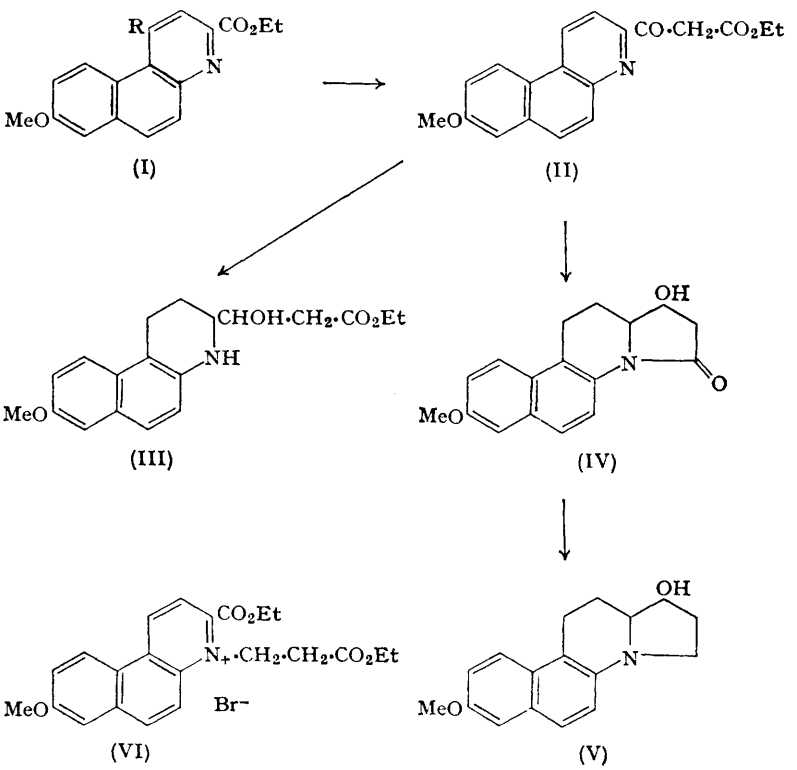
# 1138. *Quasi-steroidal Heterocycles. Part I. Benzo[f]pyrrolo[1,2-a]quinolines and Related Compounds.*

By Emrys R. H. Jones.

Two synthetic routes to derivatives of benzo[*f*]pyrrolo[1,2-*a*]quinoline, a novel ring system* structurally analogous to the steroid skeleton, are described, together with examples of the isosteric benzo[*f*]imidazo[1,5-*a*]quinoline and the related benzo[*f*]-*as*-triazino[4,5-*a*]quinoline.

In the course of work aimed at the synthesis of nitrogen-containing heterocyclic compounds structurally similar to steroids, the use of 2-naphthylamine derivatives as starting materials afforded a route to equilenin types with a nitrogen atom at the C/D ring junction. Accordingly, 6-methoxy-2-naphthylamine[1] was converted into 3-ethoxycarbonyl-1-hydroxy-8-methoxybenzo[*f*]quinoline (I; R = OH) through the oxaloacetate quinoline synthesis. Reaction of this hydroxyquinoline with phosphorus oxychloride gave the corresponding chloroquinoline (I; R = Cl) from which 3-ethoxycarbonyl-8-methoxybenzo[*f*]quinoline (I; R = H) was obtained by reduction with hydrogen and palladium. Retention of three fused aromatic rings in this compound was confirmed by its ultraviolet spectrum (strongest band at 277 mμ, ε 33,200) which closely resembled that of its chloroquinoline precursor (strongest band at 284 mμ, ε 42,300). Attempts to prepare the diester (VI) by quaternisation of the benzoquinoline (I; R = H) with ethyl β-bromopropionate were unsuccessful, the combination of

