(**d**).—The pyrromethanes X and XI were treated as under (c) except that an equivalent amount of hydrogen chloride in acetic acid was used instead of hydrogen iodide. The precipitate obtained after aeration (21%) gave the uroporphyrin ester (14%), m.p. 253–257°, after esterification, etc.

It was degraded to coproporphyrin 3 methyl ester, the X-ray powder photograph and infrared mull spectrum of which were identical with those of the low-melting form of the reference specimen. Its m.p.'s were 149–153°, 161–165° (sparkling crystals) and 174–178°, copper complex 208–214° sintering from 205°.

The Behavior of X under the Conditions of Porphyrin Synthesis.—The pyrromethane was treated with hydrogen iodide in acetic acid followed by sodium acetate and air. The solution was evaporated and the residue esterified with diazomethane in pyridine–ether (avoiding the action of methanolic hydrogen chloride on starting material, etc.). After washing colored impurities out of the chloroform solution with aqueous resorcinol, the uroporphyrin (0.9%) was determined spectroscopically.

Uroporphyrin 3 Methyl Ester from Turacin.[21]—One recrystallization from chloroform–methanol gave homogeneous needles; a second gave needles mixed with amorphous material, m.p. 254–257° sintering and changing to flat crystals from 250°. There was a trace of the extra line in the X-ray powder photograph. From benzene–heptane it formed tiny bent hairs, m.p. 254–257° sintering and changing to compact crystals from 245°, mixed m.p. with the same form of the synthetic material of method (c) 254–257° after sintering from 248°. The two forms of the natural material gave X-ray powder photographs identical with those of the corresponding forms of synthetic material; with the qualifications mentioned above the same was true of the infrared mull spectra (first form: shoulder at 1245 cm.$^{-1}$, max. at 1170 cm.$^{-1}$ >1200 cm.$^{-1}$).

This natural uroporphyrin was degraded to coproporphyrin 3 methyl ester (70%, 0.04 mg./ml. remained in the methanol) obtained as clusters of needles, X-ray powder photograph identical with that of the low-melting form of the reference specimen. The needles either melted or changed to fibrous crystals at 153–155°. The latter either melted between 163–172° usually with previous sintering or changed to plates, m.p. 178–182°. When the needles were mixed with the reference specimen, their behavior on heating was unchanged. The copper complex melted at 216–219° after sintering from 213°.

Mixtures of Uroporphyrin Methyl Esters. (**1**).—The uroporphyrin mixture from 5,5′-dicarboxypyrromethane-3,3′-dipropionic acid-4,4′-diacetic acid with formic acid at 40°[5,14] crystallized completely from chloroform–methanol in long needles, m.p. 256–258° after sintering, undepressed on admixture with the turacin uroporphyrin. From benzene–heptane it formed hairs, m.p. 255–260° after changing to flat crystals from 245°; the X-ray photograph had twenty-five measurable lines. It had been degraded to a mixture of coproporphyrin methyl esters, m.p. 135–183°. Uroporphyrin 2, the only proven component, had been obtained from the fraction separating from pyridine at room temperature.[25]

(**2**).—The uroporphyrin 3 from 2-hydroxymethyl-5-carboxypyrrole-3-propionic acid-4-acetic acid with hot dilute hydrochloric acid[7] crystallized completely from chloroform–methanol in needles, m.p. 253–257°, and from benzene–heptane as curled hairs, m.p. 250–254° after changing to flat crystals from 245°. There was a trace of the extra line in the X-ray photograph of the form from chloroform–methanol. It degraded to a coproporphyrin methyl ester, m.p. 133–210°. The only component we identified was uroporphyrin 2 methyl ester, m.p. 313–315° after sintering from 300°, isolated by crystallization from pyridine, thrice from acetone, then from chloroform–acetone.

(**3**).—The urinary uroporphyrin from a case ("McCawl") of *porphyria cutanea tarda*[15] crystallized completely from chloroform–methanol in needles and hairs, m.p. 254–258°, undepressed on admixture with the turacin uroporphyrin. There was no extra line in the X-ray powder photograph. From benzene–heptane it formed bent hairs, m.p. 254–257°. Both forms sintered and changed to flat crystals from 245°. Crystallization from pyridine did not raise the m.p. above 265°.

(**4**).—A mixture of the pure synthetic uroporphyrin 1,2,3 and 4 methyl esters in the ratio 1:1:4:2 was crystallized from chloroform–methanol as homogeneous hair-like crystals, m.p. 255–259° after sintering and changing to flat crystals from 250°. There was a trace of the extra line in the X-ray powder photograph which had 25 measurable lines. From benzene–heptane homogeneous fine hairs separated, m.p. 255–259° after changing to flat crystals from 245°. The corresponding coproporphyrin mixture behaved otherwise.[13]

(**5**).—A mixture of the pure synthetic uroporphyrin 1,2,3 and 4 methyl esters in the ratio 1:1:2:4 was crystallized from chloroform–methanol as needles together with some hair-like crystals and amorphous material, m.p. 255–259° after sintering from 248°. From benzene–heptane fine curled hairs separated, m.p. 255–262° after partly changing to flat crystals from 245°.

A mixture of the synthetic uroporphyrin 3 and 4 methyl esters, mixed m.p. 252–255° after sintering from 245°, crystallized from chloroform–methanol completely as long needles, m.p. 254–257° after sintering and changing to flat crystals. The losses on crystallizing all the above mixtures were insignificant.

(25) The fraction remaining in pyridine at 0°, m.p. 252–256°, behaved as uroporphyrin 3 or 4 on paper chromatography with 2,6-lutidine or dioxane. It degraded to a coproporphyrin which behaved on paper with 2,6-lutidine–ammonia as coproporphyrin 3 or 4 with tailing suggesting 5% of coproporphyrin 1 but no coproporphyrin 2. However, the solubility (0.5 mg./ml. in methanol) and m.p. (half at 140–165°, half at 215–225°) of the coproporphyrin methyl ester showed that it was a mixture and contained much of the type 1 or type 2 isomers.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY]

Alkaloids of *Balfourodendron riedelianum*. Balfourodine and Isobalfourodine

BY HENRY RAPOPORT AND KENNETH G. HOLDEN[1]

RECEIVED DECEMBER 22, 1959

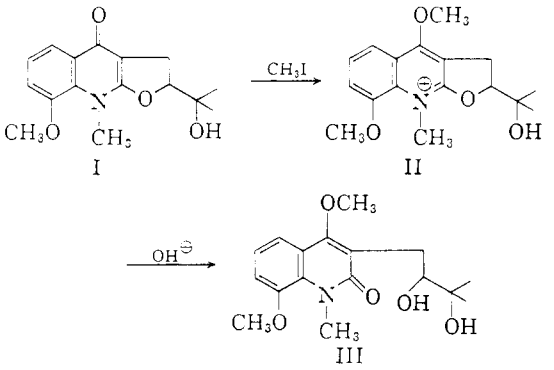
The structures of two alkaloids of *Balfourodendron riedelianum*, balfourodine and isobalfourodine, as well as two of their isomeric transformation products, ψ-balfourodine and ψ-isobalfourodine, have been determined. These compounds represent the four possible isomeric linear and angular dihydrofuro- and dihydropyrano-quinolones corresponding to 2-alkoxy-4-quinolones and 4-alkoxy-2-quinolones. Through the use of synthetic compounds of unquestioned structure, a general spectral method for distinguishing these various isomeric ring systems has been developed. In addition, four known alkaloids have been isolated, bringing to seven the number of characterized alkaloids from this plant source.

In a previous publication[2] the isolation of alkaloids from *Balfourodendron riedelianum*, a rutaceous plant indigenous to Brazil and Argentina, was described, and structural assignments were made to the two alkaloids present in the plant in highest concentration. Balfourolone (III) was shown to be an artifact of this isolation procedure. It arose from alkali attack on the O^4-methylbalfourodinium

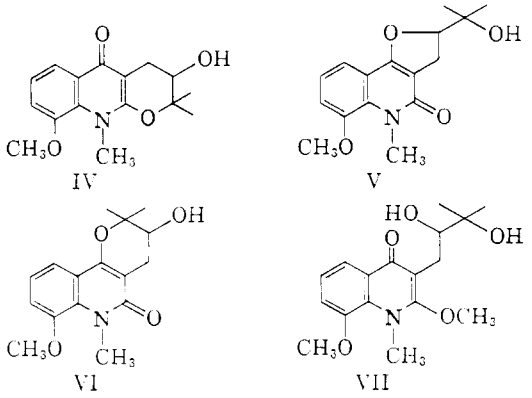
(1) Public Health Service Predoctoral Research Fellow of the National Heart Institute.

(2) H. Rapoport and K. G. Holden, THIS JOURNAL, **81**, 3738 (1959).

cation whose structure accordingly was assigned as II. Balfourodine tentatively was assigned structure I, largely on the basis of its quaternization to a balfourodinium salt as shown in the transformations

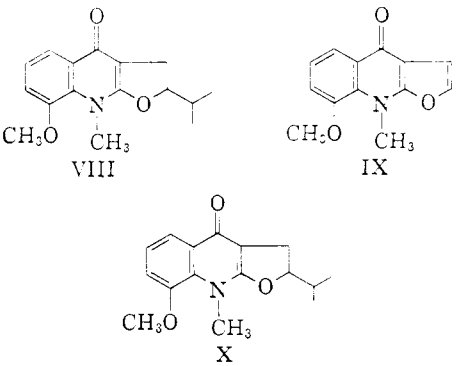


However, since there are two hydroxyl groups in the side chain of balfourolone (III), either of which might have arisen during ring opening, it was not possible to rule out the isomeric dihydropyrano structure IV[3] for balfourodine, as this also could conceivably give rise to balfourolone by a similar path. The isomeric, angular structures V and VI were not considered for balfourodine as this would require that balfourolone (III) have the isomeric structure VII.

