The Synthesis of Furano(3′ : 2′-3 : 4)*quinolines and the Structure of Dictamnic Acid.*

By M. F. GRUNDON, N. J. MCCORKINDALE, and (in part) M. N. RODGER.

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The dihydrofuranoquinolones (VI; R = H and R = OMe) have been prepared from diethyl (2-ethoxyethyl)malonate and aromatic amines, and one of these (VI; R = H) has been converted into 2-methoxyfurano (3′ : 2′-3 : 4)quinoline, an isomer of the alkaloid dictamnine. The structures of the products have been established by degradation and infrared and ultraviolet spectroscopy.

The structure of ethyl dictamnate has been confirmed by its conversion into 3-carboxy-2-chloro-4-methoxyquinoline.

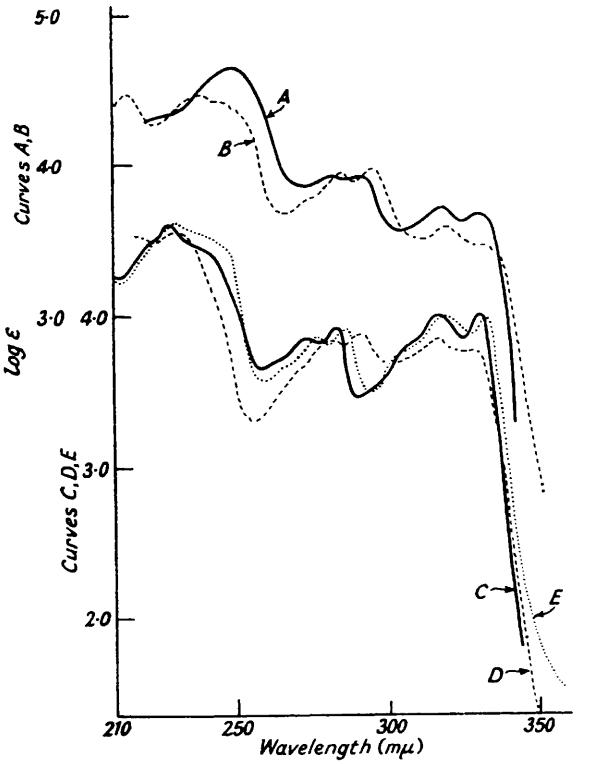
THE alkaloid dictamnine has been assigned structure (I; R = R′ = H) (Asahina, Ohta, and Inubuse, *Ber.*, 1930, **63**, 2045). Most of the degradative experiments did not distinguish between structures (I) and (II), but the linear structure was favoured by the isolation of an oxidation product, dictamnic acid (III; R = H). Asahina *et al.* (*loc. cit.*) did not synthesise dictamnic acid, but showed that it was not identical with a synthetic compound thought to be the isomeric acid (IV). The structures of other furanoquinoline alkaloids such as γ-fagarine (I; R = OMe, R′ = H) (Berinzaghi, Muruzabal, Labriola, and Deulofeu, *J. Org. Chem.*, 1945, **10**, 181) and skimmianine (I; R = R′ = OMe) (Asahina and Inubuse, *Ber.*, 1930, **63**, 2052) were derived by analogy with dictamnine. In view of the inconclusive nature of this evidence we investigated the synthesis of furanoquinolines and confirmed the structure of dictamnic acid.

Furanopyridines and furanoquinolines have been prepared previously from α-pyrone derivatives (Asahina and Inubuse, *Ber.*, 1932, **65**, 61; Robinson and Watt, *J.*, 1934, 1536), but the preparation of dihydrofuranopyridines from 3-substituted 2-pyridones (Matejka, Robinson, and Watt, *J.*, 1932, 2019; Stephens, Beutel, and Chamberlin, *J. Amer. Chem. Soc.*, 1942, **64**, 1093) suggested a more direct method. Ethyl (2-ethoxyethyl)malonate condensed with aniline in boiling diphenyl ether to give a dihydrofuranoquinolone by the elimination of 3 mols. of ethanol. Only one of the two possible isomers (V or VI; R = H) was obtained. Similarly, *o*-anisidine, in the same condensation, gave only a single component (V or VI; R = OMe). The isolation of 3-2′-ethoxyethyl-2 : 4-dihydroxy-8-methoxyquinoline after only 2 mols. of ethanol had been evolved suggested that dihydroxyquinolines are intermediates in this type of condensation, at least in the reaction with *o*-anisidine. The dihydrofuranoquinolone (V or VI; R = H) with phosphorus oxychloride gave 2 : 4-dichloro-3-2′-chloroethylquinoline.