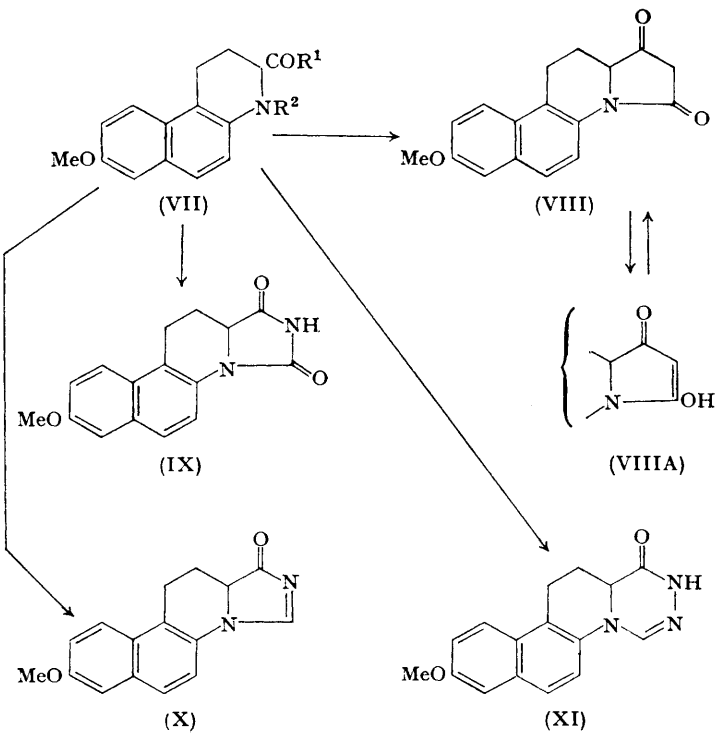



* While this work was being prepared for publication, a preliminary account of a different synthesis of this ring system appeared (R. H. Poirier, R. D. Morin, F. Benington, and T. F. Page, Abstracts 145th Meeting Amer. Chem. Soc., 1963, p. 44Q).

[1] F. H. S. Curd, C. G. Raison, and F. L. Rose, *J.*, 1946, 366.

electron withdrawal and steric hindrance making this quinoline a weak nucleophile; this was reflected in the direct isolation of the free base from reduction experiments in which hydrochloric acid was liberated. However, the benzoquinoline ester (I; R = H) underwent a Claisen condensation with ethyl acetate to give the keto-ester (II). This was reduced with hydrogen and platinum in ethanol solution to the hydroxy-ester (III), the structure of which was confirmed by its ultraviolet (strongest band at 244 mμ, ε 68,400) and infrared (a single carbonyl band at 1735 cm.$^{-1}$) spectra. With hydrogen and platinum in acetic acid solution, reduction of the heterocyclic ring was followed by an intramolecular acylation to give the tetracyclic amide (IV) (amide carbonyl, 1670 cm.$^{-1}$). Reduction of this with a mixture of sodium borohydride and aluminium chloride in diglyme[2] removed the amide carbonyl function to give the compound (V) as a mixture of the two possible iosmers.

Reduction of the chlorobenzoquinoline (I; R = Cl) with hydrogen and platinum gave the tetrahydrobenzoquinoline (VII; $R^1$ = OEt, $R^2$ = H); the presence of two conjugated rings in this compound was shown by its ultraviolet spectrum (strongest band at 246 mμ, ε 57,300). This tetrahydrobenzoquinoline was resistant to *N*-alkylation with acrylonitrile, ethyl acrylate, or propiolactone, thus preventing the synthesis of compounds such as (VII; $R^1$ = OEt, $R^2$ = $CH_2$·$CH_2$CN). It could, however, be *N*-acylated to give the derivative (VII; $R^1$ = OEt, $R^2$ = COMe), which underwent sodium hydride-catalysed intramolecular condensation to give the amide (VIII). The ester and amide carbonyl bands (1760, 1680 cm.$^{-1}$) present in the infrared spectrum of (VII; $R^1$ = OEt, $R^2$ = COMe) were replaced by three bands (1775w, 1685m, 1635s cm.$^{-1}$) in the spectrum of the cyclic amide (VIII), indicating that the latter exists in the solid largely as the enolic form shown in partial structure (VIIIA). This is confirmed by the n.m.r. spectrum (in trifluoroacetic acid, in which the position of equilibrium might be expected to differ from that in the solid) which shows a signal at 4·13 τ corresponding to about one third of an olefinic proton. The tetra-




[2] H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.*, 1956, **78**, 2582.

