cis-2,4-Dimethylcyclohexanone (V).—This ketone was prepared by the alkaline degradation of cycloheximide according to a known procedure; yield, 44.7%; b.p. 73–74° (20 mm.); ν (film) 1720 cm.$^{-1}$ (C=O); $[\alpha]^{22}D$ +3.4° (*c* 7.0, $CHCl_3$). The reported constants for this compound are b.p. 69.5° (17 mm.), $[\alpha]^{25}D$ + 4.3° (*c* 6, EtOH).

Preparation of the Pyrrolidine Enamine from *cis*-2,4-Dimethylcyclohexanone.—The enamine was prepared from *cis*-2,4-dimethylcyclohexanone and pyrrolidine under the same conditions that were used for the *trans* enamine (II). The product that was isolated in a 62.4% yield was N-(*trans*-2,4-dimethylcyclohex-6-enyl)pyrrolidine (II), b.p. 72–74° (1.4 mm.); ν (film) 1720 (weak, C=O) and 1645 cm.$^{-1}$ (C=C); $[\alpha]^{21}D$ −44.6° (*c* 2.3, benzene).

Anal. Calcd. for $C_{12}H_{21}N$: C, 80.38; H, 11.80; N, 7.81. Found: C, 80.16; H, 11.67; N, 7.58.

Vapor phase chromatography using an 8 ft × 4 mm. column, 200°, helium inlet pressure 15 p.s.i., established that the pyrrolidine enamine from the *cis* ketone (V) and from the *trans* ketone (I) were identical; each enamine exhibited a single peak having 200-sec. retention time with respect to air.

Hydrolysis of the Pyrrolidine Enamine Prepared from *cis*-2,4-Dimethylcyclohexanone.—This enamine was hydrolyzed in a manner similar to that described for II; thus, *trans*-2,4-dimethylcyclohexanone was obtained with $[\alpha]^{22}D$ +40.8° (*c* 1.8, $CHCl_3$). The observed optical rotation corresponds to 68% retention of configuration.

Attempted Isomerization of (+)-*trans*-2,4-Dimethylcyclohexanone (I).—To a solution of 3.11 g. (24.6 mmoles) of I in 30 ml. of chloroform was added 4 ml. of 20% hydrochloric acid, and the mixture was stirred for 45 min. at room temperature. The organic layer was separated, washed with water (20 ml.), and dried over anhydrous magnesium sulfate. After filtration the chloroform was removed *in vacuo* from the filtrate, and the residue on distillation gave 1.54 g. (50.0%) of (+)-*trans*-2,4-dimethylcyclohexanone, b.p. 80° (20 mm.), $[\alpha]^{24}D$ +55.5° (*c* 6.1, $CHCl_3$). Thus, treatment of II with hydrochloric acid gave 92.5% retention of configuration.

Acknowledgment.—The authors wish to express their appreciation to Drs. A. J. Solo and H. Tieckelmann for their helpful discussion and suggestions during the preparation of this paper.

The Furanoquinoline Alkaloids. II.[1] Synthetic Approaches to Demethoxylunacrine

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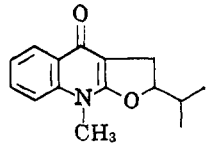
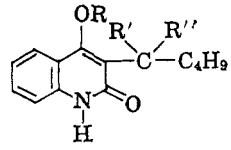
Two new synthetic approaches to the furoquinoline alkaloids have been explored. In the first, 3-isovaleryl-4-hydroxy-2-quinolone is converted to 2-isopropyl-3,4-dioxo-2,3,4,5-tetrahydrofuro[3.2-*c*]quinoline. This compound on reduction, dehydration and hydrogenation gave 2-isopropyl-4-oxo-2,3,4,5-tetrahydro[3,2-*c*]quinoline. In contrast to compounds lacking the 2-isopropyl group, the dihydro furan ring was inert to phosphorous oxychloride. In a second approach 3-isovaleryl-4-methoxy-2-quinolone was reduced to the alcohol and upon reaction with either dimethyl sulfoxide or phosphorus oxychloride–pyridine gave 2-isopropyl-4-methoxy-2,3-dihydrofuro[2,3-*b*]quinoline. This compound with methyl iodide gave the N-methyl derivative, which was converted to demethoxylunacrine upon treatment with lithium bromide–acetonitrile.

Although the general synthesis of furoquinoline alkaloids devised by Grundon and co-workers[3] has been applied to the synthesis of several furoquinoline alkaloids, the scope of this synthesis is limited by the availability of appropriately substituted malonic esters. Since many of these malonic esters are not easily obtainable, and in the Grundon synthesis they are employed in large excess in the first step, we felt it was desirable to devise an alternative general synthesis employing more readily available starting materials. The initial goal of our synthetic efforts was demethoxylunacrine (I), the parent compound of the series of furoquinoline alkaloids containing an isopropyl group in the α-position of the furan ring. Although this compound has not yet been obtained from natural sources, it bears the same relationship to an N-methyl platydesmine[4] as lunacrine does to balfourodine,[5] and it is quite possible that it will ultimately prove to be a naturally occurring substance.



