807. *The Synthesis of* Lunasia *Alkaloids. Part III.*[1] *(±)-Balfourodine and (±)-O-Methylbalfourodinium Perchlorate. The Biogenesis of Some Rutaceae Alkaloids.*

By E. A. Clarke and M. F. Grundon.

Reaction of the 4-hydroxy-3-(3-methylbut-2-enyl)quinolone (VI; R= H, R′ = Me) with peroxylauric acid furnished (±)-balfourodine (I) in almost quantitative yield. (±)-*O*-Methylbalfourodinium perchlorate (III; R = OH, X = ClO_4) was obtained by oxidation of the quinolone (VI; R = R′ = Me). The biogenesis of *Lunasia* alkaloids and some other structurally-related Rutaceae alkaloids is discussed.

In previous Papers of this Series,[1,2] we described the conversion of the 3-methylbut-2-enyl quinolone (VI; R = H, R′ = Me) into the isopropyltetrahydrofuranoquinoline, lunacrine (IV), and into related pyranoquinolines. Certain other *Lunasia* and *Balfourodendron* alkaloids are closely related to lunacrine (IV) and to lunasine (III; R = H), but contain an additional hydroxyl group. Thus, the alkaloids balfourodine and isobalfourodine from

[1] Part II, preceding Paper.
[2] Clarke and Grundon, *J.*, 1964, 438.

Balfourodendron riedelianum Engl. were shown by Rapoport and Holden [3,4] to be the isopropyltetrahydrofuranoquinoline (I) and its pyrano-isomer (V), respectively. An *O*-methylbalfourodinium salt (III; R = OH) also occurs naturally, and was isolated as the perchlorate.[3] Lunasia II (lunacrinol [5]), the enantiomer of isobalfourodine, was found in *Lunasia amara* Blanco, and its structure was established independently by Beyerman and Rooda; [6,7] hydroxylunacrine,[5] a minor alkaloid of this species, is probably enantiomeric with balfourodine. We decided to study the synthesis of these alkaloids from the same precursor (VI) used previously for the preparation of lunacrine.

Oxidation of the 4-hydroxy-3-(3-methylbut-2-enyl)quinolone (VI; R = H, R′ = Me) with a peroxy-acid should lead either to an epoxide formed by addition to the double bond in the side-chain or to products of a subsequent intramolecular reaction; in the latter case, attack by the 2- or 4-amino-oxygen atoms could yield a mixture of balfourodine (I), isobalfourodine (V), and their angular isomers. Reaction in neutral solution should favour nucleophilic attack at the least-substituted carbon of the epoxide, resulting in the preferential formation of furanoquinolines. In fact, treatment of the quinolone (VI; R = H, R′ = Me) in chloroform with peroxylauric acid afforded a single crystalline compound (78%), which was further characterised as its perchlorate. Analysis indicated that one oxygen atom had been added, but the product was not a 4-hydroxyquinoline epoxide because it was insoluble in aqueous alkali. The nuclear magnetic resonance spectrum showed the downfield shift characteristic of the 5-proton of a 4-quinolone, and the infrared spectrum ($\nu_{max.}$ 1625 cm.$^{-1}$) was consistent with this formulation.[1] The product was clearly (±)-balfourodine (I) because its ultraviolet spectrum in neutral or in acid solution corresponded to that of the (+)-enantiomer,[3] and because the two compounds showed identical behaviour on thin-layer chromatograms. Furthermore, the product, like the natural enantiomer,[4] rearranged with acetic anhydride, and, after saponification of the intermediate acetate, (±)-isobalfourodine (V) was isolated. The spectral properties of the latter compound correspond with the data given for (+)-isobalfourodine [4] (Lunasia II [6]). When the reaction with peroxylauric acid was carried out in the presence of sulphuric acid (conditions which might be expected to promote the formation of pyranoquinolines), the sole product (95%) was again (±)-balfourodine.