hydrobenzoquinoline (VII; $R^1 = OEt$, $R^2 = H$) was converted into the compound (IX) by treatment with urea in boiling dimethylformamide; the same product was obtained from the corresponding amide (VII; $R^1 = NH_2$, $R^2 = H$) or hydrazide (VII; $R^1 = NH{\cdot}NH_2$, $R^2 = H$) under the same conditions. The two carbonyl bands (1770m, 1730s cm.$^{-1}$) in the infrared spectrum of the amide (IX) are reminiscent of those in the spectra of phthalimide (1770m, 1740s), succinimide (1760, 1685), and their derivatives. The tetrahydrobenzoquinoline amide (VII; $R^1 = NH_2$, $R^2 = H$) was converted by boiling ethyl orthoformate into the compound (X). The corresponding hydrazide (VII; $R^1 = NH{\cdot}NH_2$, $R^2 = H$), by the same treatment, gave (XI).

## Experimental

Ultraviolet spectra were obtained in 0·001% methanolic solution using an Optica CF4 instrument, infrared spectra in Nujol using a Perkin-Elmer Infracord 137, and n.m.r. spectra in trifluoroacetic acid solution in a Varian A60 spectrometer at 60 Mc./sec. using tetramethylsilane as an internal standard ($\tau = 10{\cdot}00$). Organic solvent extracts were dried over magnesium sulphate.

*3-Ethoxycarbonyl-1-hydroxy-8-methoxybenzo*[f]*quinoline* (I; R = OH).—A stirred mixture of diethyl sodio-oxaloacetate (89 g.), benzene (280 ml.), and ice (90 g.) were acidified by the slow addition of concentrated hydrochloric acid (42 ml.). The benzene layer was added to 6-methoxy-2-naphthylamine[1] (49 g.), and the solution was boiled under reflux, using a Dean and Stark trap, until no more water was evolved (*ca.* 2 hr.). The benzene was removed *in vacuo* and the dark residue was dissolved in chloronaphthalene (150 ml.). This solution was added during 15—20 min. to stirred chloronaphthalene (450 ml.) maintained at 245—250° (internal temperature), and the resulting solution was allowed to cool to room temperature overnight. The crude product was washed with light petroleum (b. p. 60—80°) and with ethanol (54·5 g., 65%), m. p. 230—233° (decomp.). Crystallisation from ethanol gave the pure *product*, m. p. 237—238° (decomp.) (Found: C, 68·5; H, 5·2; N, 4·5. $C_{17}H_{15}NO_4$ requires C, 68·7; H, 5·1; N, 4·7%).

*1-Chloro-3-ethoxycarbonyl-8-methoxybenzo*[f]*quinoline* (I; R = Cl).—The above hydroxyquinoline (10·5 g.) was added to phosphorus oxychloride (40 ml.), and the mixture was boiled under reflux for 18 hr. The excess of oxychloride was removed at the pump and the residue was washed into a mixture of ice and 30% aqueous sodium hydroxide with a little acetone. The *product*, after being washed with water, had m. p. 157—158° (from benzene) (8·4 g., 74%) (Found: C, 64·6; H, 4·5; Cl, 11·3; N, 4·5. $C_{17}H_{14}ClNO_3$ requires C, 64·7; H, 4·4; Cl, 11·3; N, 4·4%), $\lambda_{max.}$ 218 (ε 23,500), 236 (25,100), 242 (infl., 22,000), 284 (42,300), 325 (10,300), 353 (5400), and 373 mμ (4300). Repetition of the experiment with 80 g. of the hydroxyquinoline gave 53 g. (63%) of chloroquinoline.

