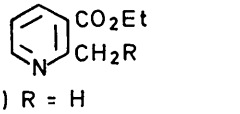
Annulation of Pyridine as a Route to Quinolines, Isoquinolines, and Cycloheptapyridines

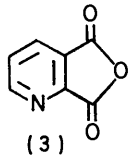
By **Gurnos Jones** * and **R. K. Jones**, Department of Chemistry, University of Keele, Keele, Staffordshire ST5 5BG

Pyridine-2,3- and -3,4-dicarboxylates have been condensed with dialkyl succinates and dialkyl glutarates to give diethyl 5,8-dihydroxyquinoline-6,7-dicarboxylate (7), diethyl 5,8-dihydroxyisoquinoline-6,7-dicarboxylate (24), and dialkyl 5,9-dihydroxy-7*H*-cyclohepta[*b*]- and -[*c*]pyridine-6,8-dicarboxylates (13), (14), and (26). The hydroxyquinoline and isoquinoline derivatives have been oxidised to the quinones (8) and (25); the former acts as a dienophile with cyclopentadiene. The dihydroxycycloheptapyridines have been converted into the cycloheptapyridine-5,9-diones (16) and (27) and into the cyclopropaquinolinediones (19) and (22), and the cyclopropaisoquinolinedione (29). Diels–Alder adducts (34) and (37) from pyrido[2,3-*d*]pyridazine-1,4-dione, and (35) from pyrido[3,4-*d*]pyridazine-1,4-dione have been prepared.

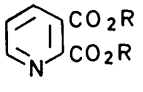
DURING work aimed at the production of tropones bearing a fused heterocyclic ring, we have investigated some methods of attaching a six- or seven-membered ring to pyridine. These experiments, leading to



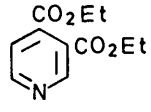
(1) R = H
(2) R = $[CH_2]_3 \cdot CO_2Et$



(3)



(4) R = Me
(5) R = Et



(6)

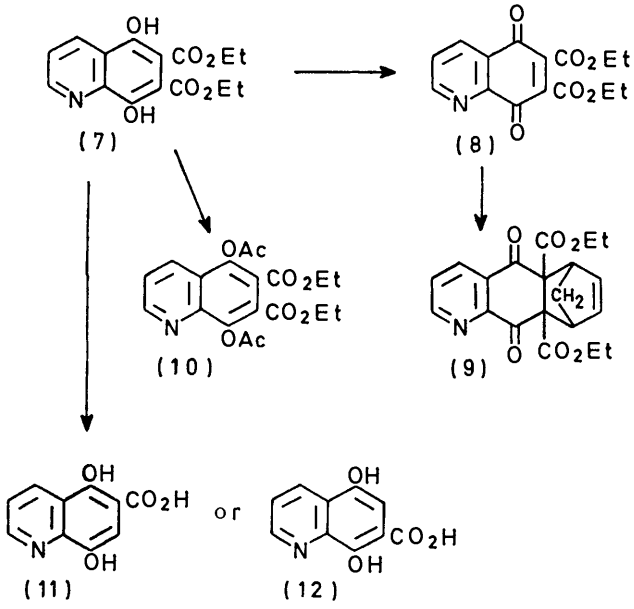
quinolines, isoquinolines, and cyclohepta[*b*]- or cyclohepta[*c*]-pyridines are now described.

A limited range of *ortho*-disubstituted pyridine derivatives is available; we have used ethyl 2-methylnicotinate (1), pyridine-2,3-dicarboxylic anhydride (3), and the diesters (4)—(6) of pyridine-2,3- and 3,4-dicarboxylic acids. An attempt to use the anion from ethyl 2-methylnicotinate (1) with ethyl γ-bromobutyrate to give the diester (2) was unsuccessful. The anhydride (3) would be expected to react with a Grignard reagent preferentially at the α-carbonyl group; other nucleophiles have been reported to act in this sense.[1] Treatment of 3-ethoxypropylmagnesium bromide with the anhydride gave no carboxylic acid or cyclic lactone, *i.e.* the desired reaction was not observed; phthalic anhydride and pyridine-3,4-dicarboxylic anhydride both give lactones with Grignard reagents.[2,3] The most satisfactory starting materials were the di-esters (4)—(6).

It has been shown that phthalates undergo sequential Claisen and Dieckmann condensations with dialkyl succinates to give naphthalene derivatives[4,5] and with glutarates to give benzocycloheptenes.[6] Similarly diethyl pyridine-2,3-dicarboxylate (5), when condensed

