79. *The Synthesis of* Lunasia *Alkaloids. Part I.* (±)-*Lunacridine and* (±)-*Lunacrine.*

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The quinolones (III; R = H and Me) have been prepared from diethyl (3-methylbut-2-enyl)malonate and the appropriate aromatic amines, and both compounds have been converted into (±)-lunacridine (VII; R = Me). The formation of lunacrine (VIII) and the angular furanoquinoline (IX) by acid cyclisation of lunacridine is discussed.

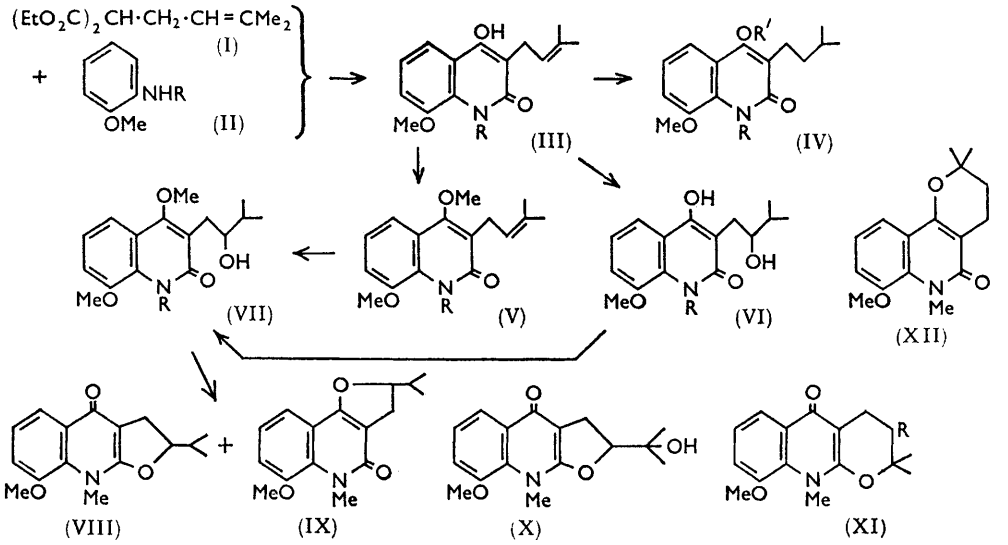
Lunasia species and related trees of the Rutaceae family contain a prodigious number of quinoline alkaloids. These include 2-arylquinolines [1-5] and furanoquinolines,[2,5] and recent investigations have led to the elucidation of the structures of a new group of quinoline alkaloids. For instance, the dihydroisopropylfuranoquinoline, (—)-lunacrine (VIII), was isolated from the leaves of *Lunasia amara* Blanco,[6] and racemic lunacrine was obtained from the bark of the same plant.[3] The secondary alcohol, lunacridine (VII; R = Me) [2,3,7] and the quinolinium salt, lunasine (cf. XIII),[7] are also present in *Lunasia* species. Balfourodine (X) is a constituent of *Balfourodendron riedelianum* Engl.,[8] and its enantiomer, hydroxylunacrine, is found in *Lunasia amara*.[2] Both enantiomers of the pyrano-isomer (XI; R = OH) of balfourodine have also been isolated from natural sources.[3,8,9] These alkaloids are 3-isopentyl-1-methylquinoline derivatives containing oxygen functions at positions 2 and 4, and their biosynthesis may therefore involve a quinoline derivative containing an isoprene side-chain. This possibility prompted us to attempt the synthesis of several types of *Lunasia* alkaloids from a single precursor, and we now report [10] the preparation of the isopentenylquinolines (III; R = Me and H) and their conversion into racemic lunacridine (VII; R = Me) and racemic lunacrine (VIII).

3-Substituted 2,4-dihydroxyquinolines and their 1-methyl derivatives can be prepared conveniently and often in high yield from aromatic amines and substituted malonic esters in diphenyl ether.[8,11,12] Quinolines containing olefinic side-chains have not been prepared previously by this method, and, indeed, it was reported that reactions of aniline [11] or *o*-anisidine [13] with diethyl allylmalonate failed to give recognisable products. We find, however, that diethyl (3-methylbut-2-enyl)malonate (I), prepared from 3-methylbut-2-enoic acid by a modification of an earlier procedure [14] (see Experimental section), reacts with *N*-methyl-*o*-anisidine (II; R = Me) in refluxing diphenyl ether to give the unsaturated 4-hydroxy-2-quinolone (III; R = Me) (26%). The corresponding 2,4-dihydroxyquinoline (III; R = H) was obtained (27%) from *o*-anisidine and the malonic ester (I); after a shorter reaction time, less of the quinoline was formed and a second component, $C_{22}H_{26}N_2O_4$, was isolated in 36% yield. The latter is thought to be the di-*o*-anisidide of 2-(3-methylbut-2-enyl)malonic acid since it shows infrared absorption at 3300 (NH), 1675 (NH·CO), and 747 cm.$^{-1}$ (*ortho*-disubstituted benzene), has an ultraviolet spectrum very similar to that of the di-*o*-anisidide of ethylmalonic acid,[8] and is reduced by hydrogen and platinum to a dihydro-derivative.