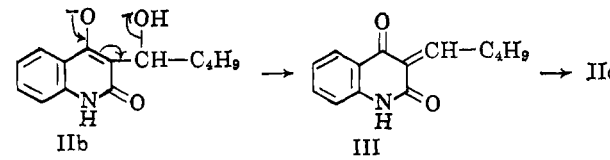
I



IIa, R = H; R′, R″ = O
b, R = H; R′ = H; R″ = OH
c, R, R′, R″ = H
d, R = CH_3; R′, R″ = O
e, R = CH_3; R′ = H; R″ = OH
f, R = CH_3; R′, R″ = H

The starting material chosen for the synthesis of I was 3-isovaleryl-4-hydroxy-2-quinolone[6] (IIa), readily obtainable from the Friedel–Crafts reaction of isovaleryl chloride and 4-hydroxy-2-quinolone.[7]

In an effort to introduce a double bond in the side chain, IIa was reduced with sodium borohydride, but, rather than the expected alcohol IIb, 3-isoamyl-4-hydroxy-2-quinolone (IIc) was obtained. Although the hydrogenolysis of a benzyl alcohol with sodium borohydride appears unprecedented, it seems probable



IIb III IIc

(1) Part I of this series: J. W. Huffman, *J. Org. Chem.*, **26**, 1470 (1961).

(2) Abstracted from the thesis presented by L. E. Browder in partial fulfillment of the requirements for the Ph.D. degree, Jan., 1964.

(3) (a) M. F. Grundon and N. J. McCorkindale, *J. Chem. Soc.*, 2177 (1957); (b) M. F. Grundon and E. A. Clarke, *Chem. Ind.* (London), 559 (1962); (c) J. R. Price ("Fortschritte der Chemie Organischer Naturstoff," Vol. XIII, L. Zechmeister, Ed., Springer, Vienna, 1956, pp. 317–330) has reviewed the earlier synthetic work in this area.

(4) P. J. Scheuer and F. Werny, *Tetrahedron*, **19**, 1293 (1963).

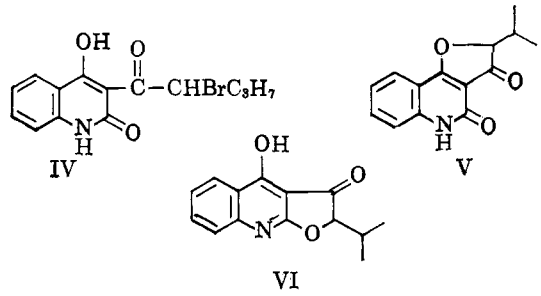
(5) H. Rapoport and K. G. Holden, *J. Am. Chem. Soc.*, **81**, 3738 (1959).

(6) K. Tomita, *J. Pharm. Soc. Japan*, **71**, 1100 (1951); *Chem. Abstr.*, **46**, 5044 (1952).

(7) 3-Acyl hydroxyquinolones are equally readily available *via* the well-known reaction of anilines and acylmalonic esters.

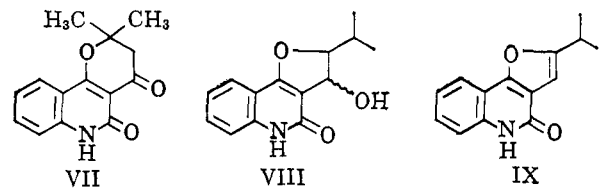
that IIb is initially formed and loses the elements of water to afford III, which is reduced to the fully saturated compound. The reduction of the methyl ether of IIa in a normal fashion (*vide infra*) lends support to the preceding mechanism.

In a second abortive approach to the synthesis of I, the isovalerylhydroxyquinolone, IIa was brominated to afford the unstable bromo ketone IV, the structure of



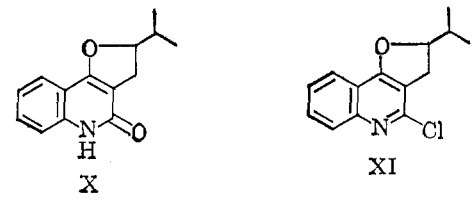
which was confirmed by its reduction to IIa with zinc in acetic acid. In an effort to purify IV, it was subjected to chromatography on alumina, whereby a compound, $C_{14}H_{13}NO_3$, was obtained. In addition to the complex series of infrared bands around 6.1 μ associated with the quinolone carbonyl, there was also a band at 5.81 μ, which is consistent with a conjugated ketone in a five-membered ring. Since this compound also afforded IIa on zinc–acetic acid reduction, it seemed apparent that it was either 2-isopropyl-3,4-dioxo-2,3,4,5-tetrahydrofuro[3,2-*c*]quinoline (V) or the corresponding linear isomer (VI). Since the ultraviolet spectrum of this substance was the same whether run in neutral, acidic, or basic solution it must be V, rather than VI.