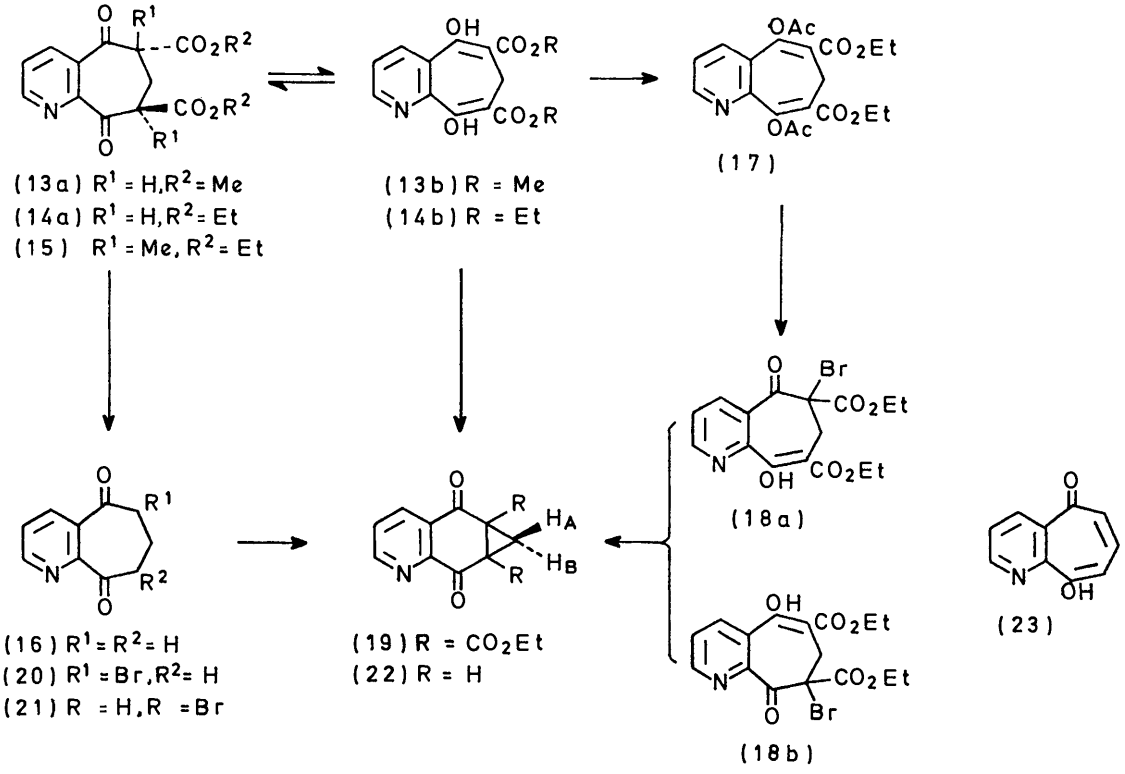
[1] D. M. Dimitrijevic, Z. D. Tadic, and R. P. Saper, *Glasnik Khem. Drushtva. Beograd.*, 1957, **22**, 201 (*Chem. Abs.*, 1960, **54**, 4565).
[2] K. van Auwers and A. Heinze, *Ber.*, 1919, **52**, 584.
[3] F. P. Mazza, *Rend. Accad. Sci. fiz. mat.* (*Napoli*), 1928, **34**, 59 (*Chem. Abs.*, 1929, **23**, 2976).
[4] E. Schwerin, *Ber.*, 1894, **27**, 112.
[5] A. H. Homeyer and V. H. Wallingford, *J. Amer. Chem. Soc.*, 1942, **64**, 798.
[6] W. Dieckmann, *Ber.*, 1899, **32**, 2227.

with diethyl succinate and sodium, gave diethyl 5,8-dihydroxyquinoline-6,7-dicarboxylate (7) in 58% yield.



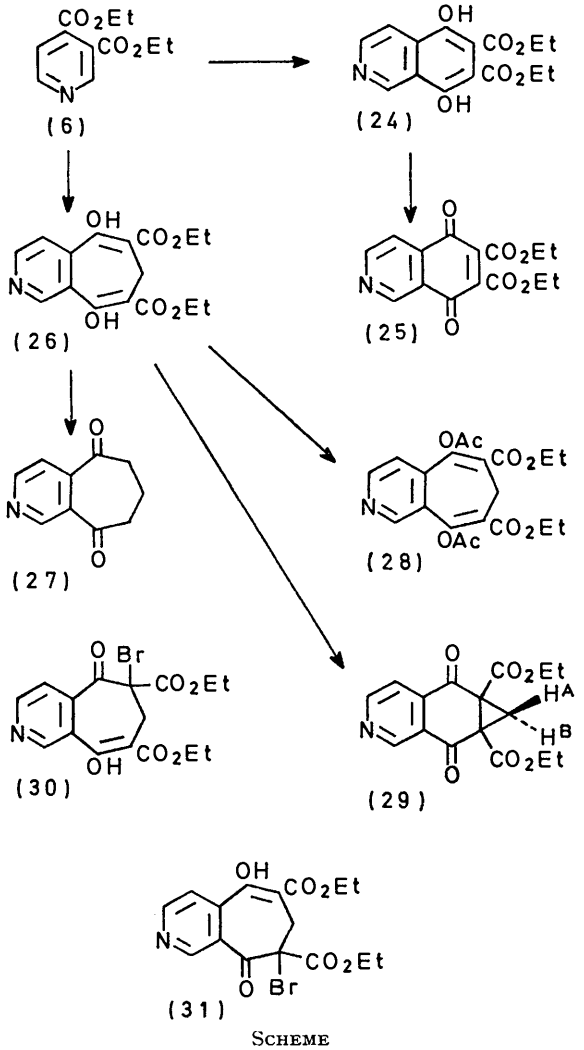
This reaction provides a relatively rare approach to quinoline synthesis by pyridine annulation. Oxidation of the diol (7) with lead tetra-acetate gave the quinone (8), which reacted readily with cyclopentadiene to give the bridged aza-anthracene (9). A similar reaction with 1,3-butadiene would provide a direct route to the benzo[*g*]quinoline series. The diol (7) was acetylated to give the diacetate (10); another route to the benzo[*g*]-quinoline series would be provided by a further annulation with diethyl succinate and a derivative such as (10). Hydrolysis of the diol diester (7) by boiling hydrobromic acid led to a dihydroxy-monocarboxylic acid; the physical data do not enable us to distinguish between structures (11) and (12).

Buchanan and Sutherland [7] used Dieckman's route [6] to 5,9-dihydroxy-7*H*-benzocycloheptene-6,8-dicarboxylates to obtain access to a wide range of tropone and tropolone derivatives. The analogous reaction between dimethyl pyridine-2,3-dicarboxylate and dimethyl glutarate (with sodium) gave a 50% yield of dimethyl 5,9-dihydroxy-7*H*-cyclohepta[*b*]pyridine-6,8-dicarboxylate (13); the diethyl ester (14) was similarly prepared. The n.m.r. spectra of the esters (Table 2) showed a 2H singlet at δ 3·0 p.p.m.; comparison with compounds of fixed structure [the dimethyl derivative (15) and the diacetate (17)] indicated that the esters exist predominantly in the bisenol forms (13b) and (14b) rather than the diketo forms (13a) and (14a). Methylation of the bisenolate from ester (14) gave the dimethyl derivative (15). The n.m.r. signals for the methyl groups and for the ester methylene groups were split; this non-equivalence suggests the *trans* arrangement as in formula (15) or its diastereoisomer. By acidic hydrolysis of the ester (13) or (14) the cyclohepta[*b*]-pyridine-5,9-dione (16) was obtained, and acetylation of