[1] Johnstone, Price, and Todd, *Austral. J. Chem.*, 1958, **11**, 562; Goodwin, Smith, and Horning, *J. Amer. Chem. Soc.*, 1957, **79**, 2239.
[2] Goodwin, Smith, Velasquez, and Horning, *J. Amer. Chem. Soc.*, 1959, **81**, 6209.
[3] Beyerman and Rooda, *Proc. k. ned. Akad. Wetenschap.*, 1959, **62**, *B*, 187.
[4] Beyerman and Rooda, *Proc. k. ned. Akad. Wetenschap.*, 1960, **63**, *B*, 427.
[5] Rapoport and Holden, *J. Amer. Chem. Soc.*, 1960, **82**, 4395.
[6] Goodwin and Horning, *J. Amer. Chem. Soc.*, 1959, **81**, 1908.
[7] Price, *Austral. J. Chem.*, 1959, **12**, 458.
[8] Rapoport and Holden, *J. Amer. Chem. Soc.*, 1959, **81**, 3738.
[9] Beyerman and Rooda, *Proc. k. ned. Akad. Wetenschap.*, 1960, **63**, *B*, 154.
[10] Cf. Clarke and Grundon, *Chem. and Ind.*, 1962, 556.
[11] Baker, Lappin, and Riegel, *J. Amer. Chem. Soc.*, 1946, **68**, 1284.
[12] Grundon, McCorkindale, and (in part) Rodger, *J.*, 1955, 4284.
[13] Sunthankar, Mehra, and Nayak, *J. Sci. Ind. Res., India*, 1961, **20**, *B*, 455.
[14] Kuhn and Schinz, *Helv. Chim. Acta*, 1952, **35**, 2008.

In these reactions, isomeric compounds might be formed by cyclisation of primary products, and it was important, therefore, to establish rigorously the constitutions of the quinoline derivatives. The gross structures of the products were shown by hydrogenation to dihydro-derivatives (IV; R = Me, R′ = H; and R = R′ = H), which were identified by independent syntheses from diethyl 3-methylbutylmalonate and the appropriate aromatic amines. The dihydro-compound (IV; R = R′ = H) was further characterised by its conversion with phosphorus oxychloride into 2,4-dichloro-8-methoxy-3-3′-methylbutylquinoline. The presence of a 4-hydroxyl group in the quinolone (III; R = Me) was indicated by the solubility of the compound in aqueous alkali, and by its reaction with diazomethane to give a methyl ether (V; R = Me), which was insoluble in alkali. Similarly, the unsaturated quinoline (III; R = H) and its dihydro-derivative (IV; R = R′ = H) afforded, respectively, the methyl ethers (V; R = H) and (IV; R = H, R′ = Me), which showed strong absorption in the infrared spectrum at 1640—1635 cm.$^{-1}$ (NH·CO) and were insoluble in alkali; this behaviour with diazomethane is typical of 2,4-dihydroxyquinolines,[12,15] and supports the postulated structures.

There is also good evidence for the presence of a trisubstituted olefinic group in the unsaturated quinolines (III; R = Me and H). Thus, the two compounds show infrared peaks of medium intensity at 840 and 820 cm.$^{-1}$, respectively, which are absent from the spectra of the corresponding dihydro-derivatives. Further, the double bonds are certainly not in conjugation with the aromatic systems, because in both series of compounds the



ultraviolet spectrum of the unsaturated compound is superimposable in the region 220—360 mμ on that of the dihydro-derivative. Finally, the structure of the unsaturated methyl ether (V; R = Me) is confirmed by its nuclear magnetic resonance spectrum. The assignments given in the Table are based on established group resonances [16] and on the relative intensities of the peaks, and are confirmed by a comparison with the spectrum of the dihydro-derivative (IV; R = R′ = Me) (prepared by reaction of the corresponding 4-hydroxy-compound with diazomethane). In particular, the triplet at 4·75 τ [J(=CH–CH$_2$–) = 7·2 c./sec.] in the spectrum of the unsaturated compound is attributed to a single olefinic proton, since this peak is absent from the spectrum of the dihydro-derivative. Further, the benzylic-allylic methylene group in the unsaturated quinolone

[15] Arndt, Ergener, and Kutlu, *Chem. Ber.*, 1953, **86**, 951.
[16] Jackman, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959.

produces a doublet at 6·63 τ,[17] which appears as a multiplet at the normal benzylic position in the spectrum of the dihydro-derivative.

We were now in a position to study the conversion of the quinolones (III; R = Me and H) into *Lunasia* alkaloids, and attention was first directed towards (±)-lunacridine (VII; R = Me). This compound was prepared by three routes, each involving anti-Markovnikov hydration. The hydroboronation procedure was chosen for this process, because Brown and Zweifel[18] showed that an analogous compound, 2-methylbut-2-ene, gave the anti-Markovnikov product, 3-methylbutan-2-ol, in 98% yield. Reaction of the 1-methylquinolone (III; R = Me) with diborane followed by alkaline hydrogen peroxide afforded the secondary alcohol (VI; R = Me) (70%). The lævorotatory enantiomer of this compound was obtained previously from (−)-lunacrine (VIII),[6,7] and the spectral data recorded for the enantiomer correspond with those of our racemate. Treatment of the 4-hydroxyquinolone (VI; R = Me) with diazomethane then gave (±)-lunacridine (VII; R = Me) in 62% yield. Hydroboronation of the 4-methoxyquinolone (V; R = Me) also afforded (±)-lunacridine, but the overall yield from the unsaturated quinoline (III; R = Me) was higher by the first route. The third synthesis of (±)-lunacridine proceeded from the 2,4-dihydroxyquinoline (III; R = H) *via* its 4-methyl ether (V; R = H). The latter compound was converted by hydroboronation into the alcohol (VII; R = H) (53%). In accord with this structure, the compound absorbed in the infrared region at 3300 (OH) and 1630 cm.$^{-1}$ (NH·CO), and had an ultraviolet spectrum almost identical with that of lunacridine (VII; R = Me). *N*-Methylation of the alcohol (VII; R = H) with dimethyl sulphate and sodium hydroxide gave (±)-lunacridine in low yield, and thin-layer chromatography of the products insoluble in alkali, indicated that two products of unknown constitution were also formed. The identification of (±)-lunacridine shows that in this series hydroboronation again results predominantly in anti-Markovnikov hydration.