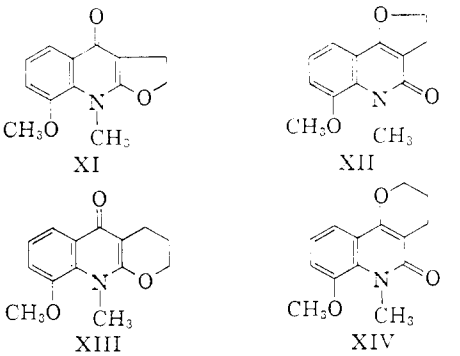


The structure III, assigned to balfourolone, rested largely on the preferential methylation by diazomethane of the 4-oxygen in 2,4-dihydroxyquinolines. Since first noted in the case of 2,4-dihydroxyquinoline and 1-methyl-4-hydroxy-2-quinolone,[4] this preferential methylation has been applied to variously substituted 2,4-dihydroxyquinolines during structural studies concerned with establishing the linearity of furoquinoline alkaloids.[5,6] Now that the linearity of many of these compounds has been established by independent syntheses,[7,8] ample confirmation has been supplied that the 4-oxygen is preferentially methylated in all compounds of this type. Hence, balfourolone is represented by structure III rather than structure VII. Physical data (infrared and ultraviolet spectra), presented in another section of this paper, provide independent evidence eliminating structure VII for balfourolone as well as structures V and VI for balfourodine.

However, the isomeric linear dihydropyrano structure IV for balfourodine was still a possibility. Thus the problem of definitely assigning the structure of balfourodine consisted of differentiating between the linear dihydrofuro and dihydropyrano structures I and IV, respectively. Degradative work on balfourodine seemed to be of little value as reactions aimed at eliminating the hydroxyl function did not proceed under mild conditions and gave unrecognizable products under more drastic conditions. However, reaction of balfourodine with concentrated sulfuric acid at room temperature gave a good yield of anhydrobalfourodine (VIII), whose ultraviolet spectrum is identical with that reported[9] for iso-γ-fagarine (IX). Hydrogenation of anhydrobalfourodine (VIII) gave *d,l*-lunacrine



(X)[10] whose infrared and ultraviolet spectra were identical with those of an authentic sample[11] of natural *l*-lunacrine. While this series of reactions might be interpreted as definite proof of the dihydrofuroquinolone structure I for balfourodine, the sulfuric acid dehydration must be regarded with caution. Under these conditions, the possibility of rearrangement exists, and a ring contraction from the isomeric pyrano structure IV to give the observed product VIII must be considered.



(3) Reference 2, footnote 8.

(4) F. Arndt, L. Ergener and O. Kutlu, *Ber.*, **86**, 951 (1953).

(5) R. F. C. Brown, P. T. Gilham, G. K. Hughes and E. Ritchie, *Austral. J. Chem.*, **7**, 181 (1954).

(6) R. G. Cooke and H. F. Haynes, *ibid.*, **11**, 225 (1958).

(7) M. F. Grundon and N. J. McCorkindale, *J. Chem. Soc.*, 2177 (1957).

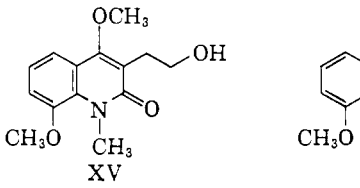
(8) H. Tuppy and F. Böhm, *Monatsh.*, **87**, 720 (1956).

(9) V. Deulofeu and D. Bassi, *Anales asoc. quim. arg.*, **40**, 249 (1952).

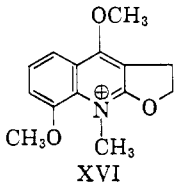
(10) S. Goodwin and E. C. Horning, THIS JOURNAL, **81**, 1908 (1959).

(11) We are indebted to Dr. Sidney Goodwin, National Heart Institute, Bethesda, for this sample.

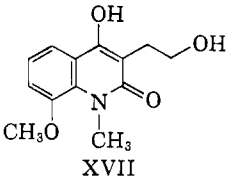
In order definitely to establish the structure of balfourodine and to find some criteria for distinguishing the various isomeric ring structures, several linear and angular dihydrofuro- and dihydropyranoquinolones were synthesized, XI, XII, XIII and XIV. The previously described alcohol XV[2] could be ring-closed in polyphosphoric acid to give, as an intermediate, the quaternary salt XVI. On refluxing this with lithium bromide in acetonitrile, the desired 8-methoxy-9-methyl-4-oxo-2,3,4,9-tetrahydrofuro[2,3-b]quinoline (XI)[12] was formed. Proof that XI has the linear structure, as designated, rather than the isomeric angular structure XII is provided by the fact that the initial product coming from the polyphosphoric acid ring closure was quaternary and displacement of a methyl group as methyl bromide was required in order to arrive at a tertiary base. Formation of angular structure XII would require direct displacement of the methyl group during the ring closure step. This latter route could be realized when the alcohol XV was heated in dilute aqueous hydrochloric acid. In this case the 4-oxygen presumably was demethylated to give, as an intermediate, the 4-hydroxy-2-quinolone XVII from which the angular compound, 6-methoxy-5-methyl-4-oxo-2,3,4,5-tetrahydrofuro[3,2-c]quinoline (XII), was generated directly. Thus the linear (XI) and angular (XII) model compounds in the dihydrofuroquinolone series have been synthesized by unambiguous routes.



XV

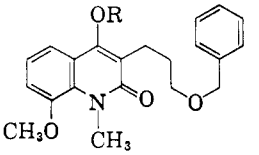


XVI

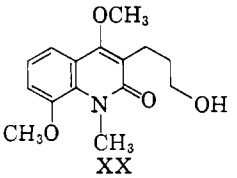


XVII

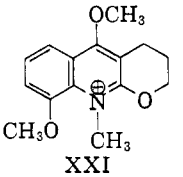
The corresponding dihydropyranoquinolones XIII and XIV were obtained by cyclization of the homologous alcohol XX which was prepared by the same general method used to prepare XV. Condensation of N-methyl-*o*-anisidine with diethyl γ-benzyloxypropylmalonate gave 1-methyl-3-(γ-benzyloxy)-propyl-4-hydroxy-8-methoxy-2-quinolone (XVIII). Treatment of this compound with diazomethane to give 1-methyl-3-(γ-benzyloxy)-propyl-4,8-dimethoxy-2-quinolone (XIX) followed by hydrogenolysis of the protecting benzyl ether gave the desired alcohol 1-methyl-3-(γ-hydroxy)-propyl-4,8-dimethoxy-2-quinolone (XX). Cyclization of this compound with polyphosphoric acid gave a mixture of the angular dihydropyranoquinolone, 7-methoxy-6-methyl-5-oxo-2,3,5,6-tetrahydropyrano[3,2-c]quinoline (XIV), and the quaternary linear dihydropyranoquinolone XXI from which the desired 9-methoxy-6-methyl-5-oxo-2,3,5,10-tetrahydropyrano[2,3-b]quinoline (XIII) was obtained by displacement with bromide ion. In this system also, the intermediacy of the quaternary compound in the one case and not in the other establishes the linear and angular structures without question.



XVIII, R = H
XIX, R = CH3



XX



XXI

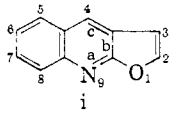
Although the ultraviolet spectra of the model compounds XI–XIV were similar, the differences were sufficient to delineate the various ring structures, and only the ultraviolet spectrum of the linear dihydrofuroquinolone (XI) was identical with that of balfourodine. Thus the linear dihydrofuroquinolone structure I is established for balfourodine.

Of particular interest, in view of the correlations in the ultraviolet region made possible by synthesis of the model compounds, was an alkaloid, A_4, isolated by careful chromatography of fraction A[2] (the other components of fraction A are discussed below). This substance, $C_{16}H_{19}O_4N$, was isomeric with balfourodine, and showed similar, but not identical, absorption in the infrared and ultraviolet. The ultraviolet absorption spectrum, however, was identical with that of the synthetic linear dihydropyranoquinolone XIII. Thus this ring structure is required for A_4, which henceforth will be referred to as isobalfourodine.

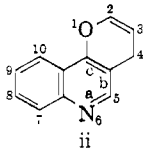
It seemed reasonable to assume that isobalfourodine might have the alternative structure IV, previously considered for balfourodine.[3] That this was indeed the case was shown by a number of transformations of isobalfourodine and balfourodine which led to identical products. Of these various transformations the most straightforward was the reaction of the two alkaloids with acetic anhydride and pyridine.

The acetates obtained from balfourodine and isobalfourodine were shown to be identical by comparison of infrared and ultraviolet spectra. Furthermore, the ultraviolet spectra were identical with that of isobalfourodine (IV), showing that no change in ring size occurred on acetylation of isobalfourodine, but that expansion of the dihydrofurano ring to a dihydropyrano ring took place under

(12) Since the nomenclature for furoquinolines is varied and no pyranoquinolines have been named in a systematic manner, the following numbering system has been adopted for these structures.

