was determined by tlc on alumina HF 254 with methanol–ethyl acetate (1:20) as solvent. One-half to two-thirds of the pyridine was removed under vacuum and the remaining solution was poured into 900 ml of water at 65–70°. This solution was stirred and cooled as the thione crystallized. The yield was 1.02 g (77%) which melted at 149–150°.

4-Amino-1-(β-D-arabinofuranosyl)-2-quinazolone (XVI).—1-(2′,3′,5′-Tri-O-acetyl-β-D-arabinofuranosyl)-4-thio-2-quinazolone (XV) (0.90 g, 2.05 mmoles) was heated in 125 ml of methanolic ammonia at 100° for 6 hr in a bomb. The reaction was cooled and filtered and the filtrate taken to dryness. Crystallization of the residue from 60 ml of methanol and 10 ml of water concentrated to 13 ml gave 0.38 g (63%) of XV. The product was crystallized from methanol–water. The melting point was 217–219° dec; $[\alpha]^{28}D$ −24° (*c* 1.0, dimethylformamide).

Anal. Calcd for $C_{13}H_{15}N_3O_5 \cdot H_2O$ (mol wt 311.29): C, 50.15; H, 5.50; N, 13.50. Found: C, 50.28; H, 5.43; N, 13.48.

2-Amino-1-(2′,3′-O-isopropylidene-β-D-ribofuranosyl)-4-quinazolone.—O^2,5′-Anhydro-1-(2′,3′-O-isopropylidene-β-D-ribofuranosyl)-4-quinazolone (XI) (660 mg) was treated with 50 ml of liquid ammonia in a sealed bomb at room temperature for 50 hr. After removal of the ammonia the product was crystallized from benzene–methanol and gave colorless needles which melted at 171–172° after sintering at 168°.

Anal. Calcd for $C_{16}H_{19}N_3O_5$ (mol wt 333.34): C, 57.65; H, 5.75; N, 12.61. Found: C, 58.35; H, 5.92; N, 12.33.

2-Amino-4-quinazolone.—All attempts to remove the isopropylidene group from 2-amino-1-(2′,3′-O-isopropylidene-β-D-ribofuranosyl)-4-quinazolone proved futile as the sugar linkage was too labile under the conditions necessary to remove the isopropylidene group. The nucleoside (200 mg) was hydrolyzed by heating on the steam bath in 25 ml of 20% formic acid for 10 min. The resulting 2-amino-4-quinazolone which was isolated was identical with the product described by Trattner, *et al.*[20]

Hydrolysis of 1-(β-D-Arabinofuranosyl)-2,4-quinazolinedione (XIII).—A solution of 5–10 mg of XIII in 2 ml of 10% hydrochloric acid was heated on the steam bath for 1 hr. The cooled solution yielded 2,4-quinazolinedione (I) as a precipitate. The filtrate was chromatogrammed against D-ribose, 2-deoxy-D-ribose, D-arabinose, and D-xylose on Whatman No. 1 paper using the ethyl acetate–*n*-propyl alcohol–water (4:1:2) system described by Hall.[21] A second chromatogram was run using butanol saturated with water as solvent. Both chromatograms were run for 40 hr and gave good separation of the known sugars with the unknown sugar at the same R_f as arabinose. The sugars were detected using the aniline hydrogen phthalate spray of Partridge.[22]

Registry No.—I, 86-96-4; II, 15135-19-0; III, 15135-20-3; IV, 15135-21-4; V, 15180-27-5; VII, 15135-22-5; VIII, 15135-23-6; IX, 15185-75-8; X, 15185-76-7; XI, 15135-24-7; XII, 15135-25-8; XIII, 15135-26-9; XIV, 15185-77-0; XV, 15180-28-6; XVI, 15135-27-0; XVIII, 15135-28-1; XIX, 15135-29-2; XX, 15135-30-5; XXI, 15135-31-6; 3-N-methyl-2,4-quinazolinedione, 607-19-2; 2-amino-1-(2′,3′-O-isopropylidene-β-D-ribofuranosyl)-4-quinazolone, 15135-33-8.

(20) R. B. Trattner, G. B. Elion, G. H. Hitchings, and D. M. Sharefkin, *J. Org. Chem.*, **29**, 2674 (1964).
(21) R. H. Hall, *Anal. Biochem.*, **4**, 395 (1962).
(22) S. M. Partridge, *Nature*, **164**, 443 (1949).