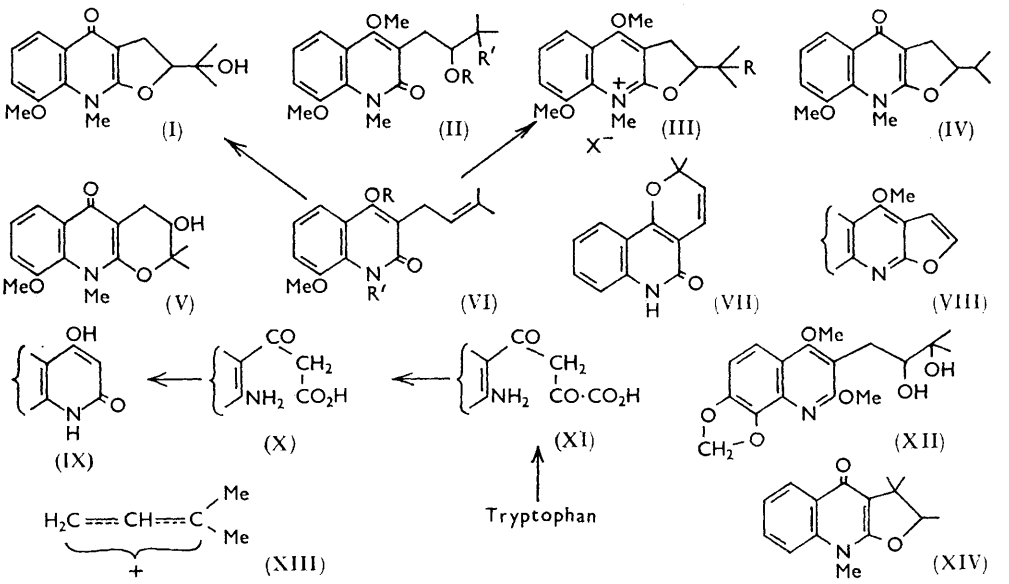
We investigated the separation of a mixture of balfourodine and isobalfourodine by thin-layer chromatography using three systems. Two spots were obtained in each case. Although the R_F values were similar, the two components afforded different colours with detecting reagents (see Experimental section), and were readily distinguished thereby. Thin-layer chromatography of the reaction mixtures from the two oxidations furnished single spots corresponding to balfourodine, indicating that isobalfourodine was certainly not formed, and that the angular isomers of balfourodine and isobalfourodine were probably absent also.

Oxidation of the quinolone (VI; R = R′ = Me) with peroxylauric acid in a strongly acidic medium yielded a product that was soluble in water. Extraction with t-butyl alcohol furnished a single compound, isolated as its perchlorate (76%), shown to be (±)-*O*-methylbalfourodinium perchlorate (III; R = OH, X = ClO_4) by comparison with an authentic sample. The latter was obtained by first converting (±)-balfourodine into (±)-*O*-methylbalfourodinium iodide (III; R = OH, X = I), and then treating the quaternary iodide with an excess of perchloric acid

Many Rutaceae alkaloids are 2,4-dioxygenated quinolines bearing an isopentyl group at position 3. Various structural types are exemplified by lunacrine (IV), lunasine (III; R = H),[8] balfourodine (I), *O*-methylbalfourodinium salt (III; R = OH), flindersine

[3] Rapoport and Holden, *J. Amer. Chem. Soc.*, 1959, **81**, 3738.
[4] Rapoport and Holden, *J. Amer. Chem. Soc.*, 1960, **82**, 4395.
[5] Goodwin, Smith, Velasquez, and Horning, *J. Amer. Chem. Soc.*, 1959, **81**, 6209.
[6] Beyerman and Rooda, *Proc. k. ned. Akad. Wetenschap.*, 1959, **62**, *B*, 187.
[7] Beyerman and Rooda, *Proc. k. ned. Akad. Wetenschap.*, 1960, **63**, *B*, 427.
[8] Price, *Austral. J. Chem.*, 1959, **12**, 458.

(VII),[9] and orixine (XII).[10] A possible biosynthetic precursor of these alkaloids is a 4-hydroxy-3-(3-methylbut-2-enyl)quinolone, *e.g.*, (VI; R = R′ = H) in the enol form. Laboratory synthesis cannot provide direct evidence for biosynthetic schemes, but the reactions of this quinoline and its methylated derivatives described in this series of Papers