Nuclear magnetic resonance spectra assignments (determined in deuteriochloroform solution at 60 Mc./sec.).

Quinolone (V; R = Me)		Quinolone (IV; R = R′ = Me)		
τ Value	Relative intensity	τ Value	Relative intensity	Assignment
2·50—3·07	3	2·49—3·07	3	aromatic *H*
4·63, 4·75, 4·87	1	—	—	$-CH{=}C<$
6·08	3	6·08	3	$>N{\cdot}CH_3$
6·15	6	6·14	6	$-O{\cdot}CH_3$
6·57, 6·69	2	7·22—7·46	2	$Ar{\cdot}CH_2-$
8·21, 8·32	6	—		$=C(CH_3)_2$
—		8·40—8·77	3	$Ar{\cdot}CH_2{\cdot}CH_2{\cdot}CH<$
—		9·00, 9·09	6	$>C(CH_3)_2$

Since racemic lunacridine has not been isolated from *Lunasia* species, we related the synthetic compound to the natural alkaloids by means of transformations already reported for the enantiomers.[6,7] First, acid cyclisation of (±)-lunacridine (VII; R = Me) gave (±)-lunacrine (VIII), which was further characterised as its picrate, and was shown to be identical with the racemate from *Lunasia amara*. Secondly, natural (±)-lunacrine afforded a methiodide (XIII; X = I), which was converted with sodium hydroxide into (±)-lunacridine, identical with our synthetic sample.

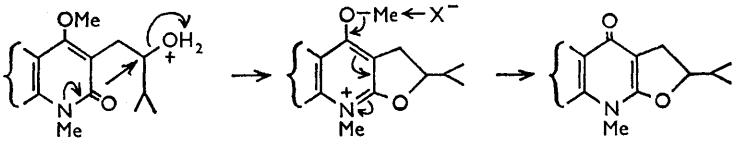
The major product of the cyclisation of lunacridine (VII; R = Me) was, not lunacrine (VIII), but an isomeric compound which, from its insolubility in acid and from its infrared and ultraviolet spectra, is the angular dihydrofuranoquinoline (IX). This structure was suggested by Price[7] for the lævorotatory by-product of the cyclisation of (+)-lunacridine, and by Beyerman and Rooda[3] for the alkaloid "Lunasia VI."

The cyclisation of lunacridine and its derivatives has been discussed previously,[6,7]

[17] Cf. Gilchrist, Hodges, and Porte, *J.*, 1962, 1780.
[18] Brown and Zweifel, *J. Amer. Chem. Soc.*, 1960, **82**, 4708.

but we have some additional observations concerning the reaction of lunacridine with hydrochloric acid. We find that lunacrine (VIII) and its angular isomer (IX) are stable under the reaction conditions; the acid cyclisation of lunacridine does not, therefore, result in an equilibrium mixture, and the two products must be produced by separate pathways. The angular dihydrofuranoquinolone (IX) could arise by prior hydrolysis of the 4-methoxy-group of lunacridine, followed by cyclisation of the phenol (VI; R = Me), and this mechanism is supported by two experiments. First, acid hydrolysis of 4-methoxyquinolines certainly occurs readily, since we find that heating the isopentylmethoxyquinolone (IV; R = R′ = Me) with aqueous acid gives the corresponding phenol (IV; R = Me, R′ = H) almost quantitatively. Secondly, Price [7] showed that acid cyclisation of the (−)-phenol (VI; R = Me) also gave a mixture of lunacrine (VIII) and its angular isomer (IX).

Lunacrine might also be formed from lunacridine *via* the phenol (VI; R = Me), and we examined this possibility by studying the acid cyclisation of lunacridine and of the phenol under standard conditions, and comparing the yields of products. Lunacridine afforded lunacrine (VIII) in 30% yield and the angular dihydrofuranoquinolone (IX) in 68% yield; the corresponding figures for cyclisation of the phenol (VI; R = Me) were 5% and 86%. These results show that the predominant route for the formation of lunacrine from lunacridine does not involve the phenol (VI; R = Me) but occurs by a process in which cyclisation precedes cleavage of the 4-methoxyl group. There is an analogy for a process of this type: Goodwin and Horning [6] showed that heating (+)-lunacridine perchlorate at 200° gave (+)-lunasine perchlorate (XIII; X = ClO_4), which with



lithium bromide in acetonitrile was converted into (+)-lunacrine; they proposed the annexed mechanism. Apparently the transformation was accompanied by inversion, thus supporting the intramolecular S_N2 reaction suggested for the first stage. It seems likely that cyclisation of lunacridine to lunacrine with hydrochloric acid proceeds mainly by a similar mechanism, the chloride ion, unlike the perchlorate ion, being sufficiently nucleophilic to effect the conversion of lunasine chloride (XIII; X = Cl) into lunacrine. If an S_N1 reaction were involved, the secondary carbonium ion intermediate would be expected to rearrange partially to the tertiary ion, and cyclisation would then produce some of the isomeric pyranoquinolines (XI; R = H) and (XII).[19] After establishing that a mixture of the four isomers (VIII), (IX), (XI; R = H), and (XII) could be separated by thin-layer chromatography, we applied the technique to the total reaction product but did not detect the pyranoquinolines (XI; R = H) and (XII); this result also supports the S_N2 mechanism.