Notes

The Isolation and Structural Elucidation of Voacristine Hydroxyindolenine

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Earlier reports have described the isolation from *Ervatamia dichotoma* (Roxb.) Blatter of coronaridine[4] and heyneanine.[5] We report herewith the isolation and characterization of voacristine hydroxyindolenine and its synthesis from voacristine.

Partition of the ethanol extract of *E. dichotoma* root bark between ether and 4% hydrochloric acid gave a crude alkaloid fraction upon neutralization of the acid and extraction with ether. The ether extract was washed with 1% sodium hydroxide to remove the phenolic bases and the nonphenolic bases were chromatographed on neutral alumina. Elution with benzene–chloroform (1:1) yielded a fraction which was further fractionated by partition chromatography.[6] Six purple bands were visible on the partition column. After elution, the third band yielded heyneanine (I).[5] The fourth band was rechromatographed on a partition column and yielded four bands. Treatment of the third band with benzene–Skellysolve B gave a crystalline material. Recrystallization from the same solvent system yielded colorless crystals, $C_{22}H_{28}N_2O_5$ (by high resolution mass spectrometry), mp 176–179° dec, $[\alpha]^{26}D$ −22° (*c* 0.51, chloroform). The ultraviolet spectrum (λ_{max}^{EtOH} 229.5, 268, 291, 300 (sh), 314; 12,380, 4400, 4780, 4410, 3810) and infrared spectrum suggested an indole-type alkaloid bearing substituents in the aromatic ring. The infrared spectrum showed broad bands at 2.80 (w) and 3.10 μ (m), indicative of the presence of hydroxyl groups, and a band at 5.76 μ (s), indicative of the presence of a carbomethoxy group. The nmr spectrum contained a doublet (1 H) centered at τ 2.66 (J_{ortho} = 8 cps), a doublet of

(1) University of California at Berkeley. This work was supported by Grant No. NsG-101 from the National Aeronautics and Space Administration.
(2) Massachusetts Institute of Technology. Investigations at M. I. T. were supported by grants from the National Institutes of Health, GM-01523 and GM-09352.
(3) University of Wisconsin. The investigation at the University of Wisconsin was supported by Public Health Service Grant No. HE-02952 from the National Heart Institute.
(4) S. M. Kupchan, A. Bright, and E. Macko, *J. Pharm. Sci.*, **52**, 598 (1963).
(5) S. M. Kupchan, J. M. Cassady, and S. A. Telang, *Tetrahedron Lett.*, 1251 (1966).
(6) K. S. Brown, Jr., and S. M. Kupchan, *J. Chromatog.*, **9**, 71 (1962).

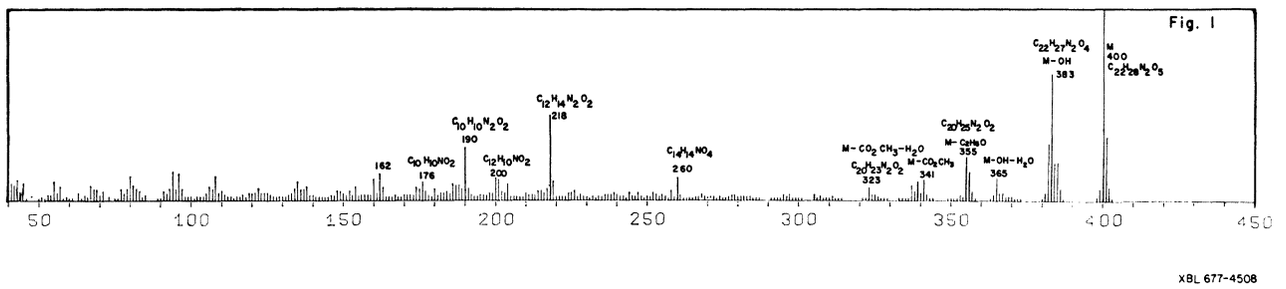
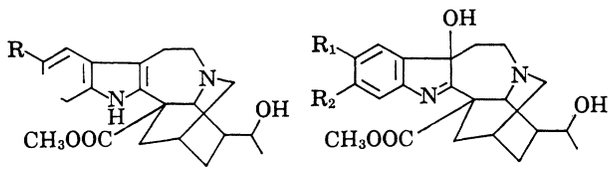


Figure 1.

doublets (1 H) centered at 3.24 (J_{ortho} = 8 cps, J_{meta} = 2.5 cps), and a doublet (1 H) centered at 3.12 (J_{meta} = 2.5 cps). This pattern is consistent with a 1,2,4-trisubstituted benzene ring. In addition, the nmr spectrum showed sharp singlets at τ 6.18 (3 H) and 6.30 (3 H), confirming the presence of a methoxyl and carbomethoxy group, respectively, a doublet (3 H) centered at 8.93 (J = 6.5 cps), and a broad multiplet (1 H) centered at 5.97, indicative of the presence of the $-CHOHCH_3$ group.