The two dihydrofuranoquinolones (V or VI; R = H and R = OMe) gave the corresponding furanoquinolones (VII or VIII; R = H and R = OMe) by dehydrogenation with palladium–charcoal. The melting point (250°) of one of these compounds (VII or VIII; R = H) corresponded with the value of 249° given for nordictamnine (VII; R = H) derived from the alkaloid, but no sample of the natural material was available for comparison.

Witkop, Patrick, and Rosenblum (*J. Amer. Chem. Soc.*, 1951, **73**, 2641) have recommended the use of infrared and ultraviolet spectra to distinguish between 2- and 4-quinolones. Model compounds (for example, Nos. 6—11, Table) suggest that 2-quinolones have strong amide-carbonyl absorption at 1660—1650 cm.$^{-1}$, whereas 4-quinolones absorb at a lower frequency (1630—1620 cm.$^{-1}$). The two synthetic dihydrofuranoquinolones and the derived furanoquinolones show strong absorption bands at the higher frequency (Table), and thus appear to be 2-quinolones of structures (VI and VIII; R = H and R = OMe). The position of the amide band in the infrared spectra of variously substituted 2-quinolones (Table; see also Grundon and Boekelheide, *J. Amer. Chem. Soc.*, 1952, **74**, 2637) remains fairly constant, and should be of general use in recognising this type of system. The peak attributed to amide absorption in 4-quinolones may easily be confused

with quinoline ring vibrations, and, further, strong absorption in this region (1620—1630 cm.$^{-1}$) also occurs in some 2-quinolones (Table). Short and Thompson (*J.*, 1952, 168) discussed this apparent doublet in the spectra of related hydroxypyrimidines. The degree



Ultraviolet light absorption in ethanol of 1 : 2-*dihydro*-8-*methoxy*-2-*oxofurano*(3′ : 2′-3 : 4)*quinoline* (*A*), 1 : 2 : 4′ : 5′-*tetrahydro*-8-*methoxy*-2-*oxofurano*(3′ : 2′-3 : 4)*quinoline* (*B*), 1 : 2-*dihydro*-2-*oxofurano*(3′ : 2′-3 : 4)*quinoline* (*C*), 1 : 2 : 4′ : 5′-*tetrahydro*-2-*oxofurano*(3′ : 2′-3 : 4)*quinoline* (*D*), *and* 1 : 2-*dihydro*-1-*methyl*-2-*oxofurano*(3′ : 2′-3 : 4)*quinoline* (*E*).

of hydrogen bonding in those compounds whose spectra were determined in the solid state introduces a variable factor, which makes interpretation less reliable.

The ultraviolet spectra of a number of quinolones (see, for example, Ewing and Steck, *J. Amer. Chem. Soc.*, 1946, **68**, 2181; Steck, Ewing, and Nachod, *ibid.*, 1949, **71**, 238;

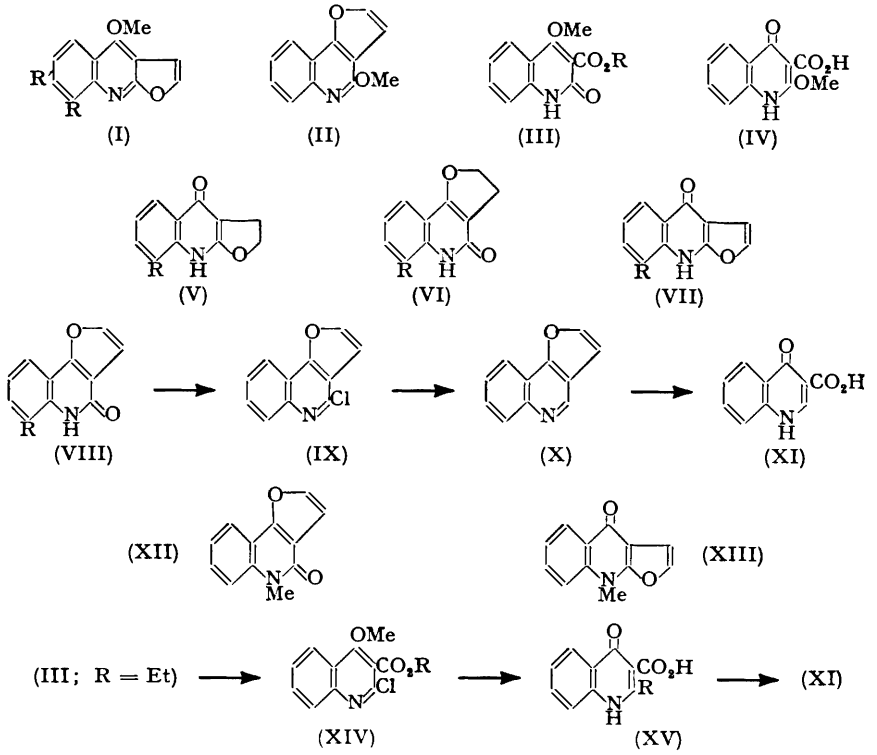
Infrared * *absorption bands in the region* 1800—1480 cm.$^{-1}$ *of* 2- *and* 4-*quinolones in Nujol suspensions* (*except when stated otherwise*).