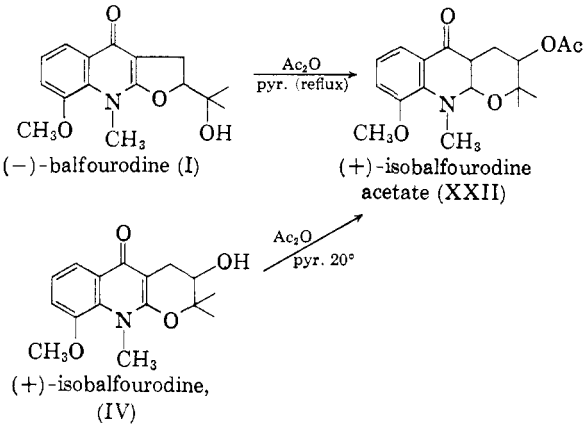


i

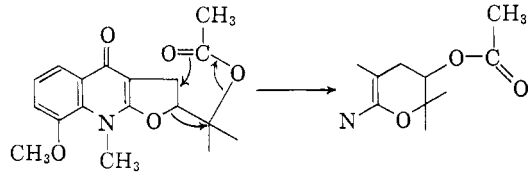


ii

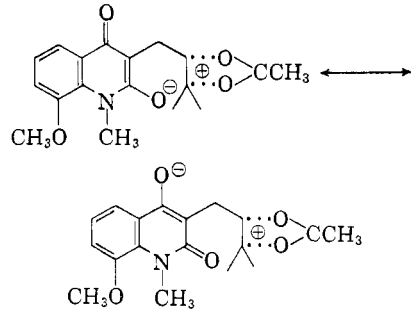
Thus, i is a furo[2,3-b]quinoline while its angular isomer is designated as [3,2-c]. Similarly ii is a pyrano[3,2-c]quinoline while its linear isomer is [2,3-b].



the more vigorous acetylation conditions to which balfourodine was exposed. As was expected, only starting material was recovered when balfourodine was acetylated under the milder conditions. Saponification of the acetates gave (+)-isobalfourodine, although both the acetate and the isobalfourodine obtained from balfourodine were about 42% racemized. This indicates that at least 58% of the ring expansion reaction followed a stereospecific course, and hence a concerted mechanism is suggested.



One might also consider a semi-concerted mechanism in which a resonance-stabilized bridged ion is responsible for the observed stereospecificity.



In either case, the conversion of balfourodine into isobalfourodine acetate must cause an inversion of the asymmetric center, indicating that balfourodine and isobalfourodine have opposite absolute configurations. This relationship is established more clearly by the transformations which these alkaloids undergo with dimethyl sulfate and concentrated base. These transformations are presented schematically in Chart 1 and are discussed below.

The structures of ψ-balfourodine and ψ-isobalfourodine were readily elucidated by their empirical formulas and their ultraviolet spectra. Both compounds have the same empirical formula, $C_{16}H_{19}O_4N$, isomeric with balfourodine, and their ultraviolet spectra are identical with those of the synthetic, angular dihydrofuro and dihydropyrano compounds XII and XIV, respectively. Thus ψ-balfourodine must have structure V while ψ-isobalfourodine is represented by VI.

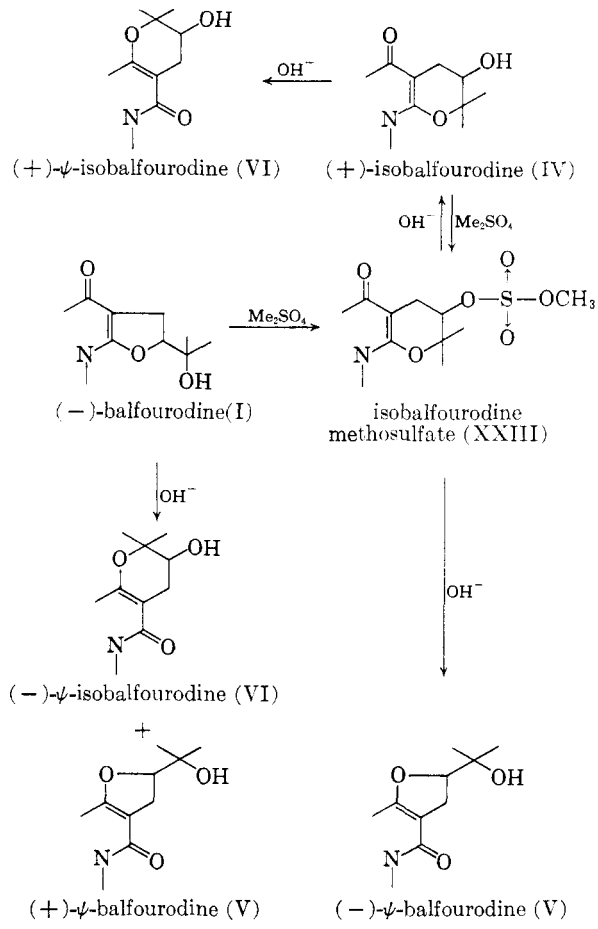


Chart 1.—Transformations of balfourodine and isobalfourodine.

The transformation of balfourodine (I) into isobalfourodine (IV) *via* the methosulfate XXIII must involve an odd number of inversions since optically antipodal ψ-isobalfourodines (VI) are obtained on treatment of balfourodine and isobalfourodine with concentrated alkali. If we assume that only one inversion takes place in the balfourodine–isobalfourodine transformation, it follows that inversion must have occurred when balfourodine (I) was treated with dimethyl sulfate, since optically antipodal ψ-balfourodines (V) are obtained from balfourodine and isobalfourodine methosulfate (XXIII) on treatment of these compounds with alkali. In agreement with the acetate work already discussed, it is evident that balfourodine and isobalfourodine must have opposite absolute configurations. A mechanism very similar to that proposed for the acetate ring expansion might be imagined for the conversion with dimethyl sulfate, in which a bridged ion or concerted mechanism is responsible for maintaining optical activity.

The various transformations with base leading to the angular balfourodines V and VI are more difficult to interpret mechanistically since the observed rotations of the products are consistent with no in-

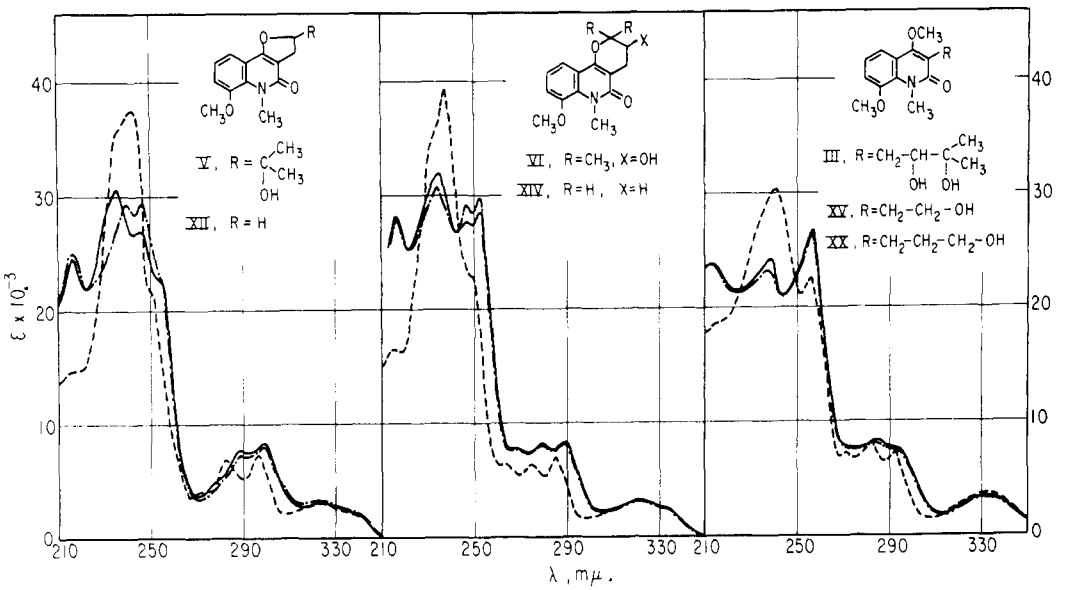
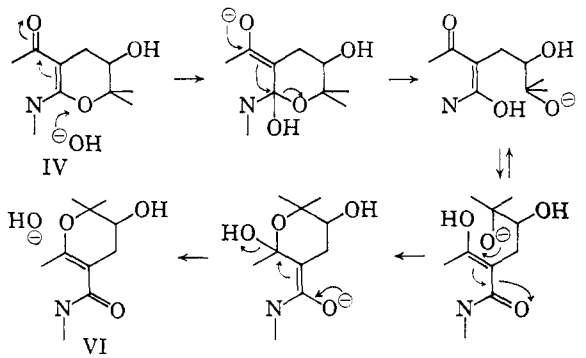


Fig. 1.—Ultraviolet absorption spectra of 4-alkoxy-2-quinolones in methanol (———); methanol, 0.2 *M* in hydrochloric acid (· – · –); and hexane (– – – –).

version or any number of inversions. Of the many possibilities, a mechanism which is similar to the alkali-catalyzed ring opening of O^4-methylbalfourodinium ion (II) to give balfourolone (III) could be conceived for the transformation of isobalfourodine (IV) into ψ-isobalfourodine (VI). In this case no in-



versions take place since the asymmetric center is not involved. An analogous mechanism, involving the asymmetric center and proceeding with retention of configuration, might be extended to the other alkali-catalyzed transformations shown in Chart 1. While the mechanistic interpretations are not proved, two facts of importance are derived from the above series of transformations: (1) The structure of isobalfourodine is established as IV since structurally identical products are obtained from isobalfourodine and balfourodine (I) under similar reaction conditions, thus completing the part structure XIII required by the ultraviolet spectrum of isobalfourodine.[13] (2) All the transformations are consistent with balfourodine and isobalfourodine having opposite absolute configurations.