[7] G. L. Buchanan and J. K. Sutherland, *J. Chem. Soc.*, 1956, 2620.

the diol diester (14) with acetic anhydride gave the bisenol acetate (17). Bromination of either the diol (14) or the diacetoxy-compound (17) with *N*-bromosuccinimide gave an unstable monobromo-derivative; spectral evidence indicated structure (18a) or (18b). The monobromo-derivative (18) was slowly converted (more rapidly in aqueous triethylamine) into a bromine-free product, $C_{16}H_{15}NO_6$. The n.m.r. spectrum of this product showed two 1H doublets (J 6 Hz) at δ 2·15 and 2·9 p.p.m., indicating the tricyclic structure (19). The same cyclopropa[*g*]quinolinedione was obtained by treatment of the diol diester (14) with lead tetra-acetate or dichlorodicyanobenzoquinone (DDQ). The chemical shift difference between H_A and H_B is in good agreement



SCHEME

with that reported for similar norcaradiene derivatives;[8-10] Rundel and Hästner[10] report shifts of δ 2·5 and 1·6 p.p.m. for the geminal protons in a norcaradienedione derived from a di-t-butyl-*p*-benzoquinone. The cyclopropane ring in compound (19) could not be opened thermally, photochemically, or with base. The ester groups in compound (19) were resistant to hydrolysis under acidic conditions, so that the diester (19) failed to provide a route to a pyridotropolone. Bromination of the dione (16) with *N*-bromosuccinimide gave a product with spectral characteristics expected for the monobromo-cycloheptanedione (20) or (21). The crude bromo-derivative was stirred with aqueous triethylamine; tedious separation gave the parent cyclopropa[*g*]quinoline-5,7-dione (22). When heated to 150—160° the cyclopropane derivative (22) gave no trace of the 9-hydroxy-5*H*-cyclohepta[*b*]pyridin-5-one (23) (the γ-tropolone).

A similar series of reactions starting from diethyl pyridine-3,4-dicarboxylate (6) is summarised in the Scheme. The product from a reaction with diethyl succinate was diethyl 5,8-dihydroxyisoquinoline-6,7-dicarboxylate (24), oxidised by lead tetra-acetate to the quinone (25). With diethyl glutarate the product was the cyclohepta[*c*]pyridine diester (26). Hydrolysis and decarboxylation of the ester (26) gave the cyclohepta[*c*]-pyridinedione (27). Bromination of the diester (26) or of the enol acetate (28) with *N*-bromosuccinimide gave the bromo-ketone (30) or its 8-bromo-isomer (31). Dehydrobromination of the bromo-ketone (30), or more conveniently direct oxidation of the diester (26), again provided the cyclopropane derivative (29) rather than the γ-tropolone derivative.

Some interest has been shown recently in the production of benzopyridazinediones which can fragment to give benzocyclobutenediones and nitrogen, or benzyne (with nitrogen and carbon monoxide loss).[11] We have prepared the cyclic hydrazides of pyridine-2,3- and 3,4-dicarboxylic acids, (32) and (33). When these cyclic hydrazides were oxidised with lead tetra-acetate in the presence of cyclopentadiene they gave the adducts of the two pyridopyridazinediones, compounds (34) and (35), respectively. The structures of the adducts were established by analyses and n.m.r. spectra, and by hydrogenation of the adduct (34) to the dihydro-derivative (36). A similar oxidation of the hydrazide (32) in the presence of penta-1,3-diene gave the methyl derivative (37) (or its isomer). Some pyrolysis experiments were performed on the adducts (34) and (35) in the hope of a fragmentation, first to the pyridopyridazinedione and thence to the pyridocyclobutenedione or the pyridyne. These pyrolyses were unsuccessful and this work has been discontinued.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. Thin- and thick-layer chromatography were performed on Merck silica gel PF_{254}, the latter on 40 cm plates. Column chromatography used Woelm alumina (activity shown in parentheses). N.m.r. shifts are given in p.p.m. from tetramethylsilane. U.v. determinations were for solutions in 95% ethanol.

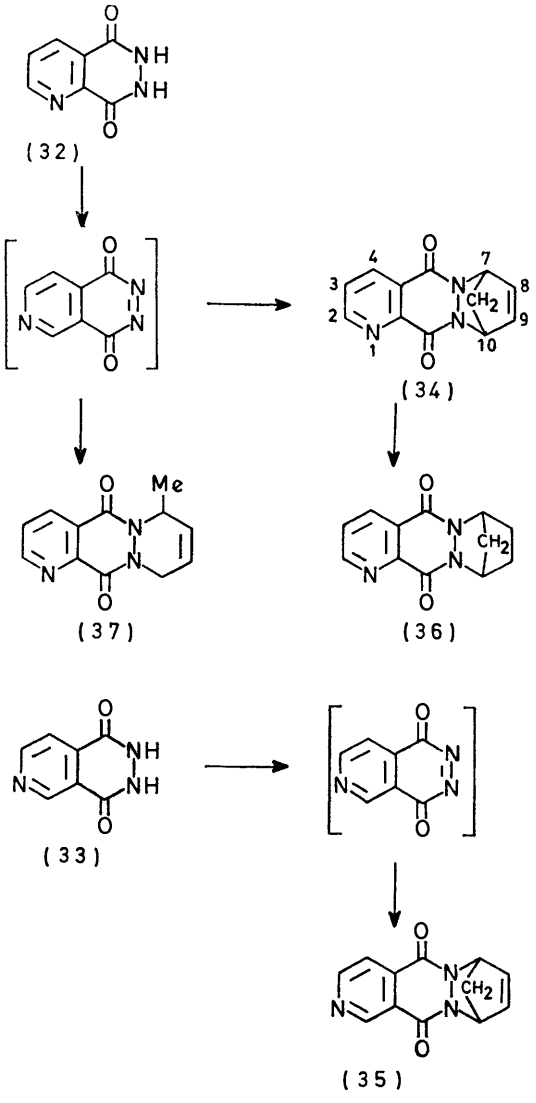
[8] F. M. Dean, P. G. Jones, and P. Sidisunthorn, *J. Chem. Soc.*, 1962, 5186.