The physical constants and spectral data we obtained for V were very similar to those reported by Brown,



et al., for the isomeric ketone VII used in the total synthesis of flindersine.[8] Direct comparison of our compound with a sample of VII prepared by the published method indicated that the compounds were in fact different. Since the structure of VII was known with certainty, based upon its conversion to flindersine, this afforded additional evidence for the structure assigned to our compound.

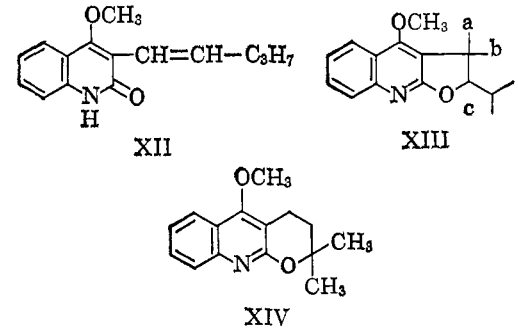
The angular ketoquinolone V appeared to be a promising intermediate for the synthesis of I *via* a modification of Grundon dictamnine synthesis.[3a] Reduction of V with sodium borohydride gave the alcohol VIII, which upon mild acid treatment afforded the furan IX. VIII and IX could also be prepared directly from IV by reduction with borohydride and isolation under basic or acidic conditions, respectively. Catalytic hydrogenation of IX gave the dihydrofuroquinolone X, which afforded the monochloro derivative XI upon treatment with phosphorus oxychloride. This is in direct contrast to the reaction of a compound



similar to X, lacking the isopropyl group, prepared by the earlier workers,[3a] which is converted to a bicyclic trichloro compound under similar conditions. More vigorous treatment of X with phosphorus oxychloride also gave only XI, and this approach to demethoxyunacrine was abandoned.

Although the reduction of 3-isovaleryl-4-hydroxy-2-quinolone with sodium borohydride afforded the 3-isoamyl compound, mechanistic considerations (*vide supra*) indicated that reduction of the methyl ether of IIa (IId) should afford the desired alcohol (IIe), and this was found to be the case.

Attempted dehydration of IIe with dimethyl sulfoxide,[9] or better with phosphorus oxychloride in pyrie dine, afforded a compound which was the result of thloss of 1 mole of water, but which did not show the be. havior expected for the unsaturated quinolone (XII), The compound was weakly basic rather than neutral and was eluted from an alumina column with much less



polar solvents than would be anticipated for XII. In addition, the ultraviolet spectrum was considerably different from that of either IIe or 3-isoamyl-4-methoxy-2-quinolone (IIf), prepared as a model compound. The spectrum was actually very similar to that reported for platydesmine,[4] and changed rather drastically in acid solution (see Experimental). On the basis of the above evidence it was apparent that cyclization had taken place during the attempted dehydration to afford 2-isopropyl-4-methoxy-2,3-dihydrofuro[2,3-*b*]quinoline (XIII) or the isomeric 2,2-dimethylpyranoquinoline (XIV). The decision as to which structure was correct was based on the n.m.r. spectrum.[10] The spectrum showed a six-proton multiplet with peaks at τ 8.92 and 9.05 (J = 6.5 c.p.s.), indicative of the presence of the isopropyl group.[11] There was also a series of peaks, equivalent to two protons between τ 6.1 and 7.1, which show the splitting typical of the AB portion of an ABC spectrum. The third proton of this system is found in a second series of peaks centered at τ 5.15. The above data are consistent only with the furoquinoline struc-

(8) F. F. C. Brown, G. K. Hughes, and E. Ritchie, *Australian J. Chem.*, **9**, 277 (1956).

(9) V. J. Traynelis, W. L. Hergenrother, J. R. Livingston, and J. A. Valicenti, *J. Org. Chem.*, **27**, 2377 (1963).

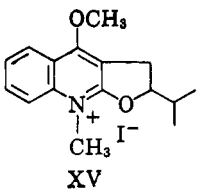
(10) We would like to thank Dr. Oscar Rodig of the University of Virginia for taking this spectrum.

(11) L. M. Jackman, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, pp. 82–98.

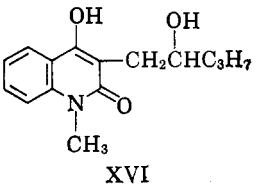
ture (XIII), protons a and b giving rise to the peaks centered at τ 6.6 with proton c appearing downfield at τ 5.15. The isomeric compound (XVI) would be expected to show a six-proton singlet caused by the geminal dimethyls, and the four aliphatic protons would give rise to an A_2B_2 spectrum.