The most useful method for distinguishing the various isomeric forms of balfourodine has been by their characteristic ultraviolet spectra (see Figs. 1 and 2). Through the synthesis of model compounds with the appropriate chromophoric systems, the structures of balfourodine, isobalfourodine and their transformation products have been elucidated with a minimum of degradative work. This method has the definite advantage of requiring only small amounts of the alkaloids and avoiding the ambiguity in interpreting degradative evidence as it reflects ring size or angular *vs.* linear structures. From Figs. 1 and 2 it can be seen that, while assigning the size of ring C (dihydrofuro or dihydropyrano) on the basis of a single ultraviolet spectrum in a given alkaloidal series would be difficult, distinguishing between the linear and angular series should be possible, that is, distinguishing between a 2-alkoxy-4-quinolone and a 4-alkoxy-2-quinolone. In every case the 4-alkoxy-2-quinolone shows a series of maxima in the range 263–298 mμ ($\epsilon \sim 8{,}000$) while the 2-alkoxy-4-quinolone has a minimum in this region at about 270 mμ. This appears to be general for 2- and 4-quinolones as noted by others,[7,14] and may be observed in the case of the parent compounds 2- and 4-quinolone.[15]

Another useful generalization about 2- and 4-quinolones and pyridones can be made on the basis of pK_a measurements.[16,17] As might be expected, 4-quinolones and -pyridones, being vinylogous amides, are stronger bases by about 3 to 5 powers of ten than 2-quinolones and -pyridones, which may be regarded as almost normal amides. This generalization is reflected in the acid-shift data presented in Figs. 1 and 2. The 2-quinolones show little change in their ultraviolet absorption when the spectra are taken in methanol, 0.2 *M* in hydrochloric acid. On the other hand, the 4-quinolones

(13) Such a linear, dihydropyranoquinolone structure, with the position of the hydroxyl group unspecified, was assigned to lunasia II, an alkaloid of *Lunasia amara*, by H. C. Beyerman and R. W. Rooda [*Koninkl. Ned. Akad. Wetenschap. Proc., Ser. B*, **62**, 187 (1959)].

(14) M. F. Grundon, N. J. McCorkindale and M. N. Rodger, *J. Chem. Soc.*, 4284 (1955).

(15) G. W. Ewing and E. A. Steck, THIS JOURNAL, **68**, 2181 (1946).

(16) A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1294 (1956).

(17) A. Albert, "Heterocyclic Chemistry," Essential Books, Fair Lawn, N. J., 1959, p. 57.

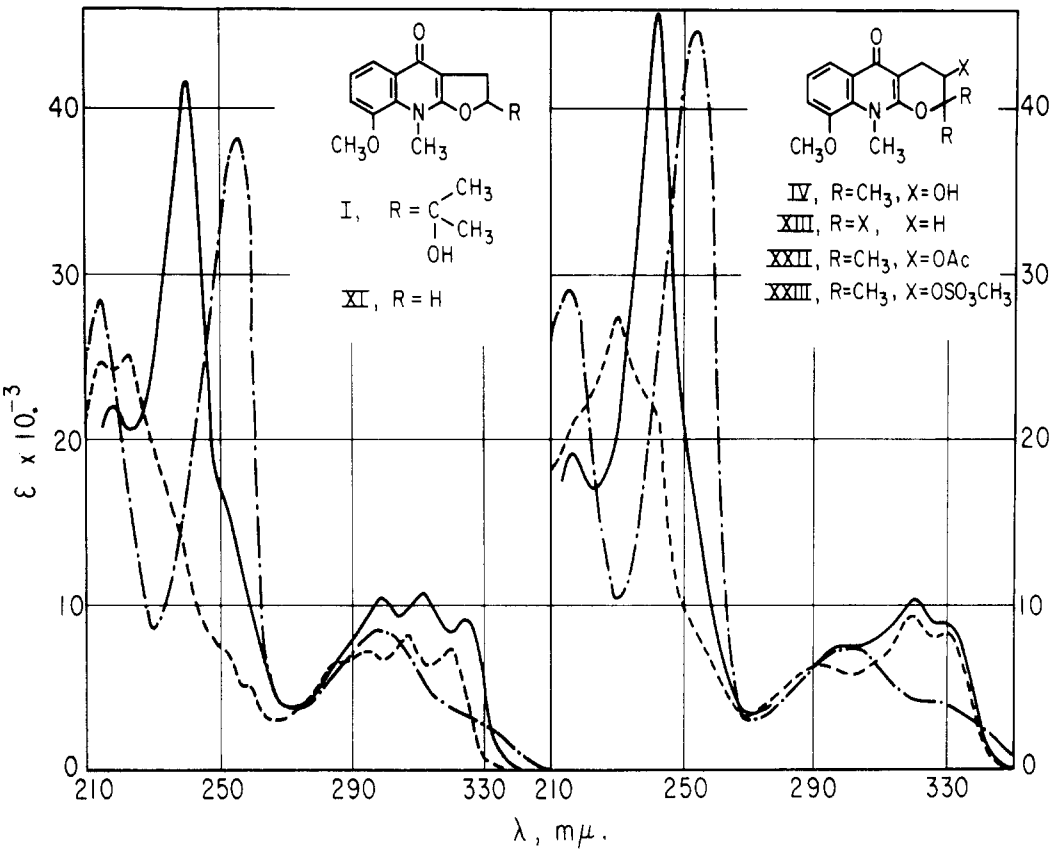


Fig. 2.—Ultraviolet absorption spectra of 2-alkoxy-4-quinolones in methanol (———); methanol, 0.2 *M* in hydrochloric acid (· – · –); and hexane (– – – –).

studied show pronounced shifts in acid, resulting in curves which are identical with their methylated, quaternary analogs (II, XVI, XXI).

Another useful physical method for distinguishing the 2- and 4-quinolones investigated by us is provided by the shifts produced in their ultraviolet absorption when the spectra are taken in *n*-hexane (Figs. 1 and 2) as opposed to methanol. The spectra of the 2-quinolones are changed very little at long wave lengths, but at shorter wave lengths there is a coalescence of bands to give a single band of high intensity at about 240 mμ (ε ~ 40,000). The opposite effect is noted for the 4-quinolones; namely, besides a shift to shorter wave lengths of about 15 mμ, there is observed a splitting of the main absorption maximum to give several unresolved maxima of lowered intensity centered at about 225 mμ (ε ~ 26,000). This rather pronounced effect of the solvent on the ultraviolet spectrum of the solute is commonly observed with compounds of the quinolone type which may easily carry a large separation of charge in excited states.[17] Since 2-alkoxy-4-quinolones show a marked decrease in intensity of the short wave length maxima when the spectra are taken in hexane while the opposite effect is noted for 4-alkoxy-2-quinolones, an additional method for distinguishing these isomeric compounds is suggested.

Finally, the infrared spectra of these compounds afford still another method of differentiation. The generalization[7] that the first absorption maximum in the 6 μ region occurs at slightly longer wave lengths in 4-quinolones than in 2-quinolones is followed for the compounds examined by us (Table I). However, the difference is small, and hence this criterion does not appear to be of as great value for distinguishing 2-alkoxy-4-quinolones and 4-alkoxy-2-quinolones. Perhaps a more useful correlation in our series of compounds is that the 2-quinolones show an absorption minimum between 6.34 and 6.65 μ, while the 4-quinolones show strong absorption in this region at about 6.43 μ.

TABLE I

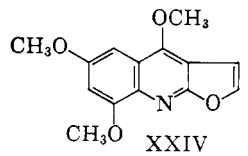
INFRARED ABSORPTION OF THE ISOMERIC 4-ALKOXY-2-QUINOLONES AND 2-ALKOXY-4-QUINOLONES

Compound	λmax in 6 μ region						
	4-Alkoxy-2-quinolones						
III	6.14	6.21	6.30	..	..	..	6.80
V	6.02	6.14	6.25	6.33	..	6.65	6.77
VI	6.11	6.20	6.27	6.32	..	6.71	6.80
XII	6.04	6.15	6.25	6.34	..	6.65	6.78
XIV	6.11	6.20	6.26	6.32	..	6.71	6.80
XV	6.12	6.18	6.28	..	..	..	6.78
XX	6.15	6.20	6.27	..	..	..	6.80
	2-Alkoxy-4-quinolones						
I	..	6.17	6.26	..	6.42	6.59	6.79
IV	..	6.20	6.25	6.32	6.45	6.64	6.82
XI	..	6.18	6.27	..	6.43	6.60	6.80
XIII	..	6.20	6.25	6.30	6.45	6.64	6.80

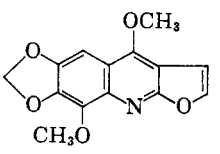
While no one method for distinguishing substituted 2- and 4-quinolones, as discussed above, should be regarded as infallible, a combination of these methods should make this differentiation unequivocal.