[9] W. Howell, M. Ktenas, and J. MacDonald, *Tetrahedron Letters*, 1964, 1719.

[10] W. Rundel and P. Kästner, *Annalen*, 1970, **737**, 87.

[11] D. L. Forster, T. L. Gilchrist, C. W. Rees, and E. Stanton, *Chem. Comm.*, 1971, 695.

Diethyl 5,8-*Dihydroxyquinoline*-6,7-*dicarboxylate* (7).—Ethanol (2 ml) was added to sodium wire (2·1 g), then to the vigorously stirred mixture were added simultaneously (dropwise) dimethyl pyridine-2,3-dicarboxylate [12] [10 g,



with dry xylene (5 ml)] and diethyl succinate [8·1 g, with dry xylene (5 ml)]. Stirring and boiling were then continued for 1·5 h, during which much solid deposited. The cooled mixture was treated with ice-cold water (200 ml), and the aqueous layer was separated and neutralised with 30% acetic acid. The mixture was extracted with chloroform (3 × 150 ml) and the extract was dried and evaporated. The residue crystallised from petroleum (b.p. 60—80°) to give the *diester* (7), m.p. 137—138° (8·4 g, 58%) (Found: C, 58·9; H, 5·2; N, 4·3. $C_{15}H_{15}NO_6$ requires C, 59·0; H, 4·9; N, 4·6%), $\nu_{max.}$ ($CHCl_3$) 3420, 1725, and 1665 cm^{-1}; $\lambda_{max.}$ 208, 232, 268, and 341 nm (log ε 4·40, 3·98, 4·46, and 3·56). For all quinoline and isoquinoline derivatives n.m.r. and mass spectral data are in Table 1.

Diethyl 5,8-*Dihydro*-5,8-*dioxoquinoline*-6,7-*dicarboxylate* (8).—A solution of the dihydroxyquinoline diester (7) (2 g) in benzene (40 ml) containing lead tetra-acetate (4·3 g) was boiled for 6 h. The benzene was evaporated off, and the residue neutralised and extracted with chloroform. The extracts were dried and evaporated, giving an oil. Extraction with hot petroleum (b.p. 60—80°) gave, on cooling the extracts, the *quinone* (8), yellow crystals, m.p. 104—105° (Found: C, 59·6; H, 4·5; N, 4·6. $C_{15}H_{13}NO_6$ requires C, 59·4; H, 4·3; N, 4·6%), $\nu_{max.}$ ($CHCl_3$) 1740 and 1685 cm^{-1}; $\lambda_{max.}$ 205, 222sh, 242, and 345sh nm (log ε 4·03, —, 4·26, —).

Diethyl 5,5a,6,9,9a,10-*Hexahydro*-5,10-*dioxo*-6,9-*methanobenzo*[g]*quinoline*-5a,9a-*dicarboxylate* (9).—A solution of the quinone (8) (2 g) and cyclopentadiene (0·5 g) in benzene (20 ml) was stirred at room temperature (7 days). Removal of the benzene left a solid, which crystallised from carbon tetrachloride to give the *Diels–Alder adduct* (9), m.p. 119—120° (1·4 g, 65%) (Found: C, 65·4; H, 5·6; N, 3·8. $C_{20}H_{19}NO_6$ requires C, 65·0; H, 5·2; N, 3·8%), $\nu_{max.}$ ($CHCl_3$) 1750 and 1690 cm^{-1}; $\lambda_{max.}$ 216, 243, and 275sh nm (log ε 4·22, 3·74, —); δ($CDCl_3$) 1·2 (6H, t), 1·75 (1H, d, *J* 10 Hz), 2·7 (1H, d, *J* 10 Hz), 4·05 (6H, m), 6·2 (2H, m), 7·8 (1H, dd), 8·45 (1H, dd), and 9·15 p.p.m. (1H, dd); m/e^{+} 369 (M^{+}), 325, 324, 305, 296, 251, 234, and 121.

Diethyl 5,8-*Diacetoxyquinoline*-6,7-*dicarboxylate* (10).—A solution of the diol (7) (3 g) in acetic anhydride (30 ml) was boiled (15 h). Acetic anhydride was removed under reduced pressure, and the residue was neutralised and extracted with chloroform. The extracts were dried and evaporated, leaving a red gum; the *diacetoxy-derivative* (10) had m.p. 167—168° (from benzene) (3·3 g, 95%) (Found: C, 58·5; H, 4·9; N, 3·6. $C_{19}H_{19}NO_8$ requires C, 58·6; H, 4·9; N, 3·6%), $\nu_{max.}$ ($CHCl_3$) 1770 and 1738 cm^{-1}; $\lambda_{max.}$ 211, 243, and 280sh nm (log ε 4·50, 4·64, —).

Hydrolysis of the Diester (7).—A solution of the diester (7) (3 g) in aqueous 48% hydrobromic acid was boiled (2 h) then cooled, and the crystalline product (2·7 g, 96%) was filtered off. The almost pure dihydroxyquinolinecarboxylic acid [(11) or (12)] hydrobromide had m.p. >300° (Found: C, 41·6; H, 3·3; N, 4·7. Calc. for $C_{10}H_7NO_4$,HBr: C, 41·9; H, 2·8; N, 4·7%).

Dimethyl 5,9-*Dihydroxy*-7H-*cyclohepta*[b]*pyridine*-6,8-*dicarboxylate* (13).—Prepared as described for compound (7) from dimethyl pyridine-2,3-dicarboxylate [12] (10 g) and dimethyl glutarate (8·1 g) in 50% yield (7·6 g), the *dimethyl ester* (13) had m.p. 139—140° (from benzene) (Found: C, 57·8; H, 4·8; N, 4·6. $C_{14}H_{13}NO_6$ requires C, 57·7; H, 4·5; N, 4·8%), $\nu_{max.}$ ($CHCl_3$) 1730, 1650, and 1610 cm^{-1}; $\lambda_{max.}$ 203, 233sh, 238, 280, and 322sh nm (log ε 4·20, —, 4·17, 4·36, —). All n.m.r. and mass spectral data for cycloheptapyridines are in Table 2.