*Reduction of the Chlorobenzoquinoline* (I; R = Cl).—(*a*) The chlorobenzoquinoline (52 g.), glacial acetic acid (900 ml.), and Adams platinum oxide (4 g.) were shaken under 100 atm. hydrogen at room temperature for 2 hr. The mixture was filtered, most of the acetic acid was removed *in vacuo*, aqueous sodium carbonate and chloroform were added, and the dried chloroform extract was evaporated to dryness. The residue was crystallised from light petroleum (b. p. 100—120°), to give *3-ethoxycarbonyl-1,2,3,4-tetrahydro-8-methoxybenzo*[f]*quinoline*, m. p. 134—135° (38 g., 81%) (Found: C, 71·5; H, 6·5; N, 4·9. $C_{17}H_{19}NO_3$ requires C, 71·6; H, 6·7; N, 4·9%), $\lambda_{max.}$ 226 (ε 28,300), 246 (57,300), 281 (9800), and 367 mμ (3100); *hydrochloride*, m. p. 179—180° (from ethanol) (Found: C, 63·5; H, 6·0; N, 4·4. $C_{17}H_{20}ClNO_3$ requires C, 63·6; H, 6·2; N, 4·4%). The *N-acetyl derivative*, prepared by heating the above tetrahydroquinoline (0·5 g.), acetic anhydride (1 ml.), and dry pyridine (5 ml.) on a steam-bath for 18 hr., had m. p. 120—122° (from methanol) (Found: C, 70·0; H, 6·3; N, 4·4. $C_{19}H_{21}NO_4$ requires C, 69·7; H, 6·4; N, 4·3%), $\nu_{max.}$ 1760, 1680 cm.$^{-1}$. Repetition of the experiment using 5·0 g. of the tetrahydroquinoline gave 4·0 g. (70%) of acetyl derivative. The free *acid* was obtained by boiling the tetrahydroquinoline ester (2·0 g.) with ethanol (20 ml.) and 30% aqueous sodium hydroxide (5 ml.) for 2 hr., and neutralising the filtered solution with acetic acid. The crude product, reprecipitated from aqueous ethanolic sodium carbonate by acetic acid, and washed with water, ethanol, and acetone, had m. p. 192—194° (decomp. 170°) (1·6 g.) (Found: C, 70·9; H, 5·5; N, 5·5. $C_{15}H_{15}NO_3$ requires C, 70·1; H, 5·8; N, 5·4%). The *amide*, prepared from the tetrahydroquinoline ester by reaction of the latter with ethanolic ammonia at 100° for 18 hr., had m. p. 204—206° (from ethanol) (3·7 g. from 5·0 g. of ester) (Found: C, 70·3; H, 6·2; N, 10·9. $C_{15}H_{16}N_2O_2$ requires C, 70·6; H, 6·3; N, 11·0%). The *hydrazide*, prepared from the ester (5·0 g.), hydrazine hydrate (5 ml.), and ethanol (25 ml.) by

boiling under reflux for 4 hr., had m. p. 189—192° (from ethanol) (4·4 g.) (Found: C, 66·7; H, 6·1; N, 15·4. $C_{15}H_{17}N_3O_2$ requires C, 66·5; H, 6·3; N, 15·5%).

Attempted alkylation of the tetrahydroquinoline with ethyl acrylate (in boiling benzene or dioxan alone, or with acetic acid or cupric acetate as catalyst), acrylonitrile (at reflux alone or in dioxan, using cupric acetate as catalyst), or propiolactone (in boiling xylene) was unsuccessful.

(*b*) The chlorobenzoquinoline (67 g.), glacial acetic acid (900 ml.), and 5% palladium–charcoal (15 g.) were shaken under 100 atm. hydrogen at room temperature for 4½ hr. The product was worked up as above, and gave 3-*ethoxycarbonyl*-8-*methoxybenzo*[f]*quinoline* (I; R = H), m. p. 150—152° (from methanol) (38 g., 64%). Further crystallisation from ethanol raised the m. p. to 157—158° (Found: C, 72·6; H, 5·2; N, 4·9. $C_{17}H_{15}NO_3$ requires C, 72·5; H, 5·3; N, 5·0%), $\lambda_{max.}$ 219 (ε 22,900), 234 (28,800), 245 (infl., 25,700), 277 (33,200), 321 (11,200), 350 (6300), and 368 mμ (5600). This compound crystallised out when 3-ethoxycarbonyl-1,2,3,4-tetrahydro-8-methoxybenzo[*f*]quinoline (0·50 g.) was boiled in xylene (10 ml.) under reflux with 5% palladium–charcoal (0·50 g.) for 17 hr., and the solution was filtered and cooled; it had m. p. and mixed m. p. 156—157°, and did not react with ethyl β-bromopropionate at 145°, either alone or with xylene as solvent.