In addition to isobalfourodine (IV) and a small amount of balfourodine (I), four other alkaloids have been isolated from the chromatography of fraction A.[2] These proved to be known compounds whose identities were established beyond question by direct comparisons with samples of the known alkaloids.

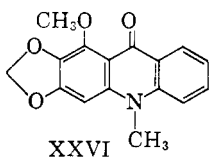
Two furoquinoline alkaloids, maculosidine (XXIV)[5] and flindersiamine (XXV),[18] as well as an acridone alkaloid, evoxanthine (XXVI),[19] were isolated.[20] The latter is present in the plant only in very small concentration. The fourth known compound had not been reported as a naturally occurring substance, but it proved to be a transformation product of 2-phenyl-4-methoxyquinoline[21] isolated from *Lunasia amara*. On heating 2-phenyl-4-methoxyquinoline with methyl iodide in a sealed tube, 1-methyl-2-phenyl-4-quinolone (XXVII)[11] was obtained. This product proved to be identical with the fourth compound isolated in this study.



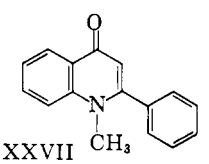
XXIV



XXV



XXVI



XXVII

Thus *Balfourodendron riedelianum* is quite prodigious in the number and variety of alkaloids it produces. A total of seven alkaloids representing six different types of quinolines (furoquinoline, dihydrofuroquinolone and its quaternary salt, dihydropyranoquinolone, acridone and quinolone) has been isolated, with the prospect of more to come.

Experimental[22]

Anhydrobalfourodine (VIII).—Balfourodine (I) (1.0 g., 3.5 mmoles) was dissolved in 15 ml. of concentrated sulfuric acid. When solution was complete (about 1 min.) the sulfuric acid solution was poured into 150 ml. of ice-water and the resulting mixture was extracted with chloroform (3 × 40 ml.). After being dried over anhydrous sodium sulfate, the chloroform was evaporated to dryness and the residue (1.0 g.) was chromatographed on 30 g. of alumina (Woelm, activity III). Elution with benzene–chloroform (3:1) and (1:1) gave anhydrobalfourodine (600 mg., 2.2 mmoles, 63%), which, after recrystallization from acetone–hexane and sublimation at 100° (10 μ,) melted at 126–126.5°.

Anal. Calcd. for $C_{16}H_{17}O_3N$: C, 70.9; H, 6.3. Found: C, 70.9; H, 6.1.

***d,l*-Lunacrine (IX).**—Anhydrobalfourodine (VIII) (17 mg., 0.063 mmole) in 10 ml. of 95% ethanol with 5 mg. of 5% palladium-on-charcoal was hydrogenated at room temperature and pressure for 5 hours. The catalyst was removed by filtration and the filtrate was evaporated to dryness under reduced pressure to give 15 mg. (0.055 mmole, 87%) of *dl*-lunacrine (X) whose ultraviolet and infrared spectra were identical with an authentic sample[11] of natural *l*-lunacrine.

Diethyl γ-Benzyloxypropylmalonate.—Sodium (25 g., 1.13 moles) was added to 400 ml. of dry ethanol in small pieces. When solution was complete, diethyl malonate (180 g., 1.13 moles) and sodium iodide (17 g., 0.113 mole) were added. Benzyl γ-chloropropyl ether[23] (204 g., 1.13 moles) was then added slowly with stirring. When addition was complete the resulting mixture was stirred at reflux for 30 hours. Pouring the warm reaction mixture into 3.5 l. of ice-water and extracting the aqueous solution with ether (3 × 500 ml.) gave, on evaporation of the dried ether phase, crude diethyl γ-benzyloxypropylmalonate. Distillation at 165–167° (1–2 mm.) gave pure material (190 g., 0.62 mole, 55%).

Anal. Calcd. for $C_{17}H_{24}O_5$: C, 66.2; H, 7.8. Found: C, 66.1; H, 7.6.

1-Methyl-3-(γ-benzyloxy)-propyl-4-hydroxy-8-methoxy-2-quinolone (XVIII).—To 70 g. (0.227 mole) of diethyl γ-benzyloxypropylmalonate in 175 ml. of refluxing Dowtherm was added, dropwise over a 1.5-hour period, 31 g. (0.227 mole) of N-methyl-*o*-anisidine.[2] The solution was boiled for an additional 2.5-hour period. At the end of this time, 24 ml. of the theoretical 26 ml. of ethanol had been evolved and the reaction mixture was cooled and diluted with 500 ml. of ether. The ethereal solution was extracted with 0.5 *N* aqueous sodium hydroxide (3 × 500 ml.), the aqueous extracts being washed with a 150-ml. portion of ether. The *p*H of the combined aqueous extracts was adjusted to 7 whereupon a heavy crystalline precipitate of crude 1-methyl-3-(γ-benzyloxy)-propyl-4-hydroxy-8-methoxy-2-quinolone (XVIII) formed (63.5 g., 0.180 mole, 79%). Recrystallization from acetone–hexane followed by sublimation at 160° (10 μ) gave the pure quinolone, m.p. 106–107°; ultraviolet absorption: λ_{max} 238 mμ (ϵ 27,500), 247 (25,200), 255 (24,800), 282 (7,700), 292 (8,000), 321sh (3,400); in methanol 0.2 *M* in HCl: λ_{max} 238 mμ (ϵ 26,400), 247 (25,100), 253 (26,400), 282 (7,500), 292 (7,800), 323 (2,800).

Anal. Calcd. for $C_{21}H_{23}O_4N$: C, 71.4; H, 6.5. Found: C, 71.6; H, 6.8.

1-Methyl-3-(γ-benzyloxy)-propyl-4,8-dimethoxy-2-quinolone (XIX).—To 21.3 g. (0.060 mole) of 1-methyl-3-(γ-benzyloxy)-propyl-4-hydroxy-8-methoxy-2-quinolone (XVIII) in 700 ml. of ether–methanol (5:1) was added *ca.* 0.13 mole of ethereal diazomethane. After 1 hour the ethereal solution was washed with 0.5 *N* aqueous sodium hydroxide (2 × 125 ml.) and the organic phase was dried over sodium sulfate. Evaporation of the solvent gave 21.6 g. (0.059 mole, 98%) of 1-methyl-3-(γ-benzyloxy)-propyl-4,8-dimethoxy-2-quinolone (XIX) as a viscous oil, which was molecularly distilled at 150° (50 μ); ultraviolet absorption: λ_{max} 238 mμ (ϵ 30,400), 256 (30,200), 283 (9,500), 291sh (8,900), 331 (4,400); in methanol 0.2 *M* in HCl: λ_{max} 239 mμ (ϵ 29,200) 256 (31,600), 282 (9,500), 291sh (8,900), 330 (4,200).

Anal. Calcd. for $C_{22}H_{25}O_4N$: C, 71.9; H, 6.8. Found: C, 71.8; H, 6.9.

1-Methyl-3-(γ-hydroxy)-propyl-4,8-dimethoxy-2-quinolone (XX).—1-Methyl-3-(γ-benzyloxy)-propyl-4,8-dimethoxy-2-quinolone (XIX) (21 g., 0.057 mole) in 125 ml. of ethanol with 1 g. of 5% palladium-on-charcoal was hydrogenated at room temperature and atmospheric pressure for 24 hours, the theoretical amount of hydrogen having been consumed during this period. Evaporation of the ethanol, after removal of the catalyst by filtration, gave 15 g. (0.054 mole, 95%) of 1-methyl-3-(γ-hydroxy)-propyl-4,8-dimethoxy-2-quinolone (XX) as a viscous oil which crystallized on molecular distillation at 135° (200 μ), m.p. 53–55°; ultraviolet absorption: λ_{max} 238 mμ (ϵ 23,700), 257 (24,800), 283 (8,000),

(18) F. A. L. Anet, P. T. Gilham, P. Gow, G. K. Hughes and E. Ritchie, *Austral. J. Sci. Research*, **5**, 412 (1952).

(19) G. K. Hughes and K. G. Neill, *ibid.*, **2**, 249 (1949).

(20) We are indebted to Dr. E. Ritchie, Chemistry Department, University of Sydney, for samples of these alkaloids.

(21) S. Goodwin, A. F. Smith and E. C. Horning, THIS JOURNAL, **79**, 2239 (1957).

(22) All melting points are corrected and those above 200° were taken in evacuated capillaries; microanalyses were performed by the Microchemical Laboratory, University of California, Berkeley. Optical rotations were measured on 1% solutions in ethanol in 1-dm. tubes at 25°; infrared spectra were taken in chloroform, and ultraviolet spectra were taken in methanol unless otherwise specified.

(23) G. M. Bennet and A. L. Hock, *J. Chem. Soc.*, 472 (1927).

291sh (7,400), 331 (3,400); in methanol 0.2 *M* in HCl: λ_{max} 238 mμ (ε 23,100), 256 (24,800), 283 (7,700), 291sh (7,200), 331 (3,400); in hexane: λ_{max} 242 mμ (ε 30,200), 256 (21,200), 271 (6,700), 282 (7,600), 292 (6,900), 335 (3,700).

Anal. Calcd. for $C_{15}H_{19}O_4N$: C, 65.0; H, 6.9. Found: C, 64.8; H, 6.9.