I, R = H
III, R = OCH_3

IIa, R_1 = OCH_3; R_2 = H
b, R_1 = H; R_2 = OCH_3

The conventional and high resolution mass spectral data (Figure 1) strongly supported the assignment of a hydroxyindolenine structure of the iboga type to the alkaloid. Peaks at m/e 383 (M − OH), 365 (M − OH − H_2O), 355 (M − C_2H_5O), and 341 (M − $COOCH_3$) confirmed the presence of two hydroxy functions, a hydroxy-substituted C_2 side chain and the carbomethoxy grouping. This pattern, together with the peaks at m/e 260, 218, 190, 176, and 162 (Figure 1), is entirely analogous to that of other hydroxyindolenines[7,8] of the iboga series. Since the position of the methoxy grouping was limited to C_{12} or C_{13} by the characteristic coupling constants observed in the nmr spectrum (see above), the mass spectral pattern established that the alkaloid should be represented by structures IIa or IIb. Structure IIa for the alkaloid was proven unambiguously by its synthesis[9] from voacristine[10-12] (III). Passage of oxygen through an irradiated solution of III in benzene, followed by chromatography on alumina, yielded an amorphous product with spectral properties essentially identical with those of the natural product. Further purification by partition chromatography furnished a product which, upon crystallization from benzene–Skellysolve B, proved identical with the hydroxyindolenine isolated from the alkaloid mixture.[13]

(7) (a) D. W. Thomas, Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, Mass., 1966; (b) D. W. Thomas and K. Biemann, manuscript in preparation. The interesting mass spectral fragmentation of these hydroxyindolenines is discussed in detail in these reports.

(8) D. F. Dickel, C. L. Holden, R. C. Maxfield, L. E. Paszek, and W. I. Taylor, *J. Amer. Chem. Soc.*, **80**, 123 (1958).

(9) For the synthesis of other hydroxyindolenines in this series, see ref 7a and 8, and also, M. F. Bartlett, D. F. Dickel, and W. I. Taylor, *ibid.*, **80**, 126 (1958).

(10) U. Renner and D. A. Prins, *Experientia*, **15**, 456 (1959).

(11) D. Stauffacher and E. Seebeck, *Helv. Chim. Acta*, **41**, 169 (1958).

(12) U. Renner and D. A. Prins, *Experientia*, **17**, 106 (1961).

Experimental Section

Melting points were determined with a Thomas–Hoover Unimelt apparatus, and are corrected. Ir spectra were measured in $CHCl_3$ solution (10%) on a Beckman double-beam recording spectrophotometer, Model IR-5A. Nmr spectra were determined in $CDCl_3$ at 60 Mc on a Varian Associates A-60 recording spectrophotometer using TMS as the internal standard, and were electronically integrated. The uv spectrum was determined in 95% EtOH on a Beckman recording spectrophotometer, Model DK2A. The optical rotation was determined in $CHCl_3$ solution with a Zeiss-Winkel polarimeter and is approximated to the nearest degree. High resolution mass spectra were obtained on a C. E. C. 21-110 instrument, with photoplate recording. Elemental compositions for all ions were determined; low resolution mass spectra were obtained both on a C. E. C. 21-103 and a C. E. C. 21-110 instrument. Skellysolve B refers to petroleum ether distilling at 60–68°. The solvent system used for partition chromatography consisted of ethylene chloride–Skellysolve B–methanol–water (2.5:15:2:0.3), using bromcresol purple as the indicator in the stationary (lower) phase. We are grateful to Smith Kline and French Laboratories for the alcohol extract of *E. dichotoma*.