Diethyl 5,9-*Dihydroxy*-7H-*cyclohepta*[b]*pyridine*-6,8-*dicarboxylate* (14).—Prepared as described for compound (7), from diethyl pyridine-2,3-dicarboxylate [12] (10 g), diethyl glutarate (8·5 g), and sodium (2·1 g) in 55% yield (7·3 g), the *cycloheptapyridine diester* (14) had m.p. 117—118° (from petroleum–ether) (Found: C, 60·5; H, 5·5; N, 4·4. $C_{16}H_{17}NO_6$ requires C, 60·2; H, 5·3; N, 4·4%), $\nu_{max.}$ (CCl_4) 1645 and 1615 cm^{-1}; $\lambda_{max.}$ 204, 225sh, 239, 281, and 322sh nm (log ε 4·11, —, 4·18, 4·35, —).

Diethyl 6,7,8,9-*Tetrahydro*-6,8-*dimethyl*-5,9-*dioxo*-5H-*cyclohepta*[b]*pyridine*-6,8-*dicarboxylate* (15).—The sodium salt of the diester (14) (2 g) was prepared by use of sodium ethoxide (1 g) in ethanol (20 ml). Methyl iodide (2·4 g) was added and the mixture was stirred overnight. The ethanol was removed and the residual red oil was extracted with hot petroleum (b.p. 60—80°). On cooling the extracts the *dimethyl derivative* (15) crystallised, m.p. 154—155°

[12] C. Engler, *Ber.*, 1894, **27**, 1784.

(0·44 g, 20%) (Found: C, 62·1; H, 6·3; N, 4·0. $C_{18}H_{21}NO_6$ requires C, 62·3; H, 6·1; N, 4·1%), $\nu_{max.}$ ($CHCl_3$) 1735 and 1710 cm^{-1}; $\lambda_{max.}$ 213, 244, and 275sh nm (log ε 4·33, 3·84, —).

6,7-Dihydro-5H-cyclohepta[b]*pyridine-5,9(8H)-dione* (16). —A solution of the diethyl ester (14) (2 g) in aqueous 48% hydrobromic acid (20 ml) was boiled (1·5 h) then evaporated under vacuum. The residue was neutralised with aqueous sodium hydrogen carbonate and extracted with chloroform. The dried chloroform solution was evaporated, giving a yellow oil. Chromatography on alumina (III) (with chloroform as eluant) gave the *cycloheptapyridinedione* (16), m.p. 63—64° (0·94 g, 85%) (Found: C, 68·4; H, 5·6; N, 8·0. $C_{10}H_9NO_2$ requires C, 68·5; H, 5·2; N, 8·0%), $\nu_{max.}$ (CCl_4) 1690 cm^{-1}; $\lambda_{max.}$ 212, 236, and 270sh nm (log ε 4·08, 3·80, —).

Diethyl 5,9-Diacetoxy-7H-cyclohepta[b]*pyridine-6,8-dicarboxylate* (17).—A solution of the diester (14) (3 g) in acetic anhydride (30 ml) was boiled (12 h), and then evaporated under reduced pressure. The residue was neutralised with aqueous sodium hydrogen carbonate and extracted with chloroform. The dried extracts were evaporated and the residue chromatographed on alumina (III). Elution with petroleum (b.p. 60—80°)–benzene (4 : 1) gave a solid, which yielded the *diacetoxy-compound* (17), m.p. 134—135° (from carbon tetrachloride) (2·9 g, 75%) (Found: C, 59·6; H, 5·7; N, 3·7. $C_{20}H_{21}NO_8$ requires C, 59·6; H, 5·3; N, 3·5%), $\nu_{max.}$ ($CHCl_3$) 1768, 1710, and 1628 cm^{-1}; $\lambda_{max.}$ 205, 236, and 252sh nm (log ε 4·09, 4·44, —).

Diethyl 6-Bromo-6,7-dihydro-9-hydroxy-5-oxo-5H-cyclohepta[b]*pyridine-6,8-dicarboxylate* (18).—(*a*) A solution of the diester (14) (3 g) and *N*-bromosuccinimide (1·4 g) in chloroform (40 ml) was boiled (15 min) over a 200 W bulb. The solution was cooled in ice and filtered, and the filtrate was washed with water (2 × 20 ml), then dried. Evaporation gave a gum, which was extracted with hot benzene; the cooled solution yielded the unstable bromo-diester (18) (3·2 g, 85%), $\nu_{max.}$ ($CHCl_3$) 1745, 1645, and 1610 cm^{-1}; $\lambda_{max.}$ 208, 223, 239, 281, and 320 sh nm (log ε 4·04, 4·09, 4·10, 4·27, —).

(*b*) A similar bromination of the diacetoxy-diester (17) gave the bromo-derivative in 80% yield.

Diethyl 5a,6,6a,7-Tetrahydro-5,7-dioxo-5H-cyclopropa[g]*quinoline-5a,6a-dicarboxylate* (19).—(*a*) A solution of the diester (14) (3 g) in benzene (50 ml) containing lead tetra-acetate (8·9 g) was boiled (8 h). Evaporation of the benzene, neutralisation of the residue ($NaHCO_3$), extraction with chloroform, and removal of the chloroform gave an oil. Extraction with hot benzene, followed by cooling of the extract, gave the *cyclopropaquinoline diester* (19), m.p.