The mechanism of the reaction which gives rise to this cyclodehydration is not immediately obvious. It seems somewhat unusual that the reaction should proceed *via* the least stable of the three possible carbonium ions derived from IIe, and in this respect it is possibly similar to the reported conversion of lunacridine to lunacrine with acid.[12]

Reaction of XIII with methyl iodide afforded the unstable demethoxylunacridinium salt (XV), which was smoothly converted to I with lithium bromide in



XV



XVI

acetonitrile.[13] Compound I showed the behavior expected of a furoquinoline of this type; the ultraviolet spectrum was similar to that of lunacrine[13] and showed the shifts in acid expected for a 4-quinolone.[14] In addition, treatment of I with base afforded 1-methyl-3-(2-hydroxy-3-methylbutyl)-4-hydroxy-2-quinolone (XVI) analogous to a similar conversion observed in the lunacrine series.[13]

The extension of this synthetic approach to other furoquinoline derivatives is being explored.

Experimental[15]

3-Isovaleryl-4-hydroxy-2-quinolone.—To 10.5 g. of 4-hydroxy-2-quinolone in 195 ml. of carbon disulfide was added 10.3 g. (10.4 ml.) of isovaleryl chloride. The mixture was heated under reflux for 30 min., cooled in an ice bath, and treated with 26.8 g. of aluminum chloride with stirring. The mixture was allowed to stand for 3 days, poured over ice–hydrochloric acid, and the carbon disulfide was removed under vacuum. The crude product was collected and recrystallized from acetic acid–water, yielding 16.3 g. (98%) of white crystals, m.p. 196–198°, lit.[6] m.p. 195–198°. A sample recrystallized three times from the same solvent pair and dried carefully had m.p. 203–204°; λ_{max} 234 mμ (log ϵ 4.19) and 300 (3.81); basic: λ_{max} 230 mμ (log ϵ 4.21), 265 (3.73), 310 (3.73).

3-Isoamyl-4-hydroxy-2-quinolone. A.—To 0.8 g. of isoamyl malonic ester and 2.0 ml. of phenyl ether at reflux was added 0.2 g. of aniline. The solution was heated under reflux for 1 hr., cooled, and diluted with hexane. The white crystals were collected, yielding 0.3 g. (60%) of the desired compound, m.p. 153–156°. Recrystallization from acetic acid–water gave needles, m.p. 156–158°.

B.—To 2.0 g. of 3-isovaleryl-4-hydroxy-2-quinolone in 75 ml. of isopropyl alcohol was added 4.0 g. of sodium borohydride. The mixture was heated under reflux for 7 hr., carefully treated with dilute hydrochloric acid to decompose the excess sodium borohydride, diluted with water, and extracted three times with dichloromethane. The organic extracts were evaporated to dryness, and the crude product was recrystallized from methanol–water, yielding 1.7 g. (90%) of the isoamyl quinoline, m.p. and m.m.p. (with material prepared by method A above) 156–158°; λ_{max} 227 mμ (log ϵ 4.44), 276 (3.72), 312 (3.67), 325 sh (3.60); basic: λ_{max} 225 mμ (log ϵ 4.4), 252 (3.86), 305 (3.90).

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72:80; H, 7.53; N, 6.07.

Bromination of 3-Isovaleryl-4-hydroxy-2-quinolone.—To a solution of 0.30 g. of 3-isovaleryl-4-hydroxy-2-quinolone in 7 ml. of glacial acetic acid was added 0.44 g. (1.1 equiv.) of pyridinium bromide perbromide. The solution was heated on a steam bath until the dark red color began to fade (approximately 1 hr.). The solution was poured into water and the yellow crystals were filtered off, yielding 0.32 g. (80%) of crude 3(α-bromoisovaleryl)-4-hydroxy-2-quinolone, m.p. 140–170 dec. Recrystallizations from either ethyl acetate–cyclohexane or methanol–water led to decomposition. Analysis gave 12.84% Br (24.65% Br calculated) after three recrystallizations. The use of 1.1 equiv. of pyridinium bromide perbromide was found to give crude material which was satisfactory for use in succeeding steps.

2-Isopropyl-3,4-dioxo-2,3,4,5-tetrahydrofuro[3,2-*c*]quinoline. A.—The crude bromination product from 8.0 g. of quinolone and 5.0 g. of pyridinium bromide perbromide was chromatographed on alumina. Elution with 10% isopropyl alcohol in chloroform yielded 3.0 g. (60% from 3-isovaleryl-4-hydroxy-2-quinolone) of the coumaranone. Recrystallization from methanol–water gave white needles, m.p. 270° dec.; λ_{max} 235 mμ (log ϵ 4.30), 248 sh (4.21), 287 (3.81), 298 (3.81).

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.20; H, 5.38; N, 5.76; mol. wt., 243. Found: C, 69.20; H, 5.46; N, 5.86; mol. wt., 264.