Extraction and Preliminary Fractionation.—The dried ground root bark (4.6 kg) was extracted with ethanol after preliminary extraction with petroleum ether. The ethanol extract was concentrated and the residue was taken up in dilute HCl. The insoluble material was removed and the filtrate brought to pH 7. The solid that separated was collected and dried (crude alkaloid fraction, 50 g). A portion (18.2 g) of the crude alkaloid fraction was partitioned between ether (125 ml) and four 80-ml portions of 4% HCl. The combined acid solutions were treated with $(NH_4)_2CO_3$ until alkaline and thoroughly extracted with four 200-ml portions of ether. The combined ether solutions were extracted with four 100-ml portions of 4% HCl. The combined acid solutions were again treated with $(NH_4)_2CO_3$ until alkaline and extracted with five 100-ml portions of ether. The combined ether solutions were washed with five 20-ml portions of 1% NaOH to remove the phenolic bases. The ether solution was washed with water, dried over fused K_2CO_3, and concentrated to yield the nonphenolic bases (8.8 g).

Isolation of Alkaloids.—The nonphenolic bases (8.8 g) were treated with benzene–Skellysolve B (4:1) and filtered to remove insoluble material (0.1 g). The filtrate was added to a column of neutral Woelm grade I alumina (210 g). Elution with benzene–Skellysolve B (1:1, 3000 ml) followed by benzene–Skellysolve B (3:1, 3000 ml) yielded a clear syrup (fraction 1, 1.51 g). Elution with benzene (3000 ml) yielded fraction 2 (0.51 g). Elution with benzene–chloroform (1:1, 3000 ml) yielded a solid yellow foam (fraction 3, 5.42 g). Partition chromatography of the third fraction (5.42 g) on a Celite 545 column (495 g) yielded six bands. Treatment of band 3 (1.33 g) with Skellysolve B yielded heyneanine.[5] Rechromatography of band 4 (460 mg) on a Celite 545 partition column (495 g) yielded four bands. Treatment of band 3 (145 mg) with benzene–Skellysolve B yielded a colorless crystalline material. Recrystallization from the same solvent system yielded voacristine hydroxyindolenine (IIa, 53 mg), $C_{22}H_{28}N_2O_5$:

(13) In view of the relatively facile autoxidation of indole alkaloids of the iboga series, the isolation of these products from the plant does not necessarily prove their natural occurrence.

mp 176–179° dec; $[\alpha]^{26}D$ −22° (c 0.51, chloroform); $\lambda_{max}^{CHCl_3}$ 2.80 (w), 3.10 (m), 5.76 (s), 5.90 (m), 6.25 (m), 6.45 (w), 6.78 (s), 6.98 μ (s); λ_{max}^{EtOH} 229.5, 268, 291, 300 (shoulder), 314 mμ (ε 12,380, 4400, 4780, 3810, 4410); nmr, τ 2.66 (one proton, doublet, J_{ortho} = 8 cps), 3.12 (one proton, doublet, J_{meta} = 2.5 cps), 3.24 (one proton, doublet of doublet, J_{ortho} = 8 cps, J_{meta} = 2.5 cps), 5.97 (one proton, broad multiplet), 6.18 (three protons, $-OCH_3$), 6.30 (three protons, $-CO_2CH_3$), and 8.93 (three protons, doublet, J = 6.5 cps); the mass spectrum is given in Figure 1.

Synthesis of Voacristine Hydroxyindolenine from Voacristine.—Voacristine (III, 500 mg) in 5 ml of benzene was illuminated by an ultraviolet lamp ("Blak-Ray", UVL-22, U.V. Products, Inc., San Gabriel, Calif.) while oxygen was slowly bubbled through the solution. Benzene was periodically added to maintain the volume. After 8 hr the product was chromatographed on 50 g of Woelm alumina III. Benzene–chloroform eluted unchanged voacristine, and chloroform eluted a 150 mg fraction containing the hydroxyindolenine together with a small amount of voacristine. Purification by tlc on silica gel H provided 116 mg of amorphous material which gave infrared, mass, and nmr spectra identical with data from the isolated product IIa. A portion of this material (16.4 mg) was subjected to gas–liquid partition chromatography on a Celite 545 column (5 g) which yielded a colorless solid (11.4 mg). Crystallization from benzene–Skellysolve B yielded colorless crystals (6.7 mg), mp 178–179° dec. This material was shown to be identical with the isolated material (mixture tlc, mixture melting point).

Registry No.—IIa, 15215-86-8.