No.	Substance	CO_2R	2-Quinolone amide I	4-Quinolone amide I	Other 5—6 μ bands
1	(VI; R = H)	—	1655 s	—	1625 m, 1606 m, 1585 m, 1507 m
2	(VI; R = OMe)	—	1654 s	—	1630 s, 1580 m, 1500 m
3	(VIII; R = H)	—	1660 s	—	1635 m, 1610 m, 1570 m
4	(XII)	—	1660 s	—	1590 m, 1510 m
5	(VIII; R = OMe)	—	1655 s	—	1600 m, 1505 m
6	2-Quinolone	—	1650 s	—	1605 m, 1555 m, 1505 w
7	4-Quinolone †	—	—	1628 m	1610 s, 1590 s, 1555 s, 1503 s
8	3 : 4-*cyclo*Penteno-2-quinolone [a]	—	1659 s	—	—
9	2 : 3-*cyclo*Penteno-4-quinolone [a]	—	—	1626 s	—
10	3-Carboxy-4-quinolone (XI) †	1670 s	—	1620 s	1580 m, 1517 m
11	Me ester of (XI) [b] ‡	1690 s	—	1630 s	1610 m, 1590 s, 1514 m
12	3-Ethoxycarbonyl-4-methoxy-2-quinolone	1730 m	1643 m	—	1600 s, 1498 s
13	(XIV; R = H) †	1710 m	—	—	1612 w, 1575 s, 1510 m
14	(XV; R = Cl) †	1690 s	—	1620 s	1555 m, 1520 s

* Spectra were determined with a Perkin–Elmer Model 13 (Double Beam) Spectrometer (NaCl prism). † KCl disc. ‡ In $CHCl_3$.

[a] Witkop *et al.*, *loc. cit.* [b] Grundon and Boekelheide, *loc. cit.*

Witkop *et al.*, *loc. cit.*) indicate that 2-quinolones have strong absorption at 2700—2850 Å which in 4-quinolones is either absent or appears as a shoulder. The ultraviolet spectra of the four synthetic compounds under consideration (see Figure) conform to the 2-quinolone pattern in having bifurcated peaks in the region 2730—2950 Å, although the presence of the second oxygen function may diminish the significance of this comparison. However, the ultraviolet spectra are closely related and show that the four compounds are of the same structural type. Thus, no rearrangement occurred during dehydrogenation.



The quinolones are insoluble in dilute aqueous alkali and fail to react with diazomethane. This lack of acidity is characteristic of 3-substituted 2-quinolones (Lamberton and Price, *Austral. J. Chem.*, 1953, **6**, 66; Arndt, Ergener, and Kutlu, *Chem. Ber.*, 1953, **86**, 951). Further, the very faint ferric chloride reactions given by these compounds are in accord with 2-quinolone structures. Proof of this conclusion was provided by the series of reactions (VIII ⟶ XI). The chlorofuranoquinoline (IX), prepared from the furanoquinolone (VIII; R = H) with phosphorus oxychloride, was unaffected by lithium aluminium hydride in ether or tetrahydrofuran. Reduction with zinc and sulphuric acid gave some furanoquinoline (X), and the small yield was possibly due to extensive hydrolysis to the furanoquinolone (VIII; R = H). The furanoquinoline (X) was prepared in good yield by conversion of the chlorofuranoquinoline into the corresponding hydrazine, which was reduced with aqueous copper sulphate. The isolation of 3-carboxy-4-quinolone (XI) by oxidation of the furanoquinoline with potassium permanganate provided convincing proof of the angular structure of the precursors.

The chlorofuranoquinoline (IX), by reaction with sodium methoxide in methanol, gave the corresponding methoxyfuranoquinoline (II), m. p. 52—53°, clearly not identical with dictamnine (m. p. 133°).

Methylation of the furanoquinolone (VIII; R = H) with methyl sulphate and alkali gave the *N*-methyl ether (XII), m. p. 130°. This compound cannot be identical either with *iso*dictamnine (XIII), m. p. 188°, or with a compound, m. p. 225° which was synthesised

from 3-formyl-2 : 4-dihydroxyquinoline through the α-pyrone derivative and assigned structure (XII) (Asahina and Inubuse, *Ber.*, 1932, **65**, 61). In view of this confusion the purity of our *N*-methyl ether was examined carefully, and chromatography showed it to be homogeneous. The conditions used for its preparation could conceivably have led to the rearrangement of the furanoquinolone system (see, for example, Lahey, Lamberton and Price, *Austral. J. Sci. Res.*, 1950, **3**, *A*, 155). The ultraviolet and infrared spectra of this product (Fig. and Table), which were very similar to that of the furanoquinolone (VIII; R = H), indicated that no such rearrangement occurred. It must, therefore, be concluded that the synthetic product, m. p. 225°, obtained by Asahina and Inubuse (*loc. cit.*) has some other structure.