1,2,3,11,12,12a-*Hexahydro*-8-*methoxy*-1,3-*dioxobenzo*[f]*pyrrolo*[1,2-a]*quinoline* (VIII).—*N*-Acetyl-3-ethoxycarbonyl-1,2,3,4-tetrahydro-8-methoxybenzo[*f*]quinoline (VII; $R^1$ = OEt, $R^2$ = COMe) (500 mg.) was dissolved in dry tetrahydrofuran (5 ml.), a 50% dispersion of sodium hydride in oil (200 mg.) was added, and the mixture boiled under reflux for 18 hr. The precipitate was dissolved by the addition of an equal volume of water, and the solution brought to pH 5 with acetic acid. The *product*, which crystallised out, was washed with dilute acetic acid and methanol, and had m. p. 265° (decomp.) (300 mg.), not changed by recrystallisation from n-butanol (Found: C, 72·3; H, 5·2; N, 4·9. $C_{17}H_{15}NO_3$ requires C, 72·6; H, 5·3; N, 5·0%), $\nu_{max.}$ 1775w, 1685m, 1635s cm.$^{-1}$, τ 4·13 (about 1/3 proton).

1,2,3,11,12,12a-*Hexahydro*-8-*methoxy*-1,3-*dioxobenz*[f]*imidazo*[1,5-a]*quinoline* (IX).—3-Ethoxycarbonyl-1,2,3,4-tetrahydro-8-methoxybenzo[*f*]quinoline (2·0 g.), urea (0·60 g.), and dimethylformamide (20 ml.) were boiled under reflux for 48 hr. The hot solution was diluted with water (15 ml.) and allowed to cool. The *product*, which crystallised out, was washed with boiling ethanol, and had m. p. 294—296° (decomp.) (0·80 g.), unchanged by recrystallisation from n-butanol or acetic acid (Found: C, 67·9; H, 5·0; N, 9·7. $C_{16}H_{14}N_2O_3$ requires C, 68·1; H, 5·0; N, 9·9%), $\nu_{max.}$ 1770m, 1730s cm.$^{-1}$. The same product was obtained when the tetrahydrobenzoquinoline ester used in the above experiment was replaced by either the corresponding amide or the corresponding hydrazide.

1,11,12,12a-*Tetrahydro*-8-*methoxy*-1-*oxobenz*[f]*imidazo*[1,5-a]*quinoline* (X).—1,2,3,4-Tetrahydro-8-methoxybenzo[*f*]quinoline-3-carboxyamide (2·5 g.) and ethyl orthoformate (50 ml.) were boiled under reflux for 24 hr. The mixture was cooled, and the *product*, washed with ether and ethanol, had m. p. 238—240° (decomp.) (1·3 g.) (Found: C, 71·8; H, 5·4; N, 10·4. $C_{16}H_{14}N_2O_2$ requires C, 72·2; H, 5·3; N, 10·5%), $\nu_{max.}$ 1695 (C=O), 1655 (C=N) cm.$^{-1}$.

1,12,13,13a-*Tetrahydro*-9-*methoxy*-1-*oxo*-2H-*benzo*[f]-as-*triazino*[4,5-a]*quinoline* (XI).—1,2,3,4-Tetrahydro-8-methoxybenzo[*f*]quinoline-3-carbohydrazide (1·5 g.) and ethyl orthoformate (15 ml.) were boiled under reflux for 17 hr. The *product*, which began to separate after a few minutes' boiling, was collected from the cooled mixture and washed with ether, and had m. p. 248—250° (decomp.) (0·60 g.), m. p. 255—256° (decomp.) (from n-butanol) (Found: C, 68·0; H, 4·8; N, 14·9. $C_{16}H_{15}N_3O_2$ requires C, 68·3; H, 5·3; N, 15·0%), $\nu_{max.}$ 1670, 1650 cm.$^{-1}$.

*Ethyl* β-(8-*Methoxybenzo*[f]*quinolin*-3-*yl*)-β-*oxopropionate* (II).—3-Ethoxycarbonyl-8-methoxybenzo[*f*]quinoline (15·5 g.), dry ethyl acetate (7·5 ml.), dry tetrahydrofuran (350 ml.), and a 50% dispersion of sodium hydride in oil (3·0 g.) were boiled under reflux for 18 hr. Water, ethyl acetate, and acetic acid (5 ml.) were added, and the aqueous layer was re-extracted with ethyl acetate. The combined ethyl acetate extracts were washed with aqueous sodium hydrogen carbonate, dried, and evaporated to dryness. The *product* had m. p. 94—98° [from light petroleum (b. p. 100—120°)] (13·8 g., 77%). Further crystallisation from the same solvent raised the m. p. to 96—99° (Found: C, 70·6; H, 5·1; N, 4·3. $C_{19}H_{17}NO_4$ requires C, 70·6; H, 5·3; N, 4·3%), $\nu_{max.}$ 1745, 1685 cm.$^{-1}$.