7-Methoxy-6-methyl-5-oxo-2,3,5,6-tetrahydropyrano[3,2-c]-quinoline (XIV).—To 1.84 g. (6.65 mmoles) of 1-methyl-3-(γ-hydroxy)-propyl-4,8-dimethoxy-2-quinolone (XX) was added 25 ml. of polyphosphoric acid. The mixture was stirred well and then heated in a nitrogen atmosphere at 115° for 1 hour. The hot polyphosphoric acid solution was poured into 150 ml. of water and the aqueous solution was extracted with ether (3 × 100 ml.) to give 0.39 g. (1.6 mmoles, 24%) of 7-methoxy-6-methyl-5-oxo-2,3,5,6-tetrahydropyrano[3,2-c]quinoline (XIV) which was recrystallized from acetone–hexane and sublimed at 110° (20 μ), m.p. 150–151°; ultraviolet absorption: λ_{max} 216 mμ (ε 26,400), 234 (30,200), 246 (27,200), 252 (27,800), 269 (7,300), 279 (7,800), 290 (7,800), 321 (3,000); in methanol 0.2 *M* in HCl: λ_{max} 216 mμ (ε 26,400), 234 (29,400), 247 (27,900), 252 (28,600), 268 (7,000), 279 (7,800), 290 (7,800), 321 (3,000); in hexane: λ_{max} 214 mμ (ε 17,000), 237 (41,400), 248sh (23,700), 262 (6,700), 274 (6,700), 285 (7,500), 322 (3,700).

Anal. Calcd. for $C_{14}H_{15}O_3N$: C, 68.6; H, 6.1; OCH_3, 12.7; CCH_3, 0.0. Found: C, 68.5; H, 6.2; OCH_3, 13.6; CCH_3, 0.0.

9-Methoxy-10-methyl-5-oxo-2,3,5,10-tetrahydropyrano-[2,3-b]quinoline (XIII).—Since extraction of the aqueous phosphoric acid solution, obtained during the cyclization of 1-methyl-3-(γ-hydroxyl)-propyl-4,8-dimethoxy-2-quinolone (XX) as described above, gave only 24% of product, the solution was adjusted to *p*H 7–8 and again extracted, to give a negligible amount of material. The ultraviolet spectrum of the aqueous solution was identical with that of isobalfourolone (IV) in acid solution, indicating the presence of the quaternary linear dihydropyranoquinoline XXII. In order to extract this quaternary compound as its chloride salt, 50 ml. of saturated sodium chloride solution was added to the aqueous solution. Extraction with 1-butanol (3 × 100 ml.) followed by evaporation of the organic solvent under reduced pressure gave 1.18 g. of material which was taken up in 25 ml. of methanol to which 2 g. of lithium bromide was added. The resulting solution was boiled for 6 hours, poured into 100 ml. of water and extracted with ether (3 × 75 ml.) to give 0.55 g. of material which was chromatographed on 15 g. of alumina. Elution with benzene–chloroform (1:1) gave 0.27 g. (1.1 mmoles, 17%) of 9-methoxy-10-methyl-5-oxo-2,3,5,10-tetrahydropyrano[2,3-b]quinoline (XIII) which was recrystallized from acetone–hexane and sublimed at 135° (10 μ), m.p. 156–157°; ultraviolet absorption: λ_{max} 216 mμ (ε 21,000), 241 (44,800), 298 (7,800), 319 (10,300), 330 (9,100); in methanol 0.2 *M* in HCl: λ_{max} 216 mμ (ε 29,400), 353 (43,200), 300 (6,900), 325sh (4,100); in hexane: λ_{max} 230 mμ (ε 27,400), 240sh (22,200), 290 (6,500), 319 (9,400), 330 (8,150).

Anal. Calcd. for $C_{14}H_{15}O_3N$: C, 68.6; H, 6.1; OCH_3, 12.7; CCH_3, 0.0. Found: C, 68.5; H, 6.1; OCH_3, 13.0; CCH_3, 0.0.

8-Methoxy-9-methyl-4-oxo-2,3,4,9-tetrahydrofuro[2,3-b]-quinoline (XI).—To 0.81 g. (3.08 mmoles) of 1-methyl-3-(β-hydroxy)-ethyl-4,8-dimethoxy-2-quinolone (XV) was added 25 ml. of polyphosphoric acid. The mixture was stirred well and then heated at 115° under nitrogen for 1 hour. The hot polyphosphoric acid solution was poured into 150 ml. of water. Extraction of the resulting acidic solution, and the same solution after adjusting the *p*H to 7–8, with ether (3 × 50 ml.) gave only negligible amounts of material. Addition of 100 ml. of saturated sodium chloride solution followed by extraction with 1-butanol (6 × 50 ml.) gave, on evaporation of the organic solvent under reduced pressure, 0.75 g. of material whose ultraviolet spectrum was identical with that of an *O*-methylbalfourodinium salt (II), indicating the presence of the quaternary linear dihydrofuroquinoline XVI. The 0.75 g. of material was taken up in 20 ml. of acetonitrile to which 5 g. of lithium bromide was added. After boiling the mixture for 12 hours most of the solvent was removed under reduced pressure and the residue taken up in 100 ml. of 1 *M* HCl. The acidic solution was extracted with methylene chloride (3 × 30 ml.) to give 120 mg. of neutral material. When the aqueous phase was adjusted to *p*H 7–8 and again extracted with methylene chloride (3 × 30 ml.), 370 mg. (1.6 mmoles, 52%) of 8-methoxy-9-methyl-4-oxo-2,3,4,9-tetrahydrofuro[2,3-b]quinoline (**XI**) was obtained. This was recrystallized twice from acetone–hexane and sublimed at 130° (30 μ), m.p. 135–137°; ultraviolet absorption: λ_{max} 217 mμ (ε 22,100), 240 (39,400), 298 (10,200), 311 (10,000), 323 (8,400); in methanol 0.2 *M* in HCl: λ_{max} 213 mμ (ε 29,000), 252 (33,800), 297 (8,000), 316sh (3,800); in hexane: λ_{max} 215 mμ (ε 24,600), 223 (25,000), 250sh (7,400), 258sh (5,000), 285sh (6,300), 294 (7,100), 307 (8,100), 320 (7,400).

Anal. Calcd. for $C_{13}H_{13}O_3N$: C, 67.5; H, 5.7. Found: C, 67.3; H, 5.7.

6-Methoxy-5-methyl-4-oxo-2,3,4,5-tetrahydrofuro[3,2-c]-quinoline (XII).—A solution of 1-methyl-3-(β-hydroxy)-ethyl-4,8-dimethoxy-2-quinolone (XV) (330 mg., 1.25 mmoles) in 100 ml. of 10% hydrochloric acid was boiled for one hour and allowed to stand for an additional 8 hours. The acidic solution was then extracted with ether (3 × 30 ml.) and the combined ether extracts were extracted with 1 *M* sodium hydroxide solution (3 × 30 ml.). The ether phase, after drying, gave 60 mg. (0.26 mmole, 21%) of 6-methoxy-5-methyl-4-oxo-2,3,4,5-tetrahydrofuro[3,2-c]quinoline(XII), which was recrystallized from acetone–hexane, methanol–water and methanol in that order and sublimed at 110° (30 μ), m.p. 144–145°; ultraviolet absorption: λ_{max} 217 mμ (ε 24,700), 236 (30,600), 247 (26,800), 254sh (23,200), 288 (8,000), 298 (8,700), 323 (2,900); in methanol 0.2 *M* in HCl: λ_{max} 217 mμ (ε 25,300), 239 (29,600), 246 (28,900), 288 (7,500), 298 (8,200), 324 (3,300); in hexane: λ_{max} 216sh mμ (ε 14,700), 242 (37,500), 250sh (21,800), 282 (6,900), 297 (7,300), 326 (3,700).

Anal. Calcd. for $C_{13}H_{13}O_3N$: C, 67.5; H, 5.7. Found: C, 67.6; H, 5.8.

Isolation of Alkaloids from Fraction A.[2] **A. Crude Separation.**—Chromatographic separation of 92 g. of fraction A was carried out on 1500 g. of alumina (Woelm, activity III). Elution with benzene–chloroform (1:1) gave a crude mixture of alkaloids, A_a (15.8 g.), which was processed further as described in section B. Elution with chloroform through chloroform–methanol (9:1) gave more alkaloidal material which could be further purified by washing with acetone. The crystalline material remaining after several acetone washings was combined (A_b, 13.0 g.) and rechromatographed as described in section C.

B. Purification of A_a.—Chromatography of A_a (15.8 g.) on 500 g. of alumina gave four distinct bands which were later separated into six pure compounds designated as A_{1-6}

Band	Solvent	Compound
1	Benzene	A_1
2	Benzene–chloroform (4:1)	A_2
3	Benzene–chloroform (1:1)	A_3, A_6
4	Chloroform through chloroform–methanol (1:1)	A_4, A_5

Compounds A_3 and A_6 were separated by subliming band 3 and recrystallizing the sublimate from acetone–hexane whereupon A_6 separated as yellow cubes. Addition of hexane to the mother liquor gave A_3 as white plates.

C. Purification of A_b.—Chromatography of fraction A_b (13.0 g.) on 400 g. of alumina gave, on elution with benzene–chloroform (1:1), A_4. Further elution with the same solvent and then with chloroform gave a mixture of A_4 and A_5. Further elution with chloroform, chloroform–methanol (9:1) and (1:1) yielded pure A_5.