The recent discovery by Brown, Hobbs, Hughes, and Ritchie (*Austral. J. Chem.*, 1954, **7**, 348) that the quinoline derivative prepared by Asahina, Ohta, and Inubuse (*loc. cit.*) was 2 : 4-dihydroxy-3-methoxycarbonylquinoline and not, as supposed, 3-carboxy-2-methoxy-4-quinolone (IV), emphasises the importance of determining the structure of dictamnic acid. Brown *et al.* (*loc. cit.*) reported a synthesis of dictamnic acid and, before the Australian publication was available, the same synthesis, with slight variations, was carried out in this laboratory (by Mr. M. N. Rodger). An important stage in this method involves the monomethylation of 3-ethoxycarbonyl-2 : 4-dihydroxyquinoline with diazomethane, which is assumed to give the 4-methyl ether by analogy with the methylation of 2 : 4-dihydroxyquinoline (Arndt *et al.*, *loc. cit.*). That this selective methylation does not always occur is shown by the reaction of 2 : 4-dihydroxy-6 : 7-dimethoxy-3-methoxycarbonylquinoline and diazomethane to give the dimethyl ether, and the failure to isolate a monomethyl ether is this reaction (Brown, *Austral. J. Chem.* 1955, **8**, 121). Such ambiguity demands further proof of the structure of dictamnic acid. Ethyl dictamnate (III; R = Et) with phosphorus oxychloride gave a small yield of 2 : 4-dichloro-3-ethoxycarbonylquinoline (also prepared from 3-ethoxycarbonyl-2 : 4-dihydroxyquinoline) but the principal product, obtained as an oil, probably consisted largely of 2-chloro-3-ethoxycarbonyl-4-methoxyquinoline (XIV; R = Et). Analysis of a distilled sample indicated some contamination with 2 : 4-dichloro-3-ethoxycarbonylquinoline, but brief alkaline hydrolysis of the crude material gave 3-carboxy-2-chloro-4-methoxyquinoline (XIV; R = H). The solubility of this compound in aqueous sodium hydrogen carbonate, its negative ferric chloride reaction, and its infrared spectrum (absence of amide-carbonyl absorption; Table) indicated that this compound was indeed a carboxymethoxyquinoline and not the isomeric methyl hydroxy-ester which might conceivably have been obtained by ester exchange. The methoxy-acid, on more prolonged alkaline hydrolysis, gave 3-carboxy-2-chloro-4-quinolone (XV; R = Cl), identical in properties with an oxidation product of chlorodeoxyflindersine, to which this structure was also ascribed (Brown *et al.*, *loc. cit.*). In the present work this assignment was confirmed by the conversion of the chloro-acid (XV; R = Cl) into the hydrazino-derivative (XV; R = $NH{\cdot}NH_2$), which was reduced with aqueous copper sulphate to 3-carboxy-4-quinolone (XI). This series of reactions (III; R = Et) ⟶ (XI) establishes the structure of dictamnic acid.

Experimental

Diethyl (2-Ethoxyethyl)malonate (Prelog and Bozicevic, *Ber.*, 1939, **72**, 1103).—In the preparation of the intermediate sulphonate, cooling the mixture of 2-ethoxyethanol and benzene sulphonyl chloride in ice–salt allowed more rapid addition of the aqueous sodium hydroxide. After reaction with diethyl malonate, the sulphonate gave diethyl (2-ethoxyethyl)malonate, fractionally distilled as a colourless oil (70% yield, based on 2-ethoxyethanol; Prelog *et al.*, *loc. cit.*, report 47%), b. p. 84—94°/0·6—0·8 mm., n_D^{16} 1·4284.

1 : 2 : 4′ : 5′-*Tetrahydro-2-oxofurano*(3′ : 2′-3 : 4)*quinoline* (VI; R = H).—A mixture of diethyl (2-ethoxyethyl)malonate (20 g.), aniline (7·3 g.), and diphenyl ether (250 c.c.) was heated under reflux. The evolution of ethanol ceased after 3 mols. (12 c.c.) had been collected (4½ hr.), but heating was continued for a further 1½ hr. The addition of light petroleum (b. p. 60—80°; 1 l.) gave a yellow precipitate (13·2 g.). By crystallisaton from pyridine, the *dihydrofuranoquinolone* was obtained as pale yellow prisms (6·68 g.), m. p. 272—275° (decomp.), raised to 280—281° (decomp.) by recrystallisation from pyridine or methanol (Found : C, 70·3; H,

4·9; N, 7·4. $C_{11}H_9O_2N$ requires C, 70·6; H, 4·9; N, 7·5%). Concentration of the pyridine solution gave a solid (2·73 g.), m. p. 269—273° (decomp.), shown to be identical with the foregoing product by a mixed m. p. and by comparison of infrared spectra. The total yield was 9·41 g. (65%). No other distinct compound was isolated.