B.—The crude bromination product from 2.0 g. of 3-isovaleryl-4-hydroxy-2-quinolone and 3.2 g. of pyridinium bromide perbromide was dissolved in 100 ml. of ethanol and 60 ml. of water. The solution was treated with 3.2 g. of silver oxide, heated to reflux, and filtered through Celite. The filtrate was diluted with water and extracted several times with chloroform. The organic extracts were combined and evaporated to dryness. Recrystallization of the crude residue from acetone yielded 0.4 g. (20%) of white needles, m.p. 265° dec., identical with the compound prepared by method A above.

When the ratio, by weight, of silver oxide to bromo compound was increased to 4.5:1, and the reaction mixture was heated at reflux 2.5 hr., a small yield of white crystals, m.p. 265° dec., was obtained. The infrared spectrum and analysis suggests that this compound may be 2-hydroxy-2-isopropyl-3,4-dioxo-2,3,4,5-tetrahydrofuro[3,2-*c*]quinoline.

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 65.26; H,4.81; N, 5.38.

Reduction of the Bromination Product.—To the bromination product from 0.10 g. of 3-isovaleryl-4-hydroxy-2-quinolone in 20 ml. of glacial acetic acid was added 0.4 g. of zinc dust. The mixture was heated on a steam bath for 4 hr., the excess zinc dust was filtered off, and water was added. The white crystals were collected, yielding 0.05 g. of 3-isovaleryl-4-hydroxy-2-quinolone, m.p. 197–200°.

Reduction of the Coumaranone.—To 0.10 g. of 2-isopropyl-3,4-dioxo-2,3,4,5-tetrohydrofuro[3,2-*c*]quinoline in 20 ml. of glacial acetic acid was added 0.4 g. of zinc dust. The mixture was heated on a steam bath for 4 hr., the excess zinc was filtered off, and water was added. The white crystals were collected, yielding 0.07 g. (70%) of material, m.p. 200–201°, identical with 3-isovaleryl-4-hydroxy-2-quinolone.

2-Isopropyl-3-hydroxy-4-oxo-2,3,4,5-tetrahydrofuro[3,2-*c*]quinoline. A.—To 0.70 g. of 2-isoproyl-3,4-dioxo-2,3,4,5-tetrahydrofuro[3,2-*c*]quinoline in 55 ml. of isopropyl alcohol was added 1.40 g. of sodium borohydride. The mixture was heated under reflux for 10 hr., treated with 20 ml. of water and 5 ml. of 10% potassium hydroxide, heated on a steam bath for 1 hr., treated with 10 ml. of 10% potassium hydroxide, cooled, diluted with water, and extracted three times with dichloromethane. The organic extracts were evaporated to dryness, yielding 0.50 g. (71%) of the alcohol, m.p. 233–235° (slight decomposition). Three recrystallizations from methanol–water gave white needles, m.p. 235–236°.

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.54; H, 6.16; N, 5.71. Found: C, 68.45; H, 5.89; N, 5.54.

B.—To 0.50 g. of crude bromination product of 3-isovaleryl-4-hydroxy-2-quinolone in 35 ml. of isopropyl alcohol was added 1.0

(12) J. R. Price, *Australian J. Chem.*, **12**, 458 (1959).

(13) S. Goodwin, J. H. Shoolery, and E. C. Horning, *J. Am. Chem. Soc.*, **81**, 1908 (1959).

(14) H. Rapoport and K. G. Holden, *ibid.*, **82**, 4395 (1960).

(15) Infrared spectra were taken as films or as potassium bromide pellets using a Perkin-Elmer Model 137 infrared spectrophotometer. Ultraviolet spectra were taken in 1-cm. cells on a Perkin-Elmer Model 4000a spectrophotometer. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Melting points were taken on a Hershberg melting point apparatus or a Fisher-Johns melting point block, and are uncorrected.

g. of sodium borohydride. The mixture was heated under reflux for 10 hr., cooled, diluted with 20 ml. of water, treated with 5 ml. of 10% potassium hydroxide, and heated on a steam bath for 1 hr. The solution was then cooled, treated with 10 ml. of 10% potassium hydroxide, diluted with water, and extracted three times with dichloromethane. The organic extracts were evaporated to dryness, yielding 0.13 g. of 2-isopropyl-3-hydroxy-4-oxo-2,3,4,5-tetrahydrofuro[3,2-*c*]quinoline, m.p. and m.m.p. (with the alcohol prepared above) 235–236°.

2-Isopropyl-4-oxo-4,5-dihydrofuro[3,2-*c*]quinoline.—To 20 ml. of 10% hydrochloric acid was added 0.92 g. of 2-isopropyl-3-hydroxy-4-oxo-2,3,4,5-tetrahydrofuro[3,2-*c*]quinoline. The mixture was heated on a steam bath for 30 min. and filtered; the white solid was washed with water, yielding 0.80 g. (94%) of furoquinoline, m.p. 185–190°. Two recrystallizations from methanol–water gave white needles, m.p. 195–196°. Melting and resolidification of the compound (infrared spectrum unchanged) gave a melting point of 214–215°; λ_{max} 230 mμ (log ε 4.56), 238 sh (4.47), 246 sh (4.36), 277 (3.39), 287 (3.97), 318 (4.08), 333 (4.11).