D. Further Purification and Identification of Compounds A_{1-6}. A_1.—Recrystallization from chloroform–methanol gave fine needles, which after sublimation at 150° (10 μ) and a second recrystallization from the same solvents, melted at 201–206° and remained unchanged on further recrystallization; mixed melting point with **flindersiamine (XXV)** (m.p. 211–212°, reported[18] m.p. 206–207°): 204–209°. Compound A_1 and flindersiamine gave identical color tests with concentrated sulfuric acid: yellow → green → blue. Very slight differences were noted in the infrared spectra of these compounds while the ultraviolet spectra were identical: λ_{max} 212 mμ (ε 15,000), 244 (69,300), 299sh (8,350), 310 (11,400), 320 (11,000), 333sh (7,500); in methanol 0.2 *M* in hydrochloric acid: λ_{max} 218 mμ (ε 21,300), 253 (51,900), 338 (14,900).

As further confirmation the iso compounds were prepared by heating both substances with methyl iodide in sealed tubes at 100° for 3 hours,[18] giving **isoflindersiamine**, m.p. 213–214° (reported[18] m.p. 209–211°), and **iso-A$_1$**, m.p. 212–213°, mixed m.p. 212–213°. The ultraviolet spectra of isoflindersiamine and iso-A$_1$ were identical: λ_{max} 265 mμ (ϵ 40,000), 308 (6,400), 332 (8,200), 346 (8,200); in methanol 0.2 *M* in hydrochloric acid: λ_{max} 256 mμ (ϵ 40,000), 333 (12,000), 343 (12,000).

A$_2$.—Recrystallization from acetone-hexane gave white plates, which after sublimation at 140° (10 μ), melted at 186–187°; mixed melting point with **maculosidine (XXIV)** (m.p. 186.5–187.0°, reported[5] m.p. 184°) 186–187°. The infrared and ultraviolet spectra of A$_2$ and maculosidine were identical; ultraviolet absorption: λ_{max} 211 mμ (ϵ 19,600), 246 (70,400), 284sh (5,200), 294 (7,200), 306 (7,500), 338 (5,700), 351sh (4,900); in methanol 0.2 *M* in hydrochloric acid: λ_{max} 313 mμ (ϵ 23,900) 254 (59,600), 306 (5,800), 317 (7,000), 353 (5,900).

A$_3$.—Recrystallization from acetone-hexane gave white plates melting at 144–145°, mixed melting point with **1-methyl-2-phenyl-4-quinolone (XXVII)** (reported[2] m.p. 143.5–144.5°) 144–145°. The infrared and ultraviolet absorption of A$_3$ and 1-methyl-2-phenyl-4-quinoline were identical.

A$_4$.—Recrystallization from methanol–acetone gave prisms of **isobalfourodine (IV)** which, after sublimation at 180° (5 μ), melted at 204–205°, $[\alpha]_D$ + 15°; ultraviolet absorption: λ_{max} 216 mμ (ϵ 17,500), 242 (46,600), 298 (7,200), 320 (10,400), 330 (8,900); in methanol 0.2 *M* in HCl: λ_{max} 215 mμ (ϵ 28,600), 253 (44,200), 304 (7,400), 326sh (4,200); in hexane: λ_{max} 230 mμ (ϵ 26,800), 240sh (23,700), 290 (5,800), 319 (9,400), 330 (8,200).

Anal. Calcd. for $C_{16}H_{19}O_4N$: C, 66.4; N, 6.6. Found: C, 66.3; H, 6.6.

A$_5$.—Recrystallization from methanol–acetone gave small clumps of crystals which were dissolved in aqueous 0.2 *M* phosphoric acid, and the resulting solution was extracted continuously with ether. The *p*H of the aqueous phase was then adjusted to 7–8 and extracted with chloroform to give material melting at 191–192°, mixed melting point with **balfourodine** (m.p. 188–189°) 189–190°. The ultraviolet and infrared spectra of this sample of A$_5$ were identical with those of balfourodine.

A$_6$.—Recrystallization from benzene gave yellow cubes, m.p. 219–220°, mixed melting point with **evoxanthine (XXVI)** (reported[19] m.p. 217–218°) 220–221°. The infrared and ultraviolet spectra of evoxanthine and A$_6$ were identical; ultraviolet absorption: λ_{max} 212 mμ (ϵ 16,700), 239sh (16,800), 274 (47,200), 322sh (3,700), 385sh (8,050), 399 (8,900); in methanol 0.2 *M* in HCl: λ_{max} 210sh mμ (ϵ 8,100), 238 (23,600), 263 (34,400), 280 (47,300), 343sh (9,200), 358 (15,800), 406sh (6,450).

Isobalfourodine Acetate (XXII). A. From Isobalfourodine.—A solution of isobalfourodine (IV) (400 mg., 1.4 mmoles) in pyridine (5 ml.) and acetic anhydride (1 ml.) was allowed to stand at room temperature for 2 days. The reaction mixture was poured into 100 ml. of water and the *p*H of the resulting solution was adjusted to 8 by addition of solid sodium carbonate. This solution was then extracted with ether (3 × 30 ml.) and the combined ether extracts were extracted with 1 *N* hydrochloric acid (3 × 30 ml.). Neutralization of the combined acidic extracts followed by extraction with ether gave 460 mg. (1.39 mmoles, 99%) of crude isobalfourodine acetate (XXII), the ether-soluble portion of which was chromatographed on 8 g. of alumina. Elution with benzene through chloroform gave 340 mg. of a viscous oil which, on molecular distillation at 150° (30 μ), gave crystalline material which quickly formed a glass on exposure to the air. This property made recrystallization of the apparently low melting substance impossible, and a melting point was not obtained. The ultraviolet spectrum of this material was identical with that of the starting isobalfourodine (IV) while the infrared spectrum showed a new band at 5.8 μ, $[\alpha]_D$ +33°.

Anal. Calcd. for $C_{18}H_{21}O_5N$: C, 65.2; H, 6.4. Found: C, 66.1; H, 6.4.

When 150 mg. of isobalfourodine acetate (XXII) was dissolved in 10 ml. of ether and 1 ml. of 1 *N* ethanolic perchloric acid was added, a thick, white precipitate of **isobalfourodine acetate perchlorate** formed, which after recrystallization from acetone–hexane melted over a range (140–165°) with decomposition in an evacuated capillary.

Anal. Calcd. for $C_{18}H_{22}O_9NCl$: C, 50.1; H, 5.1. Found: C, 49.6; H, 5.6.

B. From Balfourodine.—A solution of balfourodine (I) (400 mg., 1.4 mmoles) in pyridine (1 ml.) and acetic anhydride (5 ml.) was boiled for 3 hours. The cooled reaction mixture was worked up as described in part A to give 50 mg. of neutral material and 390 mg. (1.18 mmole, 84%) of crude isobalfourodine acetate (XXII) which was chromatographed on 15 g. of alumina. Elution with benzene–chloroform (9:1 through 1:1) gave 270 mg. of a viscous oil which on molecular distillation at 170° (30 μ) gave crystalline material with the same properties described for isobalfourodine acetate in part A. The ultraviolet and infrared spectra of these samples of isobalfourodine acetate were identical while the optical rotation for this sample was lower: $[\alpha]_D$ + 19°.

Anal. Calcd. for $C_{18}H_{21}O_5N$: C, 65.2; H, 6.4. Found: C, 64.8; H, 6.3.

Isobalfourodine acetate perchlorate prepared from this sample of acetate, as in part A, gave similarly poor melting point data. As before, the perchlorate melted over a range with decomposition; however, in both cases and when the perchlorates were mixed the major part of the melting and decomposition occurred at about 163°.

Anal. Calcd. for $C_{18}H_{22}O_9NCl$: C, 50.1; H, 5.1. Found: C, 49.7; H, 5.7.

Saponification of Isobalfourodine Acetate (XXII). A.—The acetate (120 mg., 0.36 mmole) obtained from isobalfourodine (IV) as described in part A of the previous section was dissolved in a solution of methanol (5 ml.) and 0.5 *M* aqueous sodium hydroxide (10 ml). and allowed to stand for one day. The solution was then diluted with water to 75 ml. and extracted with chloroform (3 × 25 ml.) to give 100 mg. (0.35 mmole, 97%) of isobalfourodine (IV), m.p. 204–205° alone or mixed with isobalfourodine.

B.—Saponification of the acetate (90 mg., 0.27 mmole) obtained from balfourodine (I) as described in part B of the previous section gave 70 mg. (0.24 mmole, 89%) of isobalfourodine (IV), m.p. 182–183°, mixed with isobalfourodine (m.p. 204–205°) 195–196°. The optical rotation of this sample of isobalfourodine ($[\alpha]_D$ + 8°) showed partial racemization, but the ultraviolet and infrared spectra were identical with those of isobalfourodine.

Isobalfourodine Methosulfate (XXIII). A. From Isobalfourodine (IV).—A solution of isobalfourodine (2 g., 6.9 mmoles) in 35 ml. of methanol containing 2 ml. of dimethyl sulfate was boiled for one hour. The reaction mixture was cooled to 0° and the precipitate of isobalfourodine methosulfate (XXIII) was collected (2.58 g., 6.2 mmoles, 90%). Its ultraviolet spectrum was identical with that of isobalfourodine and it gave the same shift on addition of acid; m.p. 128–129° dec.