*Reduction of the Quinolinyl Oxopropionate* (II).—(*a*) The oxopropionate (0·50 g.), ethanol (40 ml.), and Adams platinum oxide catalyst (20 mg.) were shaken under 100 atm. hydrogen at room temperature for 18 hr. The mixture was filtered and the filtrate evaporated to dryness. The residue, after crystallisation from light petroleum (b. p. 100—120°), gave *ethyl* β-(1,2,3,4-*tetrahydro*-8-*methoxybenzo*[f]*quinolin*-3-*yl*)-β-*hydroxypropionate* (III), m. p. 135—141° (0·35 g.).

Recrystallisation from methanol raised the m. p. to 140—142° (Found: C, 69·3; H, 6·9; N, 4·3. $C_{19}H_{23}NO_4$ requires C, 69·3; H, 7·0; N, 4·3%), $\lambda_{max.}$ 221 (ε 40,100), 244 (68,400), 280 (18,700), and 370 mμ (1400), $\nu_{max.}$ 1735 cm.$^{-1}$ (no ketone CO).

(*b*) The oxopropionate (10·7 g.), acetic acid (300 ml.), and Adams platinum oxide catalyst (250 mg.) were shaken under 100 atm. hydrogen at 50° for 18 hr. The mixture was filtered and evaporated to dryness. The residue was washed with ethanol, to give 1,2,3,11,12,12*a*-*hexahydro*-1-*hydroxy*-8-*methoxy*-3-*oxobenzo*[f]*pyrrolo*[1,2-a]*quinoline* (IV), m. p. 236—237° (decomp.), unchanged by crystallisation from n-butanol (8·0 g., 85%) (Found: C, 71·8; H, 6·2; N, 4·9. $C_{17}H_{17}NO_3$ requires C, 72·1; H, 6·0; N, 4·9%), $\nu_{max.}$ 1670 cm.$^{-1}$. Repetition of the reduction at room temperature gave the same product in lower yield.

1,2,3,11,12,12a-*Hexahydro*-1-*hydroxy*-8-*methoxybenzo*[f]*pyrrolo*[1,2-a]*quinoline* (V).—The above compound (IV) (2·83 g.) and sodium borohydride (2·28 g., 6 mol.) were dissolved in dry diglyme (150 ml.) by heating the mixture to 60°. Aluminium chloride (2·66 g., 2 mol.), dissolved in diglyme (50 ml.), was then added dropwise with stirring during a few minutes. The mixture was set aside for 2 hr., poured into water, made definitely alkaline with caustic liquor, and extracted with ethyl acetate, filtering from insoluble material. The extract was shaken with dilute aqueous hydrochloric acid, and the aqueous layer was basified (30% aqueous sodium hydroxide), and re-extracted with ethyl acetate. The final extract was dried, evaporated to small volume, and diluted with water. The *product* which was precipitated had m. p. 115—117° (from methanol) (1·35 g., 51%) raised to 126—128° by recrystallisation from light petroleum (b. p. 100—120°) (Found: C, 75·7; H, 7·0; N, 5·3. $C_{17}H_{19}NO_2$ requires C, 75·8; H, 7·1; N, 5·2%). Thin-layer chromatography on alumina in 25% ethyl acetate–benzene showed two spots, $R_F$ 0·28, 0·35 (weak). The *acetate*, prepared from the hydroxy-compound (1·00 g.), acetic anhydride (2 ml.), and dry pyridine (5 ml.) by reaction overnight at room temperature, had m. p. 160° (from ethanol) (Found: C, 73·0; H, 6·7; N, 4·5. $C_{19}H_{21}NO_3$ requires C, 73·3; H, 6·8; N, 4·5%).

IMPERIAL CHEMICAL INDUSTRIES LIMITED, PHARMACEUTICALS DIVISION,
ALDERLEY PARK, MACCLESFIELD.
[Present address: PFIZER LTD., SANDWICH, KENT.]

[*Received, September 24th,* 1964.]