Experimental

The infrared spectra of solids were determined as KBr discs and of liquids as liquid films.

Ethyl 3-Methylbut-2-enoate.—3-Methylbut-2-enoic acid (100 g.) was converted by azeotropic esterification [20] into the ethyl ester (125 g., 98%), b. p. 49°/12 mm., n_D^{18} 1·4372 (lit.,[21] b. p. 76—76·5°/58 mm., n_D^{20} 1·4360). Vapour-phase chromatography (8% of trixylyl phosphate on Celite; 80°) gave a single peak.

3-Methylbut-2-enol.—A suspension of lithium aluminium hydride (7·5 g.) in ether (200 c.c.) was added during 80 min. to ethyl 3-methylbut-2-enoate (25·3 g.) in ether (100 c.c.) at −10°,

[19] Prepared by Beyerman and Rooda, ref. 3, and by Clarke and Grundon, unpublished work.
[20] Cf. Baker, Querry, Safir, and Bernstein, *J. Org. Chem.*, 1947, **12**, 138.
[21] Corey, *J. Amer. Chem. Soc.*, 1952, **74**, 5897.

and the mixture was refluxed for 3 hr. The excess of the reagent was decomposed with water, and the mixture was filtered. Evaporation of the filtrate and distillation of the residue afforded the alcohol as an oil (14·9 g., 88%), b. p. 50°/12 mm., n_D^{18} 1·4420 (lit.,[22] b. p. 51°/14 mm., n_D^{20} 1·4410). Vapour-phase chromatography (8% of tritolyl phosphate on Celite; 80°) gave a single peak. The phenylurethane separated from light petroleum (b. p. 40—60°) in needles, m. p. 65° (lit.,[23] 65—66°).

1-*Chloro*-3-*methylbut*-2-*ene*.—Thionyl chloride (20·9 g.) in ether (100 c.c.) was added slowly during 1 hr. to a solution of 3-methylbut-2-en-1-ol (10 g.) and tri-n-butylamine (21·6 g.) in ether (200 c.c.) at −5°. The solution was kept at −5° for 2 hr. and at 20° for 2 hr., added to ice, and then extracted with ether (5 × 150 c.c.). Evaporation of the ether solution and fractional distillation of the residue gave 1-chloro-3-methylbut-2-ene (5·5 g., 45%), b. p. 110°/768 mm., n_D^{18} 1·4490 (lit.,[24] b. p. 111—113°/760 mm., n_D^{20} 1·4480). Vapour-phase chromatography (8% of trixylyl phosphate on Celite; 40°) showed an intense peak (retention time 14·5 min.) and a small peak (retention time 3·3 min.).

Diethyl 3-*Methylbut*-2-*enylmalonate* (I).—(*a*) 1-Chloro-3-methylbut-2-ene (5·1 g.) in ether (50 c.c.) was added to diethyl sodiomalonate [prepared as a suspension in ether from diethyl malonate (8·3 g.), sodium (1·1 g.), and ether (40 c.c.)], and the mixture was refluxed for 40 hr., added to water, and then extracted with ether (4 × 200 c.c.). The yellow oil obtained by evaporation of the ether solution was shaken overnight with 40% aqueous ammonia (30 c.c.) and extracted with ether (3 × 50 c.c.). Evaporation of the ether solution and distillation of the residue furnished the malonate (5·3 g., 48%), b. p. 130°/13 mm., n_D^{18} 1·4426 (lit.,[25] b. p. 125—126°/11 mm., n_D^{18} 1·4417 (Found: C, 63·4; H, 8·9. Calc. for $C_{12}H_{20}O_4$: C, 63·1; H, 8·8%). Vapour-phase chromatography (8% of tritolyl phosphate on Celite; 140°) gave a single peak with retention time 22·1 min.

(*b*) Crude 1-chloro-3-methylbut-2-ene [prepared as described above from 3-methylbut-2-enol (94 g.)] was converted by the method given in (*a*) into diethyl 3-methylbut-2-enylmalonate (83 g.), b. p. 119—121°/8 mm., n_D^{20} 1·4424, shown by vapour-phase chromatography to be homogeneous. The yield was 33%, based on the weight of the alcohol.