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.98; H, 5.76; N, 6.16. Found: C, 74.16; H, 6.07; N, 6.07.

This furan was also formed in 75% yield from the sodium borohydride reduction of the coumaranone when the excess borohydride was decomposed with dilute hydrochloric acid.

Oxidation of the Alcohol.—Kiliani's reagent was added dropwise to 0.10 g. of 2-isopropyl-3-hydroxy-4-oxo-2,3,4,5-tetrahydrofuro[3,2-*c*]quinoline in 50 ml. of acetone at 0° until a green precipitate was formed and the solution turned brown. After 5 min., a few drops of water were added, and the green material was removed by filtration. After evaporation of the acetone to a small volume, 0.2 ml. of 1 *N* sodium hydroxide was added, the solution was poured into 100 ml. of water, and the aqueous solution was extracted with dichloromethane. The organic layer was evaporated to dryness, leaving an oil which was crystallized from pentane, giving a white solid, m.p. 260° dec., which was identical with the coumaranone.

2-Isopropyl-4-oxo-2,3,4,5-tetrahydrofuro[3,2-*c*]quinoline.—To a solution of 0.13 g. of the furoquinoline in 100 ml. of 95% ethanol was added 0.02 g. of 5% palladium on carbon, and the mixture was shaken under hydrogen at 50 p.s.i. and 54° for 10 hr. The catalyst was filtered off, and the solvent was removed at reduced pressure, leaving a white solid, m.p. 183–185°. Repeated recrystallization from aqueous methanol gave white needles, m.p. 186–187°.

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.60; N, 6.11. Found: C, 73.37; H, 6.77; N, 6.03.

The course of this reduction was exceedingly dependent upon the concentration of the furan and the temperature of the reaction. At temperatures less than 50°, no reduction occurred, and, with concentration of substrate greater than 0.13 g./100 ml., a hexahydro compound, 2-isopropyl-4-oxo-2,3,4,5,6,7,8,9-octahydrofuro[3,2-*c*]quinoline, was obtained; λ_{max} 288 mμ (log ε 3.76).

Anal. Calcd. for $C_{14}H_{10}NO_2$: C, 72.21; H, 8.21; N, 6.00. Found: C, 72.05; H, 7.97; N, 5.92.

2-Isopropyl-4-chloro-2,3-dihydrofuro[3,2-*c*]quinoline.—A solution of 0.50 g. of 2-isopropyl-4-oxo-2,3,4,5-tetrahydrofuro[3,2-*c*]-quinoline in 7.0 ml. of phosphorus oxychloride was heated under reflux for 13 hr. The solution was cooled and poured cautiously into water. The milky aqueous solution was extracted with chloroform and the organic extracts were evaporated to dryness. Crystallization from methanol–water gave 0.43 g. (80%) of the chloroquinoline, m.p. 71–76°. Repeated recrystallization from methanol–water gave white needles, m.p. 79–80°.

Anal. Calcd. for $C_{14}H_{14}ClNO$: C, 67.88; H, 5.70; Cl, 14.31; N, 5.66. Found: C, 67.65; H, 5.60; Cl, 14.26; N, 5.66.

3-Isovaleryl-4-methoxy-2-quinolone.—To a slurry of 5.0 g. of 3-isovaleryl-4-hydroxy-2-quinolone in 50 ml. of anhydrous ether containing a few drops of methanol was added an ethereal solution of diazomethane prepared from 15 g. of N-nitroso-N-methylurea. The resulting solution was allowed to stand at room temperature for 8 hr., evaporated to near dryness, and treated with hexane. The solution was then reduced to a small volume and cooled, giving the desired 4-methoxy compound as white needles, yield 2.3 g. (43%), m.p. 180–184°. Chromatography of the filtrate on alumina with elution by 5% isopropyl alcohol in chloroform gave an additional 0.3 g. The analytical sample was prepared by recrystallization from chloroform–hexane, m.p. 186–187°.

Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.70; H, 6.80; N, 5.34.

3-(1-Hydroxy-3-methylbutyl)-4-methoxy-2-quinolone.—To a solution of 4.3 g. of 3-isovaleryl-4-methoxy-2-quinolone in 400 ml. of isopropyl alcohol was added 8.0 g. of sodium borohydride. The resulting slurry was heated under reflux for 12 hr., allowed to cool, and treated cautiously with dilute hydrochloric acid to decompose the excess borohydride. The solution was diluted with water and extracted three times with dichloromethane. The combined organic extracts were evaporated to dryness, methanol was added, and the desired compound was precipitated with water as white crystals, m.p. 138–142°, yield 3.9 g. (90%). The analytical sample was prepared by recrystallization from methanol–water, m.p. 143–145°.