The dihydrofuranoquinolone was insoluble in 2N-aqueous sodium hydroxide and was recovered after refluxing with potassium hydroxide in ethanol or with concentrated hydrochloric acid. The compound gave a faint yellow reaction with ferric chloride in ethanol.

2 : 4-*Dichloro*-3-2′-*chloroethylquinoline*.—The dihydrofuranoquinolone (0·5 g.) and phosphorus oxychloride (5 c.c.) were refluxed for 1½ hr. The solid, obtained after removal of the phosphorus oxychloride under reduced pressure and addition of water, separated from ethanol in brown crystals (0·17 g.), which were extracted with ether (100 c.c.). Evaporation of the ether solution gave 2 : 4-*dichloro*-3-2′-*chloroethylquinoline* in colourless rectangular plates (0·12 g.), m. p. 112—114° (Found: C, 50·4; H, 3·6; Cl, 40·7. $C_{11}H_8NCl_3$ requires C, 50·7; H, 3·1; Cl, 40·8%).

1 : 2-*Dihydro*-2-*oxofurano*(3′ : 2′-3 : 4)*quinoline* (VIII; R = H).—The dihydrofuranoquinolone (8 g.), 10% palladium–charcoal (6 g.), and diphenyl ether (50 c.c.) were heated under reflux for 14 hr. The mixture was treated with light petroleum (b. p. 60—80°), and the residue, obtained by filtration, was washed with light petroleum (b. p. 60—80°) and extracted with several portions of boiling ethanol. The combined extract was concentrated to small bulk, and brown crystals of the *furanoquinolone* (4·3 g.), m. p. 234—237°, separated on cooling. A further quantity (0·3 g.) crystallised from the diphenyl ether–light petroleum solution (total yield 4·6 g., 58%). Repeated crystallisation from ethanol (charcoal) gave colourless prisms, m. p. 249—250° (Found: C, 71·3; H, 3·6. $C_{11}H_7O_2N$ requires C, 71·3; H, 3·8%).

The compound was insoluble in 2N-aqueous sodium hydroxide, and gave a faint yellow colour with ferric chloride in ethanol.

1 : 2 : 4′ : 5′-*Tetrahydro*-8-*methoxy*-2-*oxofurano*(3′ : 2′-3 : 4)*quinoline* (VI; R = OMe).—A solution of *o*-anisidine (2·41 g.) and diethyl (2-ethoxyethyl)malonate (5 g.) in diphenyl ether (7 c.c.) was heated at 260° until 3 mols. of ethanol (3 c.c.) were evolved (3 hr.), and allowed to cool. The solid (3·92 g.), m. p. 212—216°, obtained by filtration and washing with light petroleum (b. p. 60—80°), gave the *quinolone* as yellow prisms (2·80 g.), m. p. 219—220° (from pyridine) (Found: C, 66·4; H, 4·9. $C_{12}H_{11}O_3N$ requires C, 66·3; H, 5·1%). Concentration of the pyridine solution afforded a further quantity (0·60 g.) (total yield 3·40 g., 80%). The quinolone was insoluble in 2N-aqueous sodium hydroxide, and gave a faint red colour with ferric chloride in ethanol.

3-2′-*Ethoxyethyl*-2 : 4-*dihydroxy*-8-*methoxyquinoline*.—The foregoing experiment was repeated with *o*-anisidine (4·81 g.), but the heating was discontinued after 2 mols. of ethanol had been obtained (50 min.). Addition of light petroleum (b. p. 60—80°) gave a dark brown oil, yielding a cream-coloured solid (4·2 g.), m. p. 114—117°, by trituration with ether. Crystallisation from ethyl acetate gave the *dihydroxyquinoline* as colourless prisms (1·0 g., 10%), m. p. 130—131° [Found: C, 63·7; H, 6·3; OMe, 23·0. $C_{14}H_{17}O_4N$ requires C, 63·8; H, 6·5; 1OEt + 1OMe (expressed as 2OMe), 23·6%]. This was soluble in 2N-aqueous sodium hydroxide and gave a deep red colour with ferric chloride in ethanol.