4-*Hydroxy*-8-*methoxy*-1-*methyl*-3-(3-*methylbut*-2-*enyl*)-2-*quinolone* (III; R = Me).—A solution of diethyl 3-methylbut-2-enylmalonate (7·04 g.) and *N*-methyl-*o*-anisidine (4·02 g.) in diphenyl ether (50 c.c.) was refluxed for 2·5 hr. under nitrogen, and the ethanol that was formed was allowed to escape. Diphenyl ether was removed under reduced pressure, and the residue in methylene chloride (100 c.c.) was shaken with 2N-aqueous sodium hydroxide (4 × 100 c.c.). Carbon dioxide was passed into the alkaline solution, until the latter was brought to pH 8. The solid obtained by extraction with methylene chloride (3 × 100 c.c.) was treated with ethanol (150 c.c.), and the resultant mixture was filtered. Dilution of the filtrate with water gave the *quinolone* (2·2 g., 26%), m. p. 145—148°, separating from aqueous ethanol in prisms, m. p. 153—154°, $\nu_{max.}$ 1640s, 840m cm.$^{-1}$, $\lambda_{max.}$ (in MeOH) 218 (ε 22,400), 240 (ε 29,500), 246 (ε 27,500), 255 (ε 26,900), 284 (ε 8300), 294 (ε 8700), and 319 mμ (ε 3300) (Found: C, 70·2; H, 6·9; N, 5·2. $C_{16}H_{19}NO_3$ requires C, 70·3; H, 7·0; N, 5·1%).

4-*Hydroxy*-8-*methoxy*-3-(3-*methylbut*-2-*enyl*)-2-*quinolone* (III; R = H).—(*a*) A solution of diethyl 3-methylbut-2-enylmalonate (7·68 g.) and *o*-anisidine (4·1 g.) in diphenyl ether (50 c.c.) was refluxed for 2·5 hr., and then evaporated. A solid was formed by triturating the residue with light petroleum (b. p. 40—60°). A solution of the solid in methylene chloride (300 c.c.) was shaken with 2N-aqueous sodium carbonate (3 × 70 c.c.). Acidification of the alkaline solution with 6N-hydrochloric acid gave a precipitate of the *quinolone* (1·51 g., 18%), m. p. 216—221°, which crystallised from aqueous ethanol in needles (1·41 g.), m. p. 228—230°, $\nu_{max.}$ 1640 and 820 cm.$^{-1}$, $\lambda_{max.}$ (in MeOH) 243 (ε 28,200), 250 (ε 26,900), 280 (ε 8700), 288 (ε 8900), and 320 mμ (ε 4100) (Found: C, 69·1; H, 6·4; N, 5·0. $C_{15}H_{17}NO_3$ requires C, 69·5; H, 6·6; N, 5·4%).

After separation of the alkaline extract, the methylene chloride solution was washed with 2N-hydrochloric acid. Evaporation gave NN′-*di*-o-*methoxyphenyl*-2-(3-*methylbut*-2-*enyl*)*malonamide* (2·32 g., 36%) in prisms (from ethanol), m. p. 163—164°, $\lambda_{max.}$ (in MeOH) 249 (ε 21,000),

[22] Normant, *Compt. rend.*, 1955, **240**, 314; Anosov, Savostin, Pines, Miropol'skaya, Fedotova, and Samokhvalov, U.S.S.R., Patent 136,344 (*Chem. Abs.*, 1961, **55**, 23,343).
[23] Miller and Nord, *J. Org. Chem.*, 1951, **16**, 728.
[24] Ultée, *J.*, 1948, 530.
[25] Simon, Kaufmann, and Schinz, *Helv. Chim. Acta*, 1946, **29**, 1133.

284 (ε 12,000), and 291 mμ (ε 11,000) (Found: C, 69·1; H, 6·9; N, 7·5. $C_{22}H_{26}N_2O_4$ requires C, 69·1; H, 6·9; N, 7·3%). Reduction with hydrogen and platinum gave the *3-methylbutyl derivative*, separating from aqueous ethanol in prisms, m. p. 157—158° (Found: C, 68·9; H, 7·5; N, 7·0. $C_{22}H_{28}N_2O_4$ requires C, 68·7; H, 7·3; N, 7·3%).

(*b*) A solution of 3-methylbut-2-enylmalonate (4·29 g.) and *o*-anisidine (2·32 g.) in diphenyl ether was refluxed for 4·5 hr. under nitrogen. The usual isolation procedure afforded the quinolone (1·32 g., 27%), m. p. 215—220°.

4-Hydroxy-8-methoxy-1-methyl-3-3′-methylbutyl-2-quinolone (IV; R = Me, R′ = H).—(*a*) Heating diethyl 3-methylbutylmalonate (3·65 g.) *N*-methyl-*o*-anisidine (2·13 g.) and diphenyl ether (50 c.c.) as described by Huffman [26] gave the quinolone (1·20 g., 28%), m. p. 133—134°, crystallising from aqueous ethanol in prisms, m. p. 134—135° [lit.,[26] m. p. 126—128° (from aqueous acetic acid), 9·7% yield], $\nu_{max.}$ 1630 cm.$^{-1}$, $\lambda_{max.}$ (in MeOH) 217 (ε 20,000), 239 (ε 28,800), 246 (ε 27,500), 254 (ε 25,700), 284 (ε 7900), 293 (ε 8300), and 322 mμ (ε 3300) (Found: C, 70·2; H, 7·7; N, 5·4. Calc. for $C_{16}H_{21}NO_3$: C, 69·8; H, 7·7; N, 5·1%).

(*b*) A solution of the unsaturated quinolone (III; R = Me) (95 mg.) in ethanol was reduced at 16° with platinum and hydrogen at atmospheric pressure. Filtration, evaporation of the filtrate, and crystallisation of the residue from aqueous ethanol gave the dihydro-derivative (76 mg.), m. p. 134—135°, which was shown by a mixed m. p. determination and by a comparison of infrared spectra to be identical with a sample prepared as in (*a*).