Anal. Calcd. for $C_{18}H_{25}O_8NS$: S, 7.7. Found: S, 7.8.

B. From Balfourodine (I).—When balfourodine was treated with dimethyl sulfate as above, isobalfourodine methosulfate was formed, m.p. 129–130° dec., mixed with isobalfourodine methosulfate (m.p. 128–129°) m.p. 128–129° dec. The ultraviolet spectrum of the isobalfourodine methosulfate from balfourodine was identical with that from isobalfourodine.

Anal. Calcd. for $C_{18}H_{25}O_8NS$: S, 7.7. Found: S, 8.1.

Reaction of Isobalfourodine Methosulfate (XXIII) with Base.—Isobalfourodine methosulfate (XXIII) (2.28 g., 5.5 mmoles) was dissolved in a warm solution of 100 ml. of 1 *M* aqueous sodium hydroxide and 20 ml. of methanol. On cooling, 1.16 g. (4.0 mmoles, 73%) of **isobalfourodine (IV)** (m.p. 203–204°) separated as white crystals. Extraction of the remaining aqueous solution gave 0.53 g. of material which was chromatographed on 20 g. of alumina. Elution with benzene-chloroform (4:1) gave (−)-**ψ-balfourodine (V)**, m.p. 144–145°, $[\alpha]_D$ −26°, ultraviolet absorption: λ_{max} 217 mμ (ϵ 24,400), 238 (30,500), 247sh (27,100), 254sh (22,200), 289 (7,500), 299 (8,100), 323 (3,400); in methanol, 0.2 *M* in hydrochloric acid: λ_{max} 216 mμ (ϵ 24,900), 242sh (28,900), 248 (29,700), 290 (6,700), 300 (7,700), 326 (3,200).

Anal. Calcd. for $C_{16}H_{19}O_4N$: C, 66.4; H, 6.6. Found: C, 66.5; H, 6.9.

Reaction of Isobalfourodine (IV) with Alkali.—Isobalfourodine (250 mg., 0.87 mmole) in 20 ml. of 30% aqueous sodium hydroxide and 5 ml. of methanol was boiled in a nitrogen atmosphere for 8 hours. The reaction mixture was

diluted to 100 ml. with water and extracted with ether (3 × 30 ml.) to give 240 mg. of (+)-α-**isobalfourodine (VI)** which, after recrystallization from acetone–hexane and sublimation at 150° (30 μ) melted at 198–201°, $[\alpha]_D$ + 30°; ultraviolet absorption: λ_{max} 217 mμ (ε 27,500), 234 (31,000), 246 (26,200), 252 (26,700), 268 (7,700), 279 (8,000), 289 (8,000), 321 (3,200); in methanol, 0.2 *M* in HCl: λ_{max} 216 mμ (ε 27,200), 234 (30,000), 246 (28,500), 251 (29,000), 267 (7,200), 278 (7,700), 288 (7,700), 320 (3,200); in hexane: λ_{max} 214 mμ (ε 16,200), 237 (37,000), 248 (22,000), 263 (6,250), 274 (6,000), 285 (6,500), 322 (3,250).

Anal. Calcd. for $C_{16}H_{19}O_4N$: C, 66.4; H, 6.6. Found: C, 66.2; H, 6.6.

Reaction of Balfourodine (I) with Alkali.—To a solution of 500 mg. (1.73 mmoles) of balfourodine (I) in 10 ml. of ethanol was added 10 ml. of 30% aqueous sodium hydroxide. After being boiled in a nitrogen atmosphere for 4 hours, the solution was diluted to 100 ml. with water and extracted with chloroform (3 × 30 ml.) to give 500 mg. of material. Chromatography on 15 g. of alumina gave, on elution with benzene and benzene–chloroform (3:1), (+)-ψ-**balfourodine (V)**, which, on recrystallization from acetone–hexane followed by sublimation at 160° (5 μ) and a second recrystallization from the same solvent, melted at 142–143°, mixed with (−)-ψ-balfourodine (m.p. 144–145°) m.p. 165–168°, $[\alpha]_D$ + 52°. The ultraviolet and infrared spectra of (+)- and (−)-ω-balfourodine were identical. Elution with benzene–chloroform (1:1) gave (−)-ψ-**isobalfourodine (VI)**, which after two recrystallizations from acetone–hexane melted at 204–205°, mixed with (+)-ψ-isobalfourodine (m.p. 198–201°) m.p. 190–191°, $[\alpha]_D$ −31°. The ultraviolet and infrared spectra of (+)- and (−)-ψ-isobalfourodine were identical.

BERKELEY, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY]

Alkaloids of Geissospermum vellosii. Further Studies on Geissospermine and the Structures of the Indolic Cleavage Products, Geissoschizine[1] and Apogeissoschizine

BY HENRY RAPOPORT, RICHARD J. WINDGASSEN, JR.,[2] NEIL A. HUGHES AND THOMAS P. ONAK

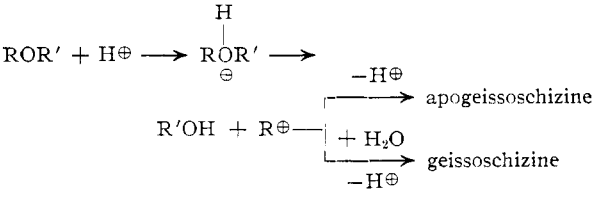
RECEIVED JANUARY 9, 1960

The nature of the ester function in geissospermine is discussed together with supporting evidence for the postulate that the indole and indoline moieties of geissospermine are joined through an ether bridge. The structures of the indolic cleavage products, geissoschizine and apogeissoschizine, have been established by degradative and spectral studies, and by the fact that apogeissoschizine can be converted to geissoschizine. From this evidence a partial structure for geissospermine itself is proposed.

In a previous communication[3] on the alkaloids of *Geissospermum vellosii* we reported that treatment of the main alkaloid, geissospermine, $C_{40}H_{48}N_4O_3$, with hydrochloric acid gives geissoschizoline, $C_{19}H_{26}N_2O$, an indoline alkaloid also present in the bark as such, and two indolic products, geissoschizine, $C_{21}H_{24}N_2O_3$, and apogeissoschizine, $C_{21}H_{22}N_2O_2$. In this paper we report further observations on the functional groups of geissospermine and the determination of the structures of geissoschizine and apogeissoschizine.

Functional Groups of Geissopermine.—The functional groups of geissospermine with which we are concerned at the moment are (1) the linkage between the indolic and indolinic portions of the molecule and (2) the nature of the carbonyl group. Both of these are pertinent to the structure determination of geissoschizine and apogeissoschizine.

The cleavage of geissospermine can be effected by concentrated acid,[3] in which the products are geissoschizine and apogeissoschizine; by 2 *N* acid[4,5] in which the products are geissoschizoline and geissoschizine; and by fuming acid[5] in which apogeissoschizine replaces most of the geissoschizine. Geissoschizine, as ultraviolet absorption spectra clearly suggest (see below), contains two essentially independent chromophores, one indolic and one sensitive to *p*H. In apogeissoschizine these isolated systems apparently have been joined through loss of a molecule of water. The fact that geissoschizine and apogeissoschizine are not interconverted to an appreciable extent under the cleavage conditions used[3] led to the hypothesis that the indole and indoline moieties of geissospermine are joined by a labile ether bridge. When this bridge is cleaved, an intermediate carbonium ion arises which can react by two different pathways to give either geissoschizine or apogeissoschizine.



Here geissospermine is designated ROR′ and geissoschizoline R′OH. In accord with the evidence, the ether postulate suggests that geissoschizine formation is favored in dilute acids were the concentration of "free" water is highest.

Since geissospermine does not form carbonyl derivatives but does contain a methoxyl group, the presence of a methyl ester is indicated. However, the carbonyl band in the infrared at 5.82 μ is sufficiently far removed from that of a normal saturated ester, 5.71–5.76 μ, that conjugation or other effects must be present. On the other hand, the fact that the ultraviolet spectrum of geissospermine is obtained by simple addition of the spectra of an indole and indoline[6,7] essentially rules out any conjugation between the ester function and one of these chromophores. With the further structural evi-

(1) See H. Rapoport, R. J. Windgassen, N. A. Hughes and T. P. Onak, THIS JOURNAL, **81**, 3166 (1959), for a preliminary communication on this subject.

(2) National Science Foundation Postdoctoral Fellow, 1958–1959.

(3) H. Rapoport, T. P. Onak, N. A. Hughes and M. G. Reincke, THIS JOURNAL, **80**, 1601 (1958).

(4) A. Bertho, M. Koll and M. I. Ferosie, *Ber.*, **91**, 2581 (1958).

(5) M. M. Janot, R. Goutarel, A. LeHir and F. Puisieux, *Compt. rend.*, **248**, 108 (1959).

(6) Recently M. Gorman, N. Neuss and G. H. Svoboda [THIS JOURNAL, **81**, 4745 (1959)] claimed to have discovered in leurosine and vincaleukoblastine representatives of a new class of dimeric alkaloids containing both indole and indoline moieties. However, this overlooked the fact that such a combination also exists in geissospermine, as has been pointed out previously (ref. 3, 4, 5, 7).

(7) K. Weisner, W. Rideout and J. A. Manson, *Experientia*, **9**, 369 (1953).