1 : 2-*Dihydro*-8-*methoxy*-2-*oxofurano*(3′ : 2′-3 : 4)*quinoline* (VIII; R = OMe).—The corresponding dihydroquinolone (VI; R = OMe) (2·0 g.), 10% palladium–charcoal (0·8 g.), and diphenyl ether (20 c.c.) were heated under reflux, and, after 7 hr., more palladium–charcoal (0·8 g.) was added, and heating was continued for a further 7 hr. On cooling, the solution deposited brown crystals of the *furanoquinolone* (1·80 g.), m. p. 190—193°, crystallising from ethanol in pale yellow prisms (0·66 g., 33%), m. p. 201—203° (Found: C, 66·9; H, 4·6. $C_{12}H_9O_3N$ requires C, 67·0; H, 4·2%). It was insoluble in 2N-aqueous sodium hydroxide and gave a faint red ferric chloride reaction in ethanol.

2-*Chlorofurano*(3′ : 2′-3 : 4)*quinoline* (IX).—A solution of the furanoquinolone (VIII; R = H) (2·25 g.) in phosphorus oxychloride (14 c.c.) was heated under reflux for 1 hr., the excess of reagent was removed under reduced pressure, and the residue was treated with water. The precipitate, on drying at room temperature and crystallising from ethanol (charcoal), afforded colourless needles of 2-*chlorofurano*(3′ : 2′-3 : 4)*quinoline* (1·25 g., 51%), m. p. 118° (Found: C, 64·7; H, 3·2; Cl, 17·3. $C_{11}H_6ONCl$ requires C, 64·9; H, 3·0; Cl, 17·4%).

2-*Methoxyfurano*(3′ : 2′-3 : 4)*quinoline* (II).—The foregoing chloroquinoline (0·10 g.) in methanol (2 c.c.) was refluxed with a solution from sodium (0·10 g.) in methanol (2 c.c.) for 1 hr., and the solution concentrated, diluted with water, and extracted with chloroform. Evaporation of the chloroform gave an oil which was extracted with light petroleum (b. p.

40—60°). Evaporation of the light petroleum and crystallisation of the residue from aqueous ethanol gave 2-*methoxyfurano*(3′ : 2′-3 : 4)*quinoline* as white needles (0·04 g., 41%), m. p. 52—53° (Found : C, 72·3; H, 4·8; OMe, 15·9. $C_{12}H_9O_2N$ requires C, 72·3; H, 4·6; 1OMe, 15·6%).

1 : 2-*Dihydro*-1-*methyl*-2-*oxofurano*(3′ : 2′-3 : 4)*quinoline* (XII).—1 : 2-Dihydro-2-oxofurano-(3′ : 2′-3 : 4)quinoline (0·25 g.), suspended in methanol (10 c.c.), was shaken with methyl sulphate (0·4 c.c.) and methanolic potassium hydroxide (1 c.c.; 20%) for 15 min. Addition of water (4 c.c.) gave a clear solution. After two similar additions of methyl sulphate and alkali at 15-min. intervals, the methanol was removed and the mixture extracted with chloroform. Evaporation of the chloroform gave a red oil which was dissolved in benzene and chromatographed on alumina. Elution with benzene, removal of the solvent, and crystallisation of the residue from light petroleum (b. p. 80—100°) gave colourless needles of the N-*methyl derivative* (0·025 g.), m. p. 129—130° (Found : C, 72·1; H, 4·6; N, 7·0; OMe, 0; *N*-Me, 6·4. $C_{12}H_9O_2N$ requires C, 72·3; H, 4·6; N, 7·0; 1*N*-Me, 7·5%). Elution of the alumina column with benzene–chloroform (2 : 1) gave a further quantity (0·066 g.) (total yield, 0·091 g., 34%). The compound slowly became red on exposure to light.

Elution with chloroform gave a brown solid, crystallising from ethanol in pale brown prisms (0·01 g.), m. p. 241—243°, alone or mixed with the starting materials.

Furano(3′ : 2′-3 : 4)*quinoline* (X).—(*a*) 2-Chlorofurano(3′ : 2′-3 : 4)quinoline (0·50 g.), 90% hydrazine hydrate (0·4 c.c.), and ethanol (3 c.c.) were heated under reflux for 3 hr., and then evaporated to dryness under reduced pressure. The residue, when treated with water, gave a yellow solid (0·49 g.), m. p. 120°, probably consisting of the hydrazine derivative. The solid was suspended in boiling water (20 c.c.), boiling 10% aqueous copper sulphate (20 c.c.) was added, and the mixture was refluxed for 1 hr. Pale yellow crystals (*ca.* 5 mg.), which distilled in steam from the mixture, proved to be 2-chlorofurano(3′ : 2′-3 : 4)quinoline (m. p. and mixed m. p. 112—113°). The solution was made alkaline with 2N-sodium hydroxide, and extracted with chloroform. Evaporation of the chloroform and distillation of the residue (0·28 g.) gave the *furanoquinoline* as a pale yellow oil, b. p. 130—140° (bath)/0·6 mm., crystallising from light petroleum (b. p. 40—60°) in colourless needles (0·25 g., 62%), m. p. 36—37° (Found : C, 77·9; H, 4·2; N, 8·5. $C_{11}H_7ON$ requires C, 78·1; H, 4·2; N, 8·3%).