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.01; H, 7.51; N, 5.21.

Oxidation of 3-(1-Hydroxy-3-methylbutyl)-4-methoxy-2-quinolone.—Kiliani's reagent was added dropwise to a solution of 0.20 g. of the alcohol in 20 ml. of acetone at 0° until a permanent yellow-brown color was obtained. A few drops of water were added and the solution was allowed to stand for 5 min. The green precipitate was removed by filtration, and the filtrate was poured into water. The milky aqueous solution was extracted with chloroform; the organic layer was evaporated to a small volume. Hexane was added, yielding 0.13 g. (66%) of white crystals, m.p. 179–182°, identical with 3-isovaleryl-4-methoxy-2-quinolone.

3-Isoamyl-4-methoxy-2-quinolone.—To a slurry of 1.00 g. of 3-isoamyl-4-hydroxy-2-quinolone in 20 ml. of anhydrous ether containing a few drops of methanol was added an ethereal solution of diazomethane (from 3.0 g. of N-nitroso-N-methylurea). The solution was allowed to stand overnight, the solvent was evaporated to dryness, and the residue was crystallized from methanol–water yielding 0.86 g. (81%) of the methyl ether, m.p. 114–117°. The analytical sample was recrystallized from methanol–water, m.p. 117–119°; λ_{max} 269 mμ (log ε 4.19), 279 (4.15), 321 (3.95), 334 (3.80).

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.67; H, 7.94; N, 5.68.

2-Isopropyl-4-methoxy-2,3-dihydrofuro[2,3-*b*]quinoline. A.—A solution of 1.00 g. of 3-(2-hydroxyisoamyl)-4-methoxy-2-quinolone in 10 ml. of dimethyl sulfoxide was heated at 130–140° for 20 hr. and poured into 150 ml. of water. The resulting suspension was extracted with chloroform and the organic extracts were chromatographed on alumina. Elution with chloroform gave 0.21 g. (22%) of the furoquinoline, m.p. 133–135°. Further elution with 10% isopropyl alcohol in chloroform gave recovered starting material. The analytical sample m.p. 135–136°, was recrystallized from hexane; λ_{max} 251 mμ (log ε 4.21), 272 (4.15), 282 (4.07), 306 (3.69), 320 (3.69); acid: λ_{max} 288 mμ (log ε 4.18), 315 sh (3.81).

Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76; $-OCH_3$, 12.75; mol. wt., 243. Found: C, 74.18; H, 7.13; N, 5.58; OCH_3, 12.70; mol. wt., 236.

B.—To a solution of 1.00 g. of 3-(2-hydroxyisoamyl)-4-methoxy-2-quinolone in 4.0 ml. of dry pyridine was added 1.0 ml. of phosphorus oxychloride. The solution was allowed to stand at room temperature for 15 min. heated on a steam bath for 1 hr., cooled to room temperature, and poured cautiously into water. The crude product was collected, dissolved in benzene, and chromatographed on alumina. Elution with chloroform gave 0.41 g. (44%) of the desired compound, m.p. 133–135°, identical with that prepared by method A.

2-Isopropyl-4-methoxy-2,3-dihydrofuro[2,3-*b*]quinoline Methiodide.—A solution of 0.39 g. of the above furoquinoline in 4 ml. of methyl iodide was heated under reflux for 2 min. and allowed to stand overnight. The pale yellow crystals were collected by filtration giving 0.43 g. of material (66% based on pure methiodide), m.p. 141–144° dec. Attempted recrystallization of this material gave erratic melting point behavior and this property, in conjunction with the changes in infrared spectrum, indicated that decomposition was taking place during attempted purification; λ_{max} 235 mμ (log ε 4.64), 296 (4.08), 317 sh (3.78).

Demethoxyunacrine.—To a solution of 0.30 g. of crude methiodide in 25 ml. of acetonitrile was added 2.4 g. of anhydrous lithium bromide. The solution was heated under reflux for 2 hr., concentrated to a small volume and poured into water. The aqueous slurry was extracted with chloroform and the organic layer was washed with water. Evaporation of the chloroform gave 0.13 g. (69% based on pure methiodide) of white crystals, m.p. 169–172°. Repeated recrystallizations from chloroform–

hexane gave needles, m.p. 177–179°; λ_{max} 235 mμ (log ε 4.40) 249 sh (4.14), 296 sh (3.94), 307 (4.03), 318 (3.98); acid: λ_{max} 233 mμ (log ε 4.72), 239 sh (4.58), 288 (4.13), 300 sh (4.09), 313 sh (3.86).

Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.14; H, 7.04; N, 5.58.

