines, as did the corresponding band of 2,3,4-trimethylpyridine at 13·61 μ. Other characteristic infrared absorptions include a strong C–Cl band of substituted α-chloropyridines (14·18—14·85 μ), and the amide bands (5·92—6·17 and 6·36—6·62 μ) which are further evidence of the pyridone configurations of the α-hydroxypyridines.[12] The former were accompanied only by much weaker bands in the 13·50—15·00 μ region and the latter, in some cases, by a relatively weak absorption near 6·25 μ, in place of the strong band found in compounds with true pyridine rings.

EXPERIMENTAL

Densities were measured in a pycnometer of 5 ml. capacity and refractive indices on an Abbé instrument. Ultraviolet absorption spectra were determined for ethanol solutions, and infrared spectra were measured for liquid films or Nujol mulls.

Diethyl αβ-Dialkyl-γ-cyanoglutaconates.—Potassium (68 g.) was added to anhydrous t-butyl alcohol (1 l.), followed by absolute ethanol (500 ml.) to obtain a clear solution, then by ethyl cyanoacetate (193 g.), and finally by ethyl acetoacetate (222 g.). After intermittent stirring

[11] Thielepape and Spreckelson, *Ber.*, 1922, **55**, 2934.
[12] Ames, Bowman, and Grey, *J.*, 1953, 3008.
[13] Andon, Cox, and Herrington, *Trans. Faraday Soc.*, 1954, **50**, 924.
[14] Tsuda and Maruyama, *Pharm. Bull.* (*Japan*), 1953, **1**, 146.
[15] Shindo and Ikekawa, *ibid.*, 1956, **4**, 192.
[16] Cook and Church, *J. Phys. Chem.*, 1957, **61**, 458.

at room temperature for 1 week, the solidified potassium derivative of diethyl α-cyano-β-methylglutaconate [4] (I; R = K, R′ = H) was collected, washed with cold ethanol and much ether, pulverized, and dried *in vacuo* (434 g., 97%). This product (198 g.) was heated under reflux with ethyl iodide (234 g.) and absolute ethanol (500 ml.) for 12 hr., to give diethyl γ-cyano-α-ethyl-β-methylglutaconate (I; R = Et, R′ = H) (141 g., 74%), b. p. 136—138°/5 mm. (lit.,[17] b. p. 168°/22 mm.), n_D^{20} 1·4634. Similar treatment with excess of methyl iodide gave diethyl γ-cyano-αβ-dimethylglutaconate (I; R = Me, R′ = H) (94%), b. p. 128°/1 mm., n_D^{20} 1·4653 (lit.,[4] n_D^{18} 1·46619).

Diethyl αβγ-Trialkyl-γ-cyanoglutaconates and Ethyl αβγ-Trialkyl-γ-cyanocrotonates.—Details of the preparations are given in Table 2. Some minor products were not isolated. In a typical experiment,[3,6] the ester (I; R = Me, R′ = H) (88·0 g.) was treated with a solution from potassium (14·4 g.) in absolute ethanol (120 ml.), ethyl iodide (86·1 g.) then being added. When the exothermic reaction abated, the mixture was heated under reflux for 1 hr. and partially evaporated. Water was added to dissolve the precipitate, the products were isolated by means of ether, and the trialkyl-substituted *cyanoglutaconic ester* (I; R = Me, R′ = Et) (38·5 g.) separated from the more volatile by-products (41·5 g.), including the analogous *crotonic ester* (II; R = Me, R′ = Et) (8·1 g.), by repeated fractionation.

3,4,5-Trialkyl-2,6-dihydroxypyridines.—In accord with the methods of Rogerson and Thorpe,[3] diethyl αβγ-trialkyl-γ-cyanoglutaconates (I) and ethyl αβγ-trialkyl-γ-cyanocrotonates (II) were cyclized by heating them under reflux with concentrated hydrochloric acid until the oily layer disappeared (method A) or with 5% methanolic potassium hydroxide solution for 3—4 hr. (method B).