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Syntheses of Rosefuran and Dehydroelsholtzione

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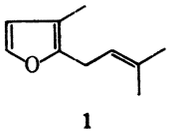
Since ancient times oil of rose has been one of the most valuable materials in perfumery. Its high price made it an obvious target for chemical examination which was begun at the beginning of the last century.[1] The major constituents were already identified by early investigators and used, without delay, for the adulteration of natural oil. The trace constituents to which the essence owes its characteristic and powerful odor were not detected by the inadequate analytical tools then available and are only now being isolated. In the course of a detailed analysis of Bulgarian rose oil (*Rosa damascena* Mill.), E. s. K. isolated a compound to which structure **1** was assigned and which was named rosefuran. To evaluate the importance of this constituent as regards the odor of rose oil, it was decided to produce rosefuran by total synthesis.



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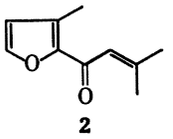
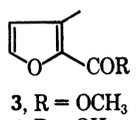


2

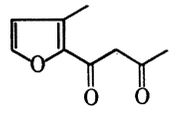
(1) E. Guenther, "The Essential Oils," Vol. 5, D. Van Nostrand Co. Inc., New York, N. Y., 1949, p 1.

Our investigation was commenced with a synthesis of dehydroelsholtzione (**2**)[2,3] (naginata ketone[4]) which we hoped to reduce to rosefuran (**1**). Efforts to prepare this ketone by a previously described procedure[5] involving condensation of 3-methylfuran with β-methylcrotonoyl chloride in the presence of boron trifluoride failed to give more than trace amounts of the desired product.[6] In any event, the exclusive formation of a 2-substituted furan seemed improbable and, after finding that the Vilsmeier reaction with 3-methylfuran did indeed give a mixture of substitution products containing 85% of 3-methyl-2-furfuraldehyde[7] and 15% of 4-methyl-2-furfuraldehyde, we made no further efforts to prepare dehydroelsholtzione (**2**) by this procedure.

Condensation of the readily accessible methyl 3-methyl-2-furoate (**3**)[8] with acetone in the presence of sodium hydride gave the anticipated compound. A nuclear magnetic resonance spectrum in carbon tetrachloride (see Experimental Section) revealed the presence of 88% of either of the two enols **7** or **8** and 12% of the diketone **6**. When subjected to the action of methylmagnesium iodide, the diketone was transformed to a mixture of products containing 85% of the hydroxy ketone **9** and 15% dehydroelsholtzione (**2**). Simple heating in hot benzene was sufficient to transform the remainder of the hydroxy ketone **9** to the unsaturated ketone **2**. The spectral properties of synthetic dehydroelsholtzione **2** were identical with those of natural material.[3]



3, R = OCH_3
4, R = OH
5, R = Cl



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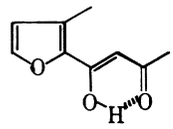

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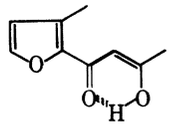

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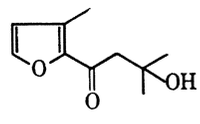

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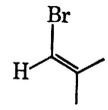

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In a second, but much less satisfactory method, the ketone **2** was prepared by condensing the acid chloride **5** with the Grignard reagent of 1-bromo-2-methyl-1-propene.[9] Numerous attempts to transform synthetic dehydroelsholtzione (**2**) to rosefuran (**1**) by Wolff–Kishner reduction, by hydrogenolysis of the corresponding allylic alcohol and by reduction of the tosylhydrazone with metal hydrides failed.

It was then decided to approach the synthesis by way of 2-lithio-3-methylfuran (**13**). By heating an aqueous solution of the sodium salt of 3-methyl-2-furoic acid (**4**) with mercuric chloride we obtained the

(2) Y. R. Naves and P. Ochsner, *Helv. Chim. Acta.*, **43**, 406 (1960).
(3) Y. R. Naves and P. Ochsner, *ibid.*, **43**, 568 (1960).
(4) Y. Fujita and T. Ueda, *Chem. Ind.* (London), 236 (1960).
(5) P. A. Finan and G. A. Fothergill, *J. Chem. Soc.*, 2262 (1962).
(6) We have not repeated the synthesis of T. Ueda, *Nippon Kagaku Zasshi*, **83**, 341 (1962); *Chem. Abstr.*, **59**, 3857 (1963), because low yields were reported.
(7) T. Reichstein, H. Zschokke, and H. Goerg, *Helv. Chim. Acta*, **14**, 1277 (1931).
(8) D. M. Burness, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 649.
(9) H. Normant in "Advances in Organic Chemistry: Methods and Results," Vol. 2, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, pp 1–65.