illustrate feasible routes to the Rutaceae alkaloids. In particular, the direct oxidations of the 4-hydroxyquinolone (VI; R = H, R′ = Me) to balfourodine (I), and of the 4-methoxyquinolone (VI; R = R′ = Me) to an *O*-methylbalfourodinium salt offer simple biosynthetic pathways to these alkaloids. Methylation of both hydroxyl groups of the dihydroxyquinoline precursor (enol form of VI; R = R′ = H) should preclude cyclisation, and lead by oxidation to the alkaloid, orixine (XII). Acid-catalysed cyclisation of the dihydroxyquinoline afforded 8-methoxydihydroflindersine in almost quantitative yield,[1] and a similar process, followed (or preceded [11]) by dehydrogenation, may be the biosynthetic route to flindersine (VII). Direct cyclisation of the *N*-methylquinolines (VI; R = H, R′ = Me) and (VI; R = R′ = Me) also yields pyranoquinolines,[1] and therefore seems to be an unlikely pathway to lunasine (III; R = H) and lunacrine (IV). By analogy with the laboratory synthesis,[2] lunasine and lunacrine could be derived from an *N*-methyl-4-methoxyquinoline by the route (VI; R = R′ = Me) ⟶ (II; R = R′ = H) ⟶ (III; R = H) ⟶ (IV), but, as a more attractive hypothesis, we suggest that lunacrine is formed from balfourodine (or its enantiomer) and lunasine is formed from an *O*-methylbalfourodinium salt (or its enantiomer) by successive stages of dehydration and reduction. Rapoport and Holden [3] showed that balfourolone (II; R = H, R′ = OH) was an artefact derived from *O*-methylbalfourodinium salt during isolation; the related alkaloid lunacridine (II; R = R′ = H) probably arises from lunasine in a similar way.[12] Several schemes for the biosynthesis of the furanoquinoline alkaloids (VIII) have been proposed,[13,14] but

[9] Brown, Hobbs, Hughes, and Ritchie, *Austral. J. Chem.*, 1954, **7**, 348.
[10] Terasaka, *Chem. and Pharm. Bull.* (*Japan*), 1959, **7**, 946; 1960, **8**, 523; Terasaka, Narahashi, and Tomikawa, *ibid.*, p. 1142.
[11] Ollis and Sutherland in " Chemistry of Natural Phenolic Compounds," Pergamon, Oxford, 1961, p. 84.
[12] Price in " Current Trends in Heterocyclic Chemistry," Butterworths, London, 1958, p. 92.
[13] Robinson, " The Structural Relations of Natural Products," Clarendon Press, Oxford, 1955.
[14] Birch and Smith, *Chem. Soc. Special Publ.* No. 12, 1958, 1; Aneja, Mukerjee, and Seshadri, *Tetrahedron*, 1959, **4**, 256.

the presence of a C_5 fragment in so many other Rutaceae alkaloids favours a route [14] in which the unsubstituted furan ring is derived by oxidative cleavage of an isoprenoid substituent; prior methylation of the 4-hydroxyl group of the precursor (VI; R = R′ = H) would ensure the production of a linear isomer.

The quinoline precursor (VI; R = R′ = H) is presumably formed from a 2,4-dihydroxyquinoline (IX) and a C_5 unit, for example (XIII),[15] derived from mevalonic acid. The alkaloid, ifflaiamine (XIV),[16] can also be accommodated in this scheme if we postulate reaction of the quinoline at the tertiary centre of the C_5 unit (XIII). The origin of the 2,4-dihydroxyquinoline (IX) is less easy to explain; condensation of the carbonyl group of anthranilic acid with acetate seems an unlikely route, since known biochemical reactions of anthranilic acid result in decarboxylation.[17] A possible alternative is cyclisation of the acid (X), which could be derived from tryptophan by oxidation by way of the α-keto-acid (XI).

Experimental

(±)-*Balfourodine* (I).—(*a*) A solution of 4-hydroxy-8-methoxy-1-methyl-3-(3-methylbut-2-enyl)-2-quinolone (VI; R = H, R′ = Me) (1·01 g.) and 90% peroxylauric acid (1·09 g.) in chloroform (20 c.c.) was kept at 18° for 3 days and extracted with 2N-hydrochloric acid (5 × 30 c.c.). The aqueous solution was made alkaline with sodium carbonate and extracted with methylene chloride. Evaporation of the solvent gave (±)-*balfourodine* (0·82 g., 78%), prisms, m. p. 189—191° (from ethyl acetate) (Found: C, 65·9; H, 6·3; N, 5·0. $C_{16}H_{19}NO_4$ requires C, 66·4; H, 6·6; N, 4·8%). The nuclear magnetic resonance spectrum showed a quartet at 1·92 τ ($J_{A,X}$ = 8, $J_{B,X}$ = 2) (1 aromatic proton) and a multiplet at 2·56—3·06 τ (2 aromatic protons). The ultraviolet (in methanol or 0·2M-methanolic hydrochloric acid) and that of (+)-balfourodine [3] corresponded, and the infrared spectra were almost identical.

The *perchlorate* separated from methanol–ether in prisms, m. p. 212—213° (Found: C, 49·3; H, 5·3. $C_{16}H_{20}ClNO_8$ requires C, 49·3; H, 5·2%).