(a) The dihydroxy-compound (III; R = R′ = Me) was prepared by method A from the ester (I; R = R′ = Me) in 53% yield. On concentration of the hydrochloric acid solution, needles of the unstable hydrated hydrochloride crystallized [m. p. 170° (preheated bath) with prior dehydration and sublimation]. Decomposition with hot water afforded the hydroxypyridone in plates, m. p. 175—176°, raised to 179° (lit.,[3,7] m. p. 180 and 179°), as waxy needles after sublimation at 140° (bath)/0·1 mm.; this had $\lambda_{max.}$ 231 (ε 3270) and 320 mμ (ε 2950); infrared bands were at 6·00 (m), 6·17 (s), 6·35 (m, shoulder), and 6·49 μ (s, broad). The *di-p-toluenesulphonate*, plates (from ethanol), m. p. 170—171°, was prepared in dry pyridine at room temperature (Found: C, 57·2; H, 4·9; N, 3·0. $C_{22}H_{23}O_6NS_2$ requires C, 57·3; H, 5·0; N, 3·0%).

(b) *3-Ethyl-2,6-dihydroxy-4,5-dimethylpyridine* (III; R = Et, R′ = Me) was obtained in 9% yield from the ester (I; R = Et, R′ = Me) by method B. The white powder, m. p. 96°, which crystallized from water, sublimed at 100° (bath)/0·05 mm. to form waxy needles, m. p. 106° (Found: C, 64·7; H, 7·7; N, 8·2. $C_9H_{13}O_2N$ requires C, 64·6; H, 7·8; N, 8·4%), $\lambda_{max.}$ 241 (ε 4110) and 322 mμ (ε 2210), $\nu_{max.}$ 5·96 (s), 6·07 (s), and 6·25 μ (w, shoulder) (weak band at 6·62 μ).

Similar sublimates from the crude semicrystalline product were contaminated by a yellow oil, and attempts to separate a carboxylic acid from phenolic and neutral constituents yielded a pale yellow, viscous, unstable distillate (0·5 ml.), b. p. 120°/0·4 mm., which was essentially *α-ethyl-βγ-dimethylglutaconic anhydride* (IV; R = Et, R′ = Me), but did not crystallize (Found: C, 64·4; H, 7·4. $C_9H_{12}O_3$ requires C, 64·3; H, 7·2%). Cyclization of the esters (I; R = Et, R′ = Me; and R = Me, R′ = Et) by method A afforded crystals, m. p. 95—97°, in yields of 16% and 37% respectively; but more hydroxypyridone was isolated as a glass, b. p. 166—170°/35 mm., from the combined dilute acid mother-liquors of several preparations, by ether-extraction and subsequent distillation (Found: N, 8·5%).

Method B, applied to the ester (II; R = Et, R′ = Me), furnished little crystalline product until the concentrated, green mother-liquors were treated with ammonia, whereby a 13% yield (m. p. 94—96°) was realized. A similar product (6%) from cyclization of the ester (II; R = Et, R′ = Me) by method A, was converted (Schötten–Baumann) into the *2,6-dibenzoate*, prisms (from ethanol), m. p. 130° (Found: C, 73·3; H, 5·6; N, 3·8. $C_{23}H_{21}O_4N$ requires C, 73·6; H, 5·6; N, 3·7%), and by acetic anhydride into the *2,6-diacetate*, cream-coloured, irregular prisms (from ethanol), m. p. 79° (Found: C, 62·3; H, 6·9; N, 5·6. $C_{13}H_{17}O_4N$ requires C, 62·1; H, 6·8; N, 5·6%).

(c) *3,5-Diethyl-2,6-dihydroxy-4-methylpyridine* (III; R = R′ = Et) was prepared by method B from the ester (I; R = R′ = Et). After distillation at 115—120°/0·3 mm., sublimation at

[17] Bland and Thorpe, *J.*, 1912, **101**, 888.