1-Methyl-3-(2-hydroxy-3-methylbutyl)-4-hydroxy-2-quinolone.—A solution of 0.08 g. of demethoxylunacrine in 5 ml. of 10% ethanolic potassium hydroxide was heated under reflux for 11 hr. The ethanol was removed by distillation and water was added simultaneously to keep a volume of no less than 5 ml. After the ethanol had been removed, the solution was diluted and extracted with chloroform. The aqueous layer was saturated with carbon dioxide and extracted three times with chloroform. Evaporation of the organic extracts and crystallization of the residue from methanol–water gave 0.06 g. (70%) of white plates, m.p. 166–168°.

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.16; H, 7.45; N, 5.14.

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Anthocyanins and Related Compounds. III. Oxidation of Substituted Flavylium Salts to 2-Phenylbenzofurans

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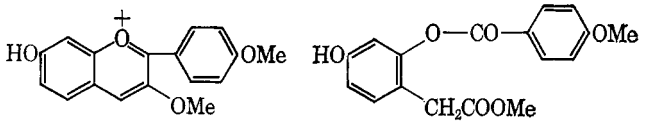
Flavylium salts with an alkyl, alkoxy, or phenoxy grouping in the 3-position are oxidized by hydrogen peroxide in aqueous methanol at pH 5–7 to yield 3-acyl-, 3-carboalkoxy-, and 3-carbophenoxy-2-phenylbenzofuran derivatives, respectively.

Hydrogen peroxide oxidation[1] or ozonolysis[2] of 3-methoxyflavylium salts in acetic acid solutions yields substituted *o*-benzoyloxyphenylacetic acids, *e.g.*, I → II. Structurally similar products were also reported

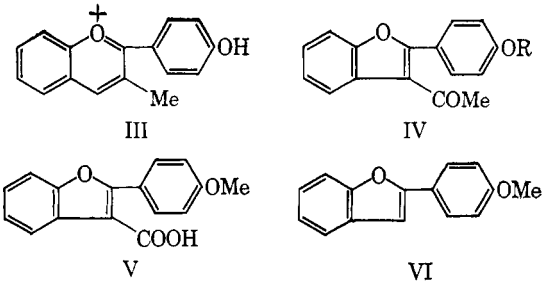


I II

by Karrer and his associates[3,4] to be formed by oxidation of natural anthocyanidin 3-glycosides in aqueous solutions. The constitution of these anthocyanin products, *e.g.*, malvone, however, has not yet been established with certainty.[5] On the basis of these early observations it has been suggested[6] that benzoyl esters of the malvone type may be formed in oxidative decoloration of anthocyanin pigments in plant juices. The rate of anthocyanin destruction, however, is pH dependent[7] and thus it seemed desirable to examine the oxidation of flavylium salts at a pH (5–7) commonly occurring in plant extracts. At these pH values it has now been determined that the major oxidation products of 3-alkyl- and 3-alkoxyflavylium salts are 3-acyl- and 3-carboalkoxy-2-phenylbenzofuran derivatives.

Thus, 3-methyl-4′-hydroxyflavylium chloride (III) rapidly reacts with hydrogen peroxide in aqueous methanol or in methanol buffered to pH 5.8 to give a cream-colored, blue fluorescent (in ultraviolet light) monohydroxy ketone, $C_{16}H_{12}O_3$, in 54% yield. This product is not easily hydrolyzed by alkalies and its λ_{max} in ethanol (314 mμ, log ε 4.15) undergoes a pronounced bathochromic shift of 50 mμ in the presence of sodium ethylate. A benzoyl ester linkage is thus excluded. The constitution of the product as 3-acetyl-2-(4-hydroxyphenyl)benzofuran (IV, R = H) was established by the formation of a benzal derivative and the reaction of its methyl ether (IV, R = Me) with iodine and alkali to give iodoform and, in small quantity, an acid, $C_{16}H_{12}O_4$ (V). Decarboxylation of this acid gave the known 2-(4-methoxyphenyl)benzofuran (VI). VI was also obtained directly from the ketone (IV, R = Me) by prolonged alkaline hydrolysis. The identity of the benzofuran VI was confirmed by direct comparison with an authentic specimen, prepared by alkaline degradation of 2-ethyl-3-anisoylbenzofuran.[8]

Peroxide oxidation of 3-aryloxy- and 3-methoxyflavylium salts similarly gave good yields (about 50%) of the aryl and methyl esters of the corresponding 2-phenylbenzofuran-3-carboxylic acids; *e.g.*, 3-phenoxy 4′-methoxyflavylium chloride and 3,4′-dimethoxyflavylium chloride gave the phenyl and methyl ester of V, respectively. Structures were assigned to these esters on the basis of their alkaline hydrolysis to yield the free acid. Benzofurans have now been



III IV

V VI

obtained from about twenty flavylium salts. Some of these are listed in Tables I and II. In view of the ready availability of flavylium salts this oxidation process offers a very favorable synthetic route to diffi-

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