(*b*) A solution of the quinolone (VI; R = H, R′ = Me) (202 mg.) in t-butyl alcohol (27 g.) containing concentrated sulphuric acid (363 mg.) was treated with an excess of peroxylauric acid. The solution was kept at 18° for 3 days and worked up as described in (*a*) to yield (±)-balfourodine (202 mg., 95%), prisms, m. p. 189—191° (from ethyl acetate), identical (mixed m. p. and infrared spectrum) with a sample obtained in (*a*).

Thin-layer chromatography of the reaction mixture from (*a*) or from (*b*) in chloroform–methanol (1 : 1) on alumina G gave a single spot (R_F 0·89) corresponding to that given by the pure product and by (+)-balfourodine. (±)-Isobalfourodine (see below), R_F 0·87, was absent. Spots were detected by spraying with the Dragendorff reagent (with which balfourodine gave an orange colour and isobalfourodine a red-orange colour) followed by 1% aqueous potassium permanganate (with which balfourodine gave a red-brown colour and isobalfourodine gave a purple colour).

(±)-*Isobalfourodine* (V).—By the method of Rapoport and Holden,[4] (±)-balfourodine (102 mg.) was converted into (±)-isobalfourodine acetate. A solution of the crude acetate in methanol (5 c.c.) and 0·5N-sodium hydroxide (10 c.c.) was kept for 24 hr., and water (60 c.c.) was added. Extraction with chloroform afforded (±)-*isobalfourodine* (88 mg., 86%), prisms, m. p. 184—186° [from ethyl acetate–light petroleum (b. p. 40—60°)], $\nu_{max.}$ ($CHCl_3$) 1610 $cm.^{-1}$, ($\varepsilon_{max.}$[a] 398) (Found: C, 66·7; H, 6·3. $C_{16}H_{19}NO_4$ requires C, 66·4; H, 6·6%). Thin-layer chromatography in chloroform–methanol (3 : 1) on alumina G gave a single spot, R_F 0·87 (balfourodine, R_F 0·90), and in methanol–ammonium hydroxide (0·88) (6 : 1) on silica gel G gave a single spot, R_F 0·77 (balfourodine, R_F 0·79). The spots were detected as in the preceding experiment.

The *perchlorate* crystallised from methanol–ether in prisms, m. p. 208—209° (Found: C, 49·3; H, 5·2; N, 3·9. $C_{16}H_{20}ClNO_8$ requires C, 49·3; H, 5·2; N, 3·6%).

(±)-O-*Methylbalfourodinium Iodide* (III; R = OH, X = I).—A solution of (±)-balfourodine (405 mg.) in methyl iodide (15 c.c.) was refluxed for 32 hr. Evaporation of the solution, trituration of the residue with ether, and crystallisation of the solid from ethanol–ether gave the

[15] Cornforth and Popjak, *Tetrahedron Letters*, 1959, No. 19, 29.
[16] Bosson, Galbraith, Ritchie, and Taylor, *Austral. J. Chem.*, 1963, **16**, 491.
[17] Scott, *Ann. Reports*, 1961, **58**, 383; Luckner and Mothes, *Tetrahedron Letters*, 1962, No. 23, 1035.

iodide, m. p. 152—153°, $\nu_{max.}$ 1630 cm.$^{-1}$ (Found: C, 46·9; H, 5·1; N, 3·3. $C_{17}H_{22}INO_4$ requires C, 47·3; H, 4·9; N, 3·2%).

(±)-O-*Methylbalfourodinium Perchlorate* (III; R = OH, X = ClO_4).—(*a*) A mixture of 4,8-dimethoxy-1-methyl-3-(3-methylbut-2-enyl)-2-quinolone (VI; R = R′ = Me) (139 mg.), concentrated sulphuric acid (200 mg.), t-butyl alcohol (30 c.c.), and 80% peroxylauric acid (250 mg.) was kept at 18° for 3 days. Water (20 c.c.) was added and t-butyl alcohol evaporated. The aqueous solution was extracted with methylene chloride, saturated with sodium chloride, and extracted with t-butyl alcohol (4 × 15 c.c.). Evaporation of the alcohol, and treatment of the residue in ethanol–ether with perchloric acid gave the *perchlorate* (148 mg., 76%), prisms, m. p. 203—204° (from methanol–ether) (Found: C, 50·9; H, 5·3; N, 3·8. $C_{17}H_{22}ClNO_8$ requires C, 50·5; H, 5·5; N, 3·5%).

(*b*) (±)-*O*-Methylbalfourodinium iodide (10 mg.) in methanol (1 c.c.) was treated with an excess of perchloric acid. Addition of ether yielded the perchlorate, m. p. and mixed m. p. 202—203°. The infrared spectrum was identical with that of a sample obtained in (*a*).

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