TABLE 1

N.m.r.† and mass spectral data for quinolines and isoquinolines

Compound	δ (p.p.m.) H-1	H-2	H-3	H-4	Other	*J*/Hz	*m/e*$^+$
(7)		8·85(dd)	7·45(dd)	8·6(dd)	11·88(OH) 4·4(4H,q) 1·4(6H,t)	$J_{2,3}$ 4·3 $J_{2,4}$ 1·7 $J_{3,4}$ 8·5	305(M^+), 261, 260, 231, 230, 159
(8)		9·15(dd)	7·8(dd)	8·5(dd)	4·4(4H,q) 1·3(6H,t)	$J_{2,3}$ 4·3 $J_{2,4}$ 1·7 $J_{3,4}$ 8·5	303(M^+), 258, 257, 231
(10)		8·95(dd)	7·4(dd)	8·15(dd)	4·4(4H,q) 2·45(6H,s) 1·35(6H,t)		389 (M^+, very small), 347, 306, 260, 232
(11) or (12)							205(M^+), 189, 188, 160, 103, 82, 80
(24)	9·68(s)		8·75(d)	8·05(d)	4·4(4H,q) 1·35(6H,t)	$J_{3,4}$ 5·5	305(M^+), 260, 257, 231, 211, 142, 137
(25)	9·25(s)		9·05(d)	7·9(d)	4·3(4H,q) 1·25(6H,t)	$J_{3,4}$ 5·5	303(M^+), 258, 231, 230, 214, 201, 186, 175

† $CDCl_3$ solution.

TABLE 2

N.m.r.† and mass spectral data for cyclohepta[*b*]- and cyclohepta[*c*]-pyridines

Compound	δ (p.p.m.) H-1	H-2	H-3	H-4	H-6	H-7	H-8	Other	*J*/Hz	*m/e*$^+$
(13)		8·9(dd)	7·5(dd)	8·35(dd)		3·0(s)		12·6br(2H,OH) 3·9(6H,s)	$J_{2,3}$ 5·1 $J_{2,4}$ 1·7 $J_{3,4}$ 8·5	291(M^+), 260, 200
(14)		8·9(dd)	7·5(dd)	8·35(dd)		3·05(s)		12·6br(OH) 4·4(4H,q) 1·45(6H,t)	$J_{2,3}$ 5·1 $J_{2,4}$ 1·7 $J_{3,4}$ 8·5	319(M^+), 274, 246, 200
(15)		8·9(dd)	7·5(dd)	8·2(dd)		2·6(s)		3·8(4H,m), 1·6(6H,s) 0·7(8H,m)		347(M^+), 302, 273, 233
(16)		8·85(dd)	7·5(dd)	8·15(dd)	2·9(m)	2·5(m)	2·4(m)			175(M^+), 147, 105
(17)		8·8(dd)	7·45(dd)	8·0(dd)		3·2(s)		4·3(4H,q) 2·3(6H,s) 1·35(6H,t)		403(M^+), 361, 319, 274, 245, 200
(18)		8·75(dd)	7·38(dd)	8·2(dd)		2·9(s)		12·6br(OH) 4·22(4H,q) 1·3(6H,t)		399(M + 2), 397(M^+), 325, 320, 274, 273 247, 245
(26)	9·2(s)		8·75(d)	7·8(d)		2·95(s)		12·5br(OH) 4·3(4H,q) 1·4(6H,t)	$J_{3,4}$ 5·5	319(M^+), 290, 273, 246, 227, 200, 199, 172
(27)	9·0(s)		9·0(d)	7·64(d)	2·85(m)	2·25(m)	2·85(m)		$J_{3,4}$ 5·5	175(M^+), 147, 119, 105, 91, 77
(28)	8·92(s)		8·68(d)	7·5(d)		3·15(s)		4·24(4H,q) 2·26(6H,s) 1·3(6H,t)		403(M^+), 361, 319, 318, 273
(30)	9·1(s)		9·1(d)	7·8(d)		4·7	3·2	9·1(OH) 4·1(4H,m) 1·1(6H,m)		399(M + 2), 397(M^+), 369, 367, 339, 337, 327, 325, 319, 317

† $CDCl_3$ solution.

155—156° (2·5 g, 85%), $\nu_{max.}$ ($CHCl_3$) 1745 and 1698 cm^{-1}; $\lambda_{max.}$ 218 and 243 nm (log ε 4·36 and 3·88); δ ($CDCl_3$) 1·3 (6H, t), 2·15 (1H, d, *J* 6 Hz, H_A), 2·9 (1H, d, *J* 6 Hz, H_B), 4·3 (4H, q), 7·8 (1H, dd, *J* 5 and 8·5 Hz), 8·5 (1H, dd, *J* 8·5 and 1·7 Hz), and 9·1 p.p.m. (1H, dd, *J* 5 and 1·7 Hz); *m/e*$^+$ 317 (M^+), 272, and 244 (Found: C, 69·5; H, 4·4; N, 7·8. $C_{10}H_7NO_2$ requires C, 69·4; H, 4·6; N, 8·1%).

(*b*) The dione (19) was also obtained from the diester (14) and DDQ in boiling benzene; the crude product was purified by chromatography.

(*c*) The bromo-compound (18) (2 g) was stirred with ether and aqueous triethylamine (30%) for 4 h. The ethereal layer was separated, dried, and evaporated to give crude dione (19) (yield of pure product 86%).

6,6a-*Dihydro*-5a*H*-*cyclopropa*[g]*quinoline*-5,7-*dione* (22).—A solution of the cycloheptapyridinedione (16) (2 g) with *N*-bromosuccinimide (2·1 g) in chloroform (40 ml) was boiled (20 min) over a 200 W bulb. The solution was cooled, filtered, and washed with water, dried, and evaporated to give an unstable oil whose spectral characteristics were those expected for bromo-dione (20) or (21). A solution of the oil in chloroform was stirred with aqueous 30% triethylamine (4 ml) for 12 h; the chloroform layer was separated, dried, concentrated, and chromatographed on alumina (III). Elution with chloroform gave the crude cyclopropaquinoline, purified by p.l.c. [benzene–chloroform (3 : 2), several elutions]. The major band yielded the *dione* (22), m.p. 138—139° (from carbon tetrachloride) (0·6 g, 30%) (Found: C, 69·5; H, 4·4; N, 7·8. $C_{10}H_7NO_2$ requires C, 69·4; H, 4·6; N, 8·1%), $\nu_{max.}$ ($CHCl_3$) 1690 cm^{-1}; $\lambda_{max.}$ 219 and 238sh nm (log ε 4·08, —); δ ($CDCl_3$) 1·85 (2H, m), 2·88 (2H, m), 7·7 (1H, dd, *J* 5 and 8·5 Hz), 8·4 (1H, dd, *J* 8·5 and 0·8 Hz), and 9·08 p.p.m. (1H, dd, *J* 5 and 0·8 Hz); *m/e*$^+$ 173 (M^+), 145, 117, 116, 106, and 105.