(*b*) A mixture of the chlorofuranoquinoline (0·5 g.), zinc dust (6·7 g.), ethanol (10 c.c.), and 2N-sulphuric acid (10 c.c.) was shaken for 2 hr., then extracted with ether. Evaporation of the ether gave only a trace of material. After the solution had been made alkaline with aqueous sodium hydroxide, ether-extraction, evaporation of the ether, and distillation of the residue gave a pale yellow oil (26 mg., 6%), b. p. 150—160° (bath)/0·03 mm., shown by comparison of infrared spectra to be identical with furano(3′ : 2′-3 : 4)quinoline obtained as in (*a*).

Potassium Permanganate Oxidation of Furano(3′ : 2′-3 : 4)*quinoline.*—Potassium permanganate (1·5 g.) in acetone (54 c.c.) was added during 1½ hr. to a solution of the furanoquinoline (0·674 g.) in acetone (10 c.c.). After addition of water, the solution was clarified with sulphur dioxide, the acetone removed, and the solution was made alkaline with sodium hydrogen carbonate and extracted with chloroform to remove traces of unchanged furanoquinoline. Acidification of the alkaline solution precipitated 3-carboxy-4-quinolone (0·127 g., 17%), m. p. 269—270° (decomp.), crystallising from ethanol in colourless needles, m. p. 265—266° (decomp.), and shown to be identical with an authentic sample [prepared by the Price–Roberts method (Riegel, Lappin, Adelson, Jackson, Albisetti, Dodson, and Baker, *J. Amer. Chem. Soc.*, 1946, **68**, 1264)] by a mixed m. p. and by comparison of infrared spectra (Found : C, 63·2; H, 3·6; N, 7·1. Calc. for $C_{10}H_7O_3N$: C, 63·5; H, 3·7; N, 7·4%).

3-*Ethoxycarbonyl*-2 : 4-*dihydroxyquinoline* (cf. Brown *et al.*, *loc. cit.*).—Methyl anthranilate (60 g.) and diethyl malonate (330 g.) were heated at 195° until 1 mol. of ethanol had been evolved (3 hr.). The crude monoamide, obtained by removal of excess of diethyl malonate, was cyclised in refluxing ether (300 c.c.) by dropwise addition of a solution of sodium (10 g.) in ethanol (180 c.c.). After 12 hr. at room temperature, the precipitate was removed and dissolved in water (1 l.). Acidification with hydrochloric acid gave the dihydroxy-ester, crystallising from ethanol in colourless needles (57·5 g., 62%), m. p. 208° (Found : C, 61·8; H, 4·8; N, 6·2. Calc. for $C_{12}H_{11}O_4N$: C, 61·8; H, 4·8; N, 6·1%).

3-*Ethoxycarbonyl*-4-*methoxy*-2-*quinolone.*—3-Ethoxycarbonyl-2 : 4-dihydroxyquinoline (3 g.), suspended in ether (25 c.c.), was treated with excess of ethereal diazomethane. After 12 hr. the solid present was removed and the solution concentrated to small bulk, more solid separating. The combined precipitate of the methoxyquinoline (1·6 g., 50%), m. p. 135—141°, crystallised from aqueous methanol in colourless plates, m. p. 144° [Found : C, 63·3; H, 5·2; N, 6·1; OMe, 24·0. Calc. for $C_{13}H_{13}O_4N$: C, 63·2; H, 5·3; N, 5·7; 1OMe + 1OEt (expressed as

2OMe), 25·1%]. Brown *et al.* (*loc. cit.*) were only able to obtain this product by adding methanol to the ether solution.

2 : 4-*Dichloro*-3-*ethoxycarbonylquinoline*.—3-Ethoxycarbonyl-2 : 4-dihydroxyquinoline (1 g.) and phosphorus oxychloride (12 c.c.) were heated under reflux for 1½ hr. After removal of the phosphorus oxychloride under reduced pressure, addition of water gave the *dichloro-compound* (1·1 g., 95%), m. p. 103—104°, crystallising from aqueous ethanol in colourless rectangular plates, m. p. 104° (Found : C, 53·4; H, 3·6. $C_{12}H_9O_2NCl_2$ requires C, 53·4; H, 3·4%).