85—90° (bath)/0·1 mm. and recrystallization from aqueous ethanol or ethanol–light petroleum (b. p. 60—80°) gave a white microcrystalline *product* (30%), m. p. 94—96°. Resublimation gave waxy needles, m. p. 105° (Found: C, 66·1; H, 8·3; N, 7·7. $C_{10}H_{15}O_2N$ requires C, 66·3; H, 8·3; N, 7·7%), $\lambda_{max.}$ 245 (ε 2250) and 325 mμ (ε 493), $\nu_{max.}$ 5·92 (s), none between 6·08 (m, shoulder) and 6·90 μ.

That part of the product, which did not crystallize, was fractionated twice to obtain a small quantity (0·5 g.) of an acidic, yellow syrup, b. p. 132—134°/0·2 mm., n_D^{16} 1·4900 (Found: C, 65·5; H, 7·9. Calc. for $C_{10}H_{14}O_3$: C, 65·9; H, 7·7%). It darkened on storage and still contained traces of nitrogen, but was evidently essentially αγ-diethyl-β-methylglutaconic anhydride (IV; R = R′ = Et) (lit.,[9] b. p. 180—200°/20 mm.).

Cyclization of the esters (I; R = R′ = Et) and (II; R = R′ = Et) by method A afforded yields of 48% and 13%, respectively, of clean but somewhat impure crystals melting above 95°. Distillation of the white needles, m. p. 95—96° (31%), produced from the ester (II; R = R′ = Et) by method B, gave a glass, b. p. 155°/15 mm., which at 95—100° became a mobile, colourless oil (Found: C, 66·5; H, 8·3; N, 8·0%). Although it did not crystallize, its identity was confirmed by the infrared absorption and by conversion into 2,6-*diacetoxy*-3,5-*diethyl*-4-*methylpyridine*, prisms or rhombs (from water), m. p. 99—100° (Found: C, 63·6; H, 7·4; N, 5·6. $C_{14}H_{19}O_4N$ requires C, 63·4; H, 7·2; N, 5·3%). However, no dibenzoate or di-*p*-toluenesulphonate was formed by the methods previously employed.

Substituted 2,6-*Dichloropyridines*.—These were prepared by the action of an excess of phosphorus oxychloride in sealed tubes at 220—250°. The mixtures were treated with crushed ice, and the vesicant and lachrymatory products obtained in colourless needles after crystallization (charcoal) from light petroleum, with the exception of 2,6-*dichloro*-3,5-*diethyl*-4-*methylpyridine* (V; R = R′ = Et), which was isolated by means of ether and purified by two distillations. Steric considerations suggested that in an experiment under somewhat milder conditions 6-*chloro*-3-*ethyl*-2-*hydroxy*-4,5-*dimethylpyridine* (VI) and not the 2-chloro-6-hydroxy-isomer had been formed, but very little (~0·1 g.) was isolated.

In addition to the experiments with clean but low-melting hydroxypyridones recorded in Table 3, both the above and the homologous *dichloro-compound* (V; R = Et, R′ = Me) were obtained from the crude cyclization products. Thus, when the crystalline dihydroxy-compound (III; R = Et, R′ = Me) had been collected, the combined mother-liquors were concentrated, treated with ammonia, and distilled to yield a viscous, yellow oil (17 g.), b. p. 140—144°/0·4 mm., which was converted into the dichloropyridine (V; R = Et, R′ = Me) (7·5 g.), m. p. 65°, in the same manner.

3,4,5-*Trimethylpyridine*.—(*a*) The hydroxypyridone (III; R = R′ = Me) (4 g.), iodine (22 g.), red phosphorus (1·8 g.), and xylene (150 ml.) were heated [10] under reflux for 4 hr., but the basic product was too small (~0·2 g.) to be isolated and was characterized as the picrate (see Table 1). This method was shown to be applicable to the pyridine series by the treatment of 6-hydroxy-2,3,4-trimethylpyridine [18] (4 g.) with red phosphorus (0·9 g.) and iodine (11·2 g.) in boiling xylene for 1 hr. to obtain 2,3,4-trimethylpyridine (0·8 g., 23%), b. p. 192°/760 mm., n_D^{20} 1·5150 (lit.,[18] $n_D^{18·6}$ 1·5161).