Diethyl 5,8-*Dihydroxyisoquinoline*-6,7-*dicarboxylate* (24).—Prepared as described for compound (7) from diethyl pyridine-3,4-dicarboxylate,[13] in 50% yield, the *dihydroxyisoquinoline diester* (24), crystallised from petroleum (b.p. 60—80°), m.p. 154—155° (Found: C, 59·4; H, 4·8; N, 4·5. $C_{15}H_{15}NO_6$ requires C, 59·0; H, 4·9; N, 4·6%), $\nu_{max.}$ ($CHCl_3$) 3400, 1728, and 1668 cm^{-1}; $\lambda_{max.}$ 219, 248, and 254 nm (log ε 4·44, 4·25, and 3·90).

Diethyl 5,8-*Dihydro*-5,8-*dioxoisoquinoline*-6,7-*dicarboxylate* (25).—Prepared as described for compound (8), from compound (24), in 85% yield, the *isoquinolinedione hydrate* (25) crystallised from petroleum (b.p. 60—80°) as yellow needles, m.p. 144—145° (85%) (Found: C, 55·6; H, 4·9; N, 4·3. $C_{15}H_{13}NO_6,H_2O$ requires C, 55·9; H, 4·9; N, 4·3%), $\nu_{max.}$ ($CHCl_3$) 1740 and 1675 cm^{-1}; $\lambda_{max.}$ 206, 254, and 310sh nm (log ε 4·15, 4·18, —).

Diethyl 5,9-*Dihydroxy*-7H-*cyclohepta*[c]*pyridine*-6,8-*dicarboxylate* (26).—Prepared as described for compound (7) from diethyl pyridine-3,4-dicarboxylate and diethyl glutarate, in 40% yield, the *cyclohepta*[c]*pyridine diester* (26), crystallised from petroleum (b.p. 60—80°), had m.p. 93—94° (Found: C, 59·8; H, 5·3; N, 4·3. $C_{16}H_{17}NO_6$ requires C, 60·2; H, 5·3; N, 4·4%), $\nu_{max.}$ ($CHCl_3$) 1645 and 1610 cm^{-1}; $\lambda_{max.}$ 206, 218sh, 252, 272, and 320 nm (log ε 4·08, —, 4·27, 4·18, and 3·94).

6,7-*Dihydro*-5H-*cyclohepta*[c]*pyridine*-5,9(8H)-*dione* (27).—Prepared as described for dione (16) from the dione diester (26) in 94% yield, the *cyclohepta*[c]*pyridinedione* (27) had m.p. 64—65° (Found: C, 68·5; H, 5·3; N, 7·8. $C_{10}H_9NO_2$ requires C, 68·5; H, 5·2; N, 8·0%), $\nu_{max.}$ ($CHCl_3$) 1688 cm^{-1}; $\lambda_{max.}$ 209, 228, and 283 nm (log ε 4·02, 3·69, and 3·35).

Diethyl 5,9-*Diacetoxy*-7H-*cyclohepta*[c]*pyridine*-6,8-*dicarboxylate* (28).—Prepared as described for compound (17), from the diester (26), in 85% yield, the *diacetoxy diester* (28), was eluted from an alumina column (III) with benzene–chloroform (9 : 1). The yellow oil failed to crystallise (Found: C, 59·5; H, 5·7; N, 3·4. $C_{20}H_{21}NO_8$ requires C, 59·6; H, 5·3; N, 3·5%), $\nu_{max.}$ ($CHCl_3$) 1775, 1710, and 1620 cm^{-1}; $\lambda_{max.}$ 212sh, 241, and 308sh nm (log ε —, 4·45, —).

5a,6,6a,7-*Tetrahydro*-5,7-*dioxo*-5H-*cyclopropa*[g]*isoquinoline*-5a,6a-*dicarboxylate* (29).—(*a*) Prepared from the diester (26) as described for compound (19), with lead tetra-acetate, in 90% yield, the *cyclopropaisoquinoline* (29) had m.p. 94—95° (from benzene) (Found: C, 60·4; H, 4·9; N, 4·2. $C_{16}H_{15}NO_6$ requires C, 60·6; H, 4·7; N, 4·4%), $\nu_{max.}$ ($CHCl_3$) 1748 and 1698 cm^{-1}; $\lambda_{max.}$ 212, 238sh, and 297 nm (log ε 4·33, —, 3·52); δ ($CDCl_3$) 1·3 (6H, t), 2·1 (1H, d, *J* 6 Hz, H_A), 2·9 (1H, d, *J* 6 Hz, H_B) 4·3 (4H, q), 7·85 (1H, d, *J* 5 Hz), 9·05 (1H, d, *J* 5 Hz), and 9·3 p.p.m. (1H, s); *m/e*$^+$ 317 (M^+), 289, 262, 245, 217, and 199.

(*b*) The dihydroxy-diester (26) was brominated with *N*-bromosuccinimide, as for compound (14). Only one product was present (t.l.c.), identified by its spectra as diethyl 6-bromo-6,7-dihydro-9-hydroxy-5-oxo-5*H*-cyclohepta[c]pyridine-6,8-dicarboxylate (30) [or the 8-bromo-isomer (31)], $\nu_{max.}$ ($CHCl_3$) 1740 and 1720 cm^{-1}; n.m.r. and mass spectral data are in Table 2. The crude bromo-compound (30) was treated with triethylamine as described for compound (22); chromatography on alumina (III) (chloroform elution) gave the cyclopropaisoquinoline (29) in 70% yield.