3-*Carboxy*-2-*chloro*-4-*methoxyquinoline* (XIV; R = H).—A solution of 3-ethoxycarbonyl-4-methoxy-2-quinolone (2 g.) in phosphorus oxychloride (10 c.c.) was refluxed for 20 min. After removal of the oxychloride under reduced pressure, water (50 c.c.) was added, and the mixture was extracted with ether (3 × 30 c.c.). The ether solution was washed with aqueous sodium carbonate and water, dried, and evaporated. Trituration of the oily residue with ether (10 c.c.) gave 3-ethoxycarbonyl-4-methoxy-2-quinolone (0·22 g.), m. p. and mixed m. p. 142—143°. The ether solution was evaporated, and the residue dissolved in ethanol (10 c.c.) giving a solid (0·47 g.), m. p. 90—96°, which crystallised from ethanol in colourless rectangular plates, m. p. 103—104°, alone or mixed with 2 : 4-dichloro-3-ethoxycarbonylquinoline.

Evaporation of the ethanol solution gave crude 2-chloro-3-ethoxycarbonyl-4-methoxyquinoline as a colourless oil (0·96 g.). A sample was distilled [b. p. 170—175° (bath)/0·2 mm.] [Found : C, 57·7; H, 4·0; Cl, 15·2; OMe, 17·8. Calc. for $C_{13}H_{12}O_3NCl$: C, 58·8; H, 4·6; Cl, 13·4; 1OMe + 1OEt (expressed as 2OMe), 23·4. Calc. for $C_{12}H_9O_2NCl_2$: C, 53·4; H, 3·4; Cl, 20·8; 1OEt (expressed as 1OMe), 11·5%]. The analysis indicated that the product was contaminated with 2 : 4-dichloro-3-ethoxycarbonylquinoline.

A solution of crude 2-chloro-3-ethoxycarbonyl-4-methoxyquinoline (0·40 g.) in methanol (10 c.c.) was heated with 15% aqueous potassium hydroxide (10 c.c.) on a steam-bath for 10 min., and the methanol removed under reduced pressure. Acidification with hydrochloric acid gave a semi-solid precipitate, which, by crystallisation from methanol, yielded 3-*carboxy*-2-*chloro*-4-*methoxyquinoline* as colourless plates (0·09 g.), m. p. 173—175° (decomp.) (Found : C, 55·4; H, 3·5; OMe, 13·1. $C_{11}H_8O_3NCl$ requires C, 55·6; H, 3·4; OMe, 13·1%). This dissolved in aqueous sodium hydrogen carbonate, and gave no colour with ferric chloride in aqueous ethanol.

3-*Carboxy*-2-*chloro*-4-*quinolone* (XV; R = Cl).—A solution of 3-carboxy-2-chloro-4-methoxyquinoline (0·075 g.) in 15% aqueous potassium hydroxide (5 c.c.) was heated on a steam-bath for 30 min. The acid, obtained by acidification with hydrochloric acid, separated from methanol in colourless needles (0·055 g.), m. p. 184—186° (decomp.), raised by recrystallisation from methanol to 194—195° (decomp.) [Brown *et al.* (*loc. cit.*) report m. p. 196° (decomp.)] (Found : C, 54·0; H, 2·7. Calc. for $C_{10}H_6O_3NCl$: C, 53·7; H, 2·7%), and gave a red-brown colour with ferric chloride in aqueous ethanol.

3-*Carboxy*-2-*hydrazino*-4-*quinolone* (XV; R = NH·NH_2).—A solution of 3-carboxy-2-chloro-4-quinolone (0·09 g.) in ethanol (20 c.c.) containing 90% hydrazine hydrate (0·5 c.c.) was heated on a steam-bath. After 15 min. white needles began to separate, and after a further 2 hr. the *hydrazino-compound* (0·08 g., 90%), m. p. 216—217° (decomp.), was collected; it separated from acetic acid in colourless needles, m. p. 224° (decomp.) (Found : C, 55·0; H, 4·3; N, 18·9. $C_{10}H_9O_3N_3$ requires C, 54·8; H, 4·1; N, 19·2%).

Reduction of 3-*Carboxy*-2-*hydrazino*-4-*quinolone*.—The hydrazino-derivative (0·08 g.), suspended in boiling water (10 c.c.), was treated with 10% aqueous copper sulphate (2 c.c.), and the mixture was refluxed for 1 hr. 2N-Sodium hydroxide (5 c.c.) was added, and heating was continued for a further 15 min. The cold, filtered solution was acidified with hydrochloric acid. The precipitate of 3-carboxy-4-quinolone (0·06 g., 87%) crystallised from ethanol or acetic acid in colourless needles, m. p. 264—266° (decomp.), shown by a mixed m. p. and by comparison of infrared spectra to be identical with an authentic sample (Found : C, 63·3; H, 3·6; N, 7·4. Calc. for $C_{10}H_7O_3N$: C, 63·5; H, 3·7; N, 7·4%).

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