4-Hydroxy-8-methoxy-3-3′-methylbutyl-2-quinolone (IV; R = R′ = H).—(*a*) The unsaturated quinolone (III; R = H) (83 mg.) was reduced with hydrogen and platinum to the dihydro-derivative, which separated from aqueous ethanol in prisms, m. p. 228° (lit.,[26] 235—236°), $\nu_{max.}$ 1635 cm.$^{-1}$, $\lambda_{max.}$ (in MeOH) 243 (ε 27,500), 280 (ε 8700), 288 (ε 8900), 319 (ε 4200), and 331 mμ (ε 2800) (Found: C, 68·5; H, 7·2; N, 5·6. Calc. for $C_{15}H_{19}NO_3$: C, 68·9; H, 7·3; N, 5·4%).

(*b*) A solution of diethyl 3-methylbutylmalonate (8·39 g.) and *o*-anisidine (4·09 g.) in diphenyl ether (50 c.c.) was refluxed for 4 hr. and evaporated. A solution of the residue in an excess of 4N-aqueous sodium hydroxide was filtered and then acidified with hydrochloric acid. The precipitate of the quinolone separated from aqueous ethanol in prisms (8·31 g., 96%), m. p. 225—227°, undepressed on admixture with the compound obtained in (*a*).

2,4-Dichloro-8-methoxy-3-3′-methylbutylquinoline.—A solution of the hydroxyquinolone (IV; R = R′ = H) (702 mg.) in phosphorus oxychloride (100 c.c.) was refluxed for 2 hr. and then evaporated. Addition of water (30 c.c.) and extraction with methylene chloride furnished the *dichloro-compound* (789 mg., 98%), crystallising from aqueous ethanol in needles, m. p. 73—74° (Found: C, 60·6; H, 5·6; N, 4·7. $C_{15}H_{17}Cl_2NO$ requires C, 60·4; H, 5·7; N, 4·7%).

4,8-Dimethoxy-1-methyl-3-(3-methylbut-2-enyl)-2-quinolone (V; R = Me).—An excess of an ethereal solution of diazomethane was added to the hydroxyquinolone (III; R = Me) (1·01 g.) in methanol (50 c.c.) at 0°. After 1 min. the solution was evaporated, and the residue in methylene chloride was washed with N-aqueous sodium hydroxide (2 × 20 c.c.) and with water. Evaporation gave the *dimethoxyquinolone* (1·01 g., 96%), identical (infrared) with a sample obtained by distillation as a viscous oil, b. p. 140°(bath)/0·00005 mm., $\nu_{max.}$ 1645 cm.$^{-1}$, $\nu_{max.}$ (in MeOH) 239 (ε 22,400), 258 (ε 21,400), 286 (ε 7400), 294 (ε 7200), and 332 mμ (ε 3400) (Found: C, 69·7; H, 7·3; N, 5·3. $C_{17}H_{21}NO_3$ requires C, 71·1; H, 7·4; N, 4·9%).

4,8-Dimethoxy-3-(3-methylbut-2-enyl)-2-quinolone (V; R = H).—The hydroxyquinolone (III; R = H) (2·31 g.) was methylated with diazomethane for 1 hr., and the mixture was worked up in the usual way. The product was chromatographed on alumina. Elution with methylene chloride gave the *dimethoxyquinolone* (1·41 g., 58%), m. p. 117—120°, crystallising from light petroleum (b. p. 60—80°) in plates, m. p. 119—120°, $\nu_{max.}$ 1640 cm.$^{-1}$, $\lambda_{max.}$ (in MeOH), 239 (ε 20,900), 254 (ε 28,800), 282 (ε 9100), 290 (ε 8300), 321 (ε 3600), 331 (ε 4200), and 344 mμ (ε 2900) (Found: C, 70·0; H, 7·3; N, 5·5. $C_{16}H_{19}NO_3$ requires C, 70·3; H, 7·0; N, 5·1%).

4,8-Dimethoxy-3-3′-methylbutyl-2-quinolone (IV; R = H, R′ = Me).—The hydroxyquinolone (IV; R = R′ = H) (1 g.) was methylated with diazomethane in the usual way. Chromatography of the product on alumina, and elution with benzene–chloroform (3 : 7), gave the *dimethoxyquinolone* (0·81 g., 77%) in needles [from light petroleum (b. p. 40—60°)], m. p. 96°, $\nu_{max.}$ 1635 cm.$^{-1}$, $\lambda_{max.}$ (in MeOH) 238 (ε 19,100), 254 (ε 25,700), 282 (ε 8100), 290 (ε 7600), and 330 mμ (ε 3900) (Found: C, 69·3; H, 7·6; N, 5·1. $C_{16}H_{21}NO_3$ requires C, 69·8; H, 7·7; N, 5·1%).

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4,8-*Dimethoxy*-1-*methyl*-3-3′-*methylbutyl*-2-*quinolone* (IV; R = R′ = Me).—Methylation of the hydroxyquinolone (IV; R = Me, R′ = H) (180 mg.) with diazomethane for 1 min. gave the *dimethoxyquinolone* (188 mg., 99%), identical (infrared) with a sample obtained by distillation as an oil, b. p. 145°(bath)/0·0005 mm., $\nu_{max.}$ 1640 cm.$^{-1}$, $\lambda_{max.}$ (in MeOH) 239 (ε 23,400), 258 (ε 21,900), 285 (ε 7400), 292 (ε 7100), and 333 mμ (ε 3400) (Found: C, 70·1; H, 7·9; N, 4·5. $C_{17}H_{23}NO_3$ requires C, 70·6; H, 8·0; N, 4·8%).