(*b*) The dichloro-compound (V; R = R′ = Me) (9 g.) was heated under reflux for 24 hr. with 100% hydrazine hydrate (50 ml.), and the crude hydrazine derivative decomposed with boiling 10% aqueous copper sulphate.[11] In addition to lower-boiling material (<1 g.), whose principal basic constituent was identified by conversion into 3,4,5-trimethylpyridine picrolonate, distillation afforded a solid fraction, b. p. 132°/30 mm., which crystallized from light petroleum (b. p. 60—80°) in white needles (~0·2 g.), m. p. 76—78°, with the expected properties of 2-*hydroxy*-3,4,5-*trimethylpyridine* (Found: C, 70·1; H, 8·2; N, 10·2. $C_8H_{11}ON$ requires C, 70·1; H, 8·1; N, 10·2%). The infrared spectrum had intense bands at 6·08, 6·23, and 6·40 μ (shoulder) compared with those at 6·03, 6·16, and 6·49 μ shown by the isomeric 6-hydroxy-2,3,4-trimethylpyridine.

(*c*) The above dichloro-compound (18 g.), potassium hydroxide (10·8 g.), 2% palladium–barium carbonate (10 g.), and methanol (200 ml.) were shaken with hydrogen at <5 atm. until a slight excess (4·7 l.) appeared to be absorbed, more catalyst (4 × 10 g.) being added when the uptake became very slow. The solution was filtered, concentrated, added to water (50 ml.), and extracted with ether. Drying (KOH), evaporation, and distillation twice from barium oxide, finally in oxygen-free nitrogen, gave 3,4,5-trimethylpyridine (10·2 g., 89%), b. p.

[18] Prelog, Konzak, and Moor, *Helv. Chim. Acta*, 1942, **25**, 1663.

102°/30 mm. (Found: C, 79·3; H, 9·1; N, 11·4. Calc. for $C_8H_{11}N$: C, 79·3; H, 9·1; N, 11·6%); $\lambda_{max.}$ 213 (ε 4310) and 263 mμ (ε 2490). The distillate crystallized in deliquescent plates, with a distinctive odour, m. p. 35° (lit.,[1,2] m. p. 10—13° and 36·8°), b. p. 210·7°/754 mm. (lit.,[1,2] b. p. 205—207° and 211·4—211·5°/759 mm.); these measurements were made under dry oxygen-free nitrogen by a cooling curve and with a short-stemmed Anschütz thermometer in a small apparatus incorporating a Cottrell pump. Siwoloboff's method gave b. p. 209—210°/755 mm.

3-*Ethyl*-4,5-*dimethylpyridine*.—The compound (V; R = Et, R′ = Me) (15·3 g.) was hydrogenated similarly, but the product required fractionation to remove chlorine-containing material. The *pyridine* (3·8 g., 38%), n_D^{20} 1·5136, b. p. 217°/744 mm. (Siwoloboff), solidified in plates at −14° (Found: C, 79·9; H, 9·7; N, 10·6. $C_9H_{13}N$ requires C, 79·9; H, 9·7; N, 10·4%); $\lambda_{max.}$ were 214 (ε 4950) and 263—264 mμ (ε 2830).

3,5-*Diethyl*-4-*methylpyridine*.—This *base* (1·2 g., 88%), b. p. 114—116°/25 mm., was prepared in the same manner from the dichloropyridine (V; R = R′ = Et) (2 g.); it had n_D^{20} 1·5119, b. p. 239°/758 mm. (Siwoloboff), m. p. *ca.* −15° (Found: C, 80·5; H, 10·2; N, 9·2. $C_{10}H_{15}N$ requires C, 80·5; H, 10·1; N, 9·4%), $\lambda_{max.}$ 214 (ε 4870) and 264 mμ (ε 2710).

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