(*c*) The diacetoxy diester (28) was brominated by *N*-bromosuccinimide, as described for compound (14). The crude product was purified by p.l.c. (chloroform) to give two main bands. The faster running band contained the cyclopropaisoquinolinedione (29) (40% yield). The slower band contained some hydrated derivative of the bromo-compound (30) [or (31)].

7,10-*Dihydro*-7,10-*methanopyridazo*[1,2-a]*pyrido*[2,3-d]-*pyridazine*-5,12-*dione* (34).—Cyclopentadiene (0·8 g) and lead tetra-acetate (5·7 g) were added to a cold (0°) solution of 6,7-dihydropyrido[2,3-*d*]pyridazine-5,8-dione [14] (32) (2 g) in methylene chloride (250 ml), and the solution was stirred (4 h) and filtered. The filtrate was evaporated and the residue neutralised (aqueous $NaHCO_3$) and extracted with chloroform. The dried extracts were evaporated; the residue crystallised from ether to give the *Diels–Alder adduct* (34), m.p. 220° (decomp.) (1·7 g, 60%) (Found: C, 63·8; H, 4·0; N, 18·7. $C_{12}H_9N_3O_2$ requires C, 63·4; H, 4·0; N, 18·5%), $\nu_{max.}$ ($CHCl_3$) 1634 cm^{-1}; $\lambda_{max.}$ 208, 230sh, 266, and 317 nm (log ε 4·38, —, 3·68, and 3·61); δ ($CDCl_3$) 2·35 (2H, m, CH_2), 6·2 (2H, m, H-7 and H-10), 6·9 (2H, m, H-8 and H-9), 7·85 (1H, dd, *J* 8·5 and 5·1 Hz, H-3), 8·65 (1H, dd, *J* 8·5 and 1·7 Hz, H-4), and 9·25 p.p.m. (1H, dd, *J* 5 and 1·7 Hz, H-2); *m/e*$^+$ 227 (M^+), 105, and 77.

7,10-*Dihydro*-7,10-*methanopyridazino*[1,2-a]*pyrido*[3,4-d]-*pyridazine*-5,12-*dione* (35).—Prepared as for compound (34), from 6,7-dihydropyrido[3,4-*d*]pyridazine-5,8-dione [14,15] (33), in 55% yield, the isomeric *Diels–Alder adduct* (35) had m.p. 227° (decomp.) (from ether) (Found: C, 63·0; H, 3·7; N, 18·3), $\nu_{max.}$ ($CHCl_3$) 1638 cm^{-1}, $\lambda_{max.}$ 205, 224sh, 270, and 320 nm (log ε 4·38, —, 3·63, and 3·66); δ ($CDCl_3$) 2·2br (2H,

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s, CH_2), 6·0 (2H, m, H-7 and H-10), 6·8 (2H, m, H-8 and H-9), 8·05 (1H, d, *J* 5 Hz, H-4), 9·05 (1H, d, *J* 5 Hz, H-3), and 9·55 p.p.m. (1H, s, H-1); *m/e*$^+$ 227 (M^+), 105, 79, and 77.

7,8,9,10-*Tetrahydro*-7,10-*methanopyridazo*[1,2-a]*pyrido*-[2,3-d]*pyridazine*-5,12-*dione* (36).—A solution of the adduct (34) (500 mg) in ethanol (60 ml) containing concentrated hydrochloric acid (0·5 ml) and palladium–charcoal (100 mg; 5%) was hydrogenated at atmospheric temperature and pressure till uptake ceased. The filtered solution was evaporated, neutralised, and extracted with chloroform. The residue obtained by removal of the chloroform crystallised from ether to give the *dihydro-adduct* (36), m.p. 206—207° (480 mg, 95%) (Found: C, 62·6; H, 5·1; N, 18·0. $C_{12}H_{11}N_3O_2$ requires C, 62·9; H, 4·8; N, 18·3%), $\nu_{max.}$ ($CHCl_3$) 1630 cm^{-1}; $\lambda_{max.}$ 205, 229sh, 258, and 315 nm (log ε 4·34, —, 3·77, and 3·66); δ ($CDCl_3$) 2·05 (6H, m, 3 × CH_2), 5·45br (2H, d, H-7 and H-10), 7·7 (1H, dd, *J* 8·5 and 5 Hz, H-3), 8·65 (1H, dd, *J* 8·5 and 1·7 Hz, H-4), and 9·1 p.p.m. (1H, dd, *J* 5 and 1·7 Hz); *m/e*$^+$ 229 (M^+), 200, 105, 85, 83, and 87.

7,10-*Dihydro*-7-*methyl*-7,10-*methanopyridazo*[1,2-a]-*pyrido*[2,3-d]*pyridazine*-5,12-*dione* (37).—Prepared as for compound (34) but with piperylene (0·8 g), the *piperylene adduct* (37) had m.p. 145° (decomp.) (from ether) (0·7 g, 25%) (Found: C, 63·2; H, 5·1; N, 18·3. $C_{12}H_{11}N_3O_2$ requires C, 62·9; H, 4·8; N, 18·3%), $\nu_{max.}$ ($CHCl_3$) 1638 cm^{-1}; $\lambda_{max.}$ 208, 230sh, 268, and 315 nm (log ε 4·35, —, 3·63, and 3·52); δ ($CDCl_3$) 1·4 (3H, d, *J* 6 Hz, Me), 4·0—5·2 (2H, m, H-10), 5·3—5·9 (1H, m, H-7), 6·1 (2H, m, H-8 and H-9), 7·85 (1H, dd, *J* 8·5 and 5 Hz, H-3), 8·7 (1H, dd, *J* 8·5 and 1·5 Hz, H-4), and 9·2 p.p.m. (1H, dd, *J* 5 and 1·5 Hz); *m/e*$^+$ 229 (M^+), 214, 187, 105, and 77.

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