4-*Hydroxy*-3-(2-*hydroxy*-3-*methylbutyl*)-8-*methoxy*-1-*methyl*-2-*quinolone* (VI; R = Me).—A solution of the unsaturated quinolone (III; R = Me) (1·54 g.) in methylene chloride (70 c.c.) and ether (70 c.c.) was treated with diborane [prepared from sodium borohydride (2 g.) and methanesulphonic acid (15 c.c.)]. After 3 hr., ice, 2N-sodium hydroxide (15 c.c.), and 30% hydrogen peroxide (8 c.c.) were added. The mixture was stirred under nitrogen for 1 hr. and then brought to pH 8 by passing in carbon dioxide. The organic layer was separated and the aqueous solution was extracted with methylene chloride. Evaporation of the combined extracts, and crystallisation of the residue from ethyl acetate, gave the *alcohol* in prisms (1·15 g., 70%), m. p. 174—175°, $\nu_{max.}$ 3250 and 1640 cm.$^{-1}$, $\lambda_{max.}$ (in MeOH) 216 (ε 22,900), 237 (ε 30,900), 245 (ε 28,800), 254 (ε 28,200), 285 (ε 9100), 295 (ε 9300), and 325 mμ (ε 3200) (Found: C, 66·2; H, 7·4; N, 4·8. $C_{16}H_{21}NO_4$ requires C, 66·0; H, 7·3; N, 4·8%).

4,8-*Dimethoxy*-3-(2-*hydroxy*-3-*methylbutyl*)-2-*quinolone* (VII; R = H).—The unsaturated quinolone (V; R = H) (456 mg.) was treated with diborane and thereby converted, by the method described in the preceding section, into 4,8-*dimethoxy*-3-(2-*hydroxy*-3-*methylbutyl*)-2-*quinolone*, which separated from light petroleum (b. p. 60—80°) in prisms (257 mg., 53%), m. p. 158—160°, $\nu_{max.}$ 3330 and 1630 cm.$^{-1}$, $\lambda_{max.}$ (in MeOH) 239 (ε 17,800), 255 (ε 25,100), 283 (ε 7600), 292 (ε 7100), 319 (ε 3100), 331 (ε 3400), and 342 mμ (ε 2800) (Found: C, 66·3; N, 6·9. $C_{16}H_{21}NO_4$ requires C, 66·0; N, 7·3%).

(±)-*Lunacridine* (VII; R = Me).—(*a*) By the method used to prepare (+)-lunacridine from (−)-lunacrine,[7] natural (±)-lunacrine (10 mg.) was converted *via* (±)-lunacrine methiodide (5 mg.), m. p. 128—132° (decomp.), into (±)-lunacridine, which crystallised from light petroleum (b. p. 40—60°) in prisms (3 mg.), m. p. 72—74°.

(*b*) Reaction of the hydroxyquinoline (VI; R = Me) (1·46 g.) with diazomethane for 5 min. gave, by the usual method, a yellow oil (1·51 g.). Crystallisation from light petroleum (b. p. 60—80°) gave (±)-*lunacridine* (0·72 g.), m. p. 69—72°, separating from the same solvent in prisms, m. p. 72—74°, $\nu_{max.}$ 3500 and 1635 cm.$^{-1}$, $\lambda_{max.}$ (in MeOH) 239 (ε 24,000), 258 (ε 26,300), 285 (ε 8300), 292 (ε 7800), and 333 mμ (ε 3100) (Found: C, 66·7; H, 7·5. $C_{17}H_{23}NO_4$ requires C, 66·9; H, 7·6%). The compound was identical (mixed m. p. and infrared spectrum) with a sample obtained as in (*a*) from (±)-lunacrine. The mother-liquors from the crystallisation were evaporated, and the residue was chromatographed on neutral alumina. Elution with benzene, evaporation of the eluate, and crystallisation of the residue from light petroleum (b. p. 40—60°) gave further (±)-lunacridine in prisms (0·22 g.), m. p. 69—72°. The total yield was 0·94 g. (62%).

(*c*) The quinolone (V; R = Me) (218 mg.) and diborane gave, in the usual way, a yellow gum (258 mg.), which was chromatographed on neutral alumina (7 g.). Elution with benzene, evaporation of the eluate, and crystallisation of the residue from light petroleum (b. p. 40—60°) furnished (±)-lunacridine in prisms (40 mg., 17%), m. p. 72—74°, undepressed on admixture with a sample obtained in (*b*).

(*d*) 4,8-Dimethoxy-3-(2-hydroxy-3-methylbutyl)-2-quinolone (VII; R = H) (68 mg.), 20% aqueous sodium hydroxide (13 c.c.), methanol (3 c.c.), and dimethyl sulphate (3 c.c.) were heated under reflux, and portions of dimethyl sulphate (12 × 0·5 c.c.) were added at 15-min. intervals. After 3 hr., water (60 c.c.) was added, and the mixture was extracted with methylene chloride (3 × 50 c.c.). Evaporation of the methylene chloride solution gave a yellow oil (76 mg.). Thin-layer chromatography on neutral silica gel G in chloroform gave three spots, R_F 0·57, 0·85, and 0·95 (trace), thus indicating the presence of (±)-lunacridine, R_F 0·57, and the absence of starting material, R_F 0·36. Chromatography of the crude product on neutral alumina and elution with benzene afforded (±)-lunacridine (1 mg.) in prisms [from light petroleum (b. p. 40—60°)], m. p. 69—71°, undepressed on admixture with an authentic sample.

(±)-*Lunacrine* (VIII).—A solution of (±)-lunacridine (85 mg.) in 6N-hydrochloric acid (10 c.c.) was refluxed for 6 hr. and diluted with water (20 c.c.). The precipitate was removed by filtration. The filtrate was treated with an excess of 2N-sodium hydroxide. Extraction with methylene chloride, evaporation of the extract, and crystallisation of the residue from

light petroleum (b. p. 40—60°) yielded (±)-lunacrine (17 mg.), m. p. 135—146°, separating from ethyl acetate–light petroleum (b. p. 40—60°) in prisms, m. p. 145—147°. The compound was identical (mixed m. p. and infrared spectrum) with a sample of natural (±)-lunacrine, m. p. 145—146°. The *picrate* crystallised from ethanol in yellow prisms, m. p. 211—212° (Found: C, 52·7; H, 4·5. $C_{22}H_{22}N_4O_{10}$ requires C, 52·6; H, 4·4%).

After the removal of (±)-lunacrine, the light petroleum solution was evaporated, and the residue was combined with the product that was insoluble in acid. Chromatography on neutral alumina and elution with benzene gave *2,3,4,5-tetrahydro-2-isopropyl-6-methoxy-5-methyl-4-oxo-furano*[3,2-c]*quinoline* (IX) (52 mg., 68%) as prisms [from light petroleum (b. p. 40—60°], m. p. 76—77°, $\nu_{max.}$ 1660, 1630, 1600, and 1575 cm.$^{-1}$, $\lambda_{max.}$ (in MeOH) 220 (ε 20,900), 239 (ε 26,300), 248 (ε 22,400), 292 (ε 6300), 301 (ε 6900), and 326 mμ (ε 2300) (Found: C, 70·4; H, 6·9. $C_{16}H_{19}NO_3$ requires C, 70·3; H, 7·0%).

Elution of the alumina column with chloroform gave a further quantity of (±)-lunacrine (7 mg.), m. p. 142—146°. The total yield was 24 mg. (30%).

Thin-layer chromatography of a sample of the total product on alumina G in chloroform–benzene (1 : 1) gave only two spots, R_F 0·17 and 0·60, corresponding respectively to lunacrine and the angular furanoquinolone. Direct comparisons with the pyrano-isomers (XI; R = H), R_F 0·27, and (XII), R_F 0·63, showed that these compounds [19] were absent.

Cyclisation of 4-*Hydroxy*-8-*methoxy*-1-*methyl*-3-(2-*hydroxy*-3-*methylbutyl*)-2-*quinolone* (VI; R = Me).—The quinolone (VI; R = Me) (72 mg.) was heated with hydrochloric acid as described for (±)-lunacridine. Chromatography of the crude product on neutral alumina and elution with benzene gave the angular furanoquinolone (IX) (58 mg., 86%), m. p. and mixed m. p. 76°. Elution with ethyl acetate afforded (±)-lunacrine (3 mg., 5%), which was identified by comparison of its infrared spectrum with that of an authentic sample, and by the formation of the picrate, m. p. and mixed m. p. 211—212°.

Treatment of Furanoquinolines with Aqueous Acid.—(*a*) A solution of lunacrine (3·4 mg.) in 6N-hydrochloric acid was refluxed for 6 hr., made alkaline with aqueous sodium hydroxide, and extracted with methylene chloride. Evaporation of the methylene chloride solution and crystallisation of the residue from light petroleum (b. p. 40—60°) gave lunacrine, m. p. and mixed m. p. 144—147°. Thin-layer chromatography of the crude product on alumina G in chloroform–benzene (1 : 1) gave a single spot, R_F 0·21, and on silica gel G in methanol–hydrochloric acid–water (10 : 1 : 2) gave a single spot, R_F 0·74. Both spots corresponded with those for authentic lunacrine.

(*b*) The angular furanoquinoline (IX) (8·8 mg.) was treated as described in (*a*) and was recovered as prisms, m. p. and mixed m. p. 73—75°. Thin-layer chromatography of the crude product on alumina G in chloroform–benzene (1 : 1) gave a single spot, R_F 0·57, corresponding to that given by an authentic sample.

Hydrolysis of 4,8-*Dimethoxy*-1-*methyl*-3-3′-*methylbutyl*-2-*quinolone* (IV; R = R′ = Me).—The dimethoxyquinolone (170 mg.) was refluxed with 6N-hydrochloric acid (16 c.c.) for 6 hr. After dilution with water (30 c.c.), the mixture was extracted with methylene chloride, the methylene chloride solution was washed with 2N-sodium hydroxide, and the alkaline solution was acidified and then extracted with methylene chloride. Evaporation of the solvent and crystallisation of the residue from aqueous ethanol gave 4-hydroxy-8-methoxy-1-methyl-3-3′-methylbutyl-2-quinolone in prisms (154 mg., 95%), m. p. and mixed m. p. 132—134°.

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