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.

Acknowledgments.—H. K. S. thanks Professor A. L. Burlingame (Berkeley) and D. W. T. thanks Professor Biemann (M. I. T.) for the use of their respective laboratory facilities.

Syntheses of Rosefuran and Dehydroelsholtzione

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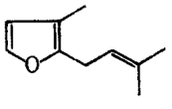
Since ancient times oil of rose has been one of the most valuable materials in perfumery. Its high price made it an obvious target for chemical examination which was begun at the beginning of the last century.[1] The major constituents were already identified by early investigators and used, without 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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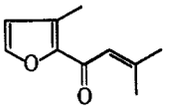
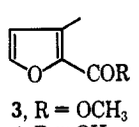


2

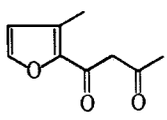
(1) E. Guenther, "The Essential Oils," Vol. 5, D. Van Nostrand Co. Inc., New York, N. Y., 1949, p 1.

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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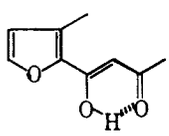

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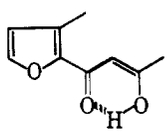

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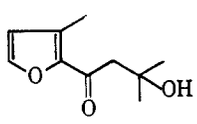

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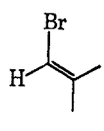

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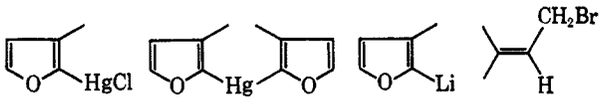
In a second, but much less satisfactory method, the ketone **2** was prepared by condensing the acid chloride **5** with the Grignard reagent of 1-bromo-2-methyl-1-propene.[9] Numerous attempts to transform synthetic dehydroelsholtzione (**2**) to rosefuran (**1**) by Wolff–Kishner reduction, by hydrogenolysis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

chloromercurifuran **11** in 86% yield.[10] Coupling brought about with sodium thiosulfate[10] afforded the corresponding difurylmercury **12** (97%). Treatment with finely dispersed lithium in ether produced 2-lithio-3-methylfuran (**13**)[11] readily converted to rosefuran (**1**) (35%) by condensation with 1-bromo-3-methyl-2-butene (**14**).[12] The infrared and nuclear magnetic resonance spectra of synthetic rosefuran (**1**) were identical with those of the natural product.



11 **12** **13** **14**

Experimental Section

Elemental analyses were performed by Midwest Microlabs, Inc., Indianapolis, Ind., and Dr. S. M. Nagy at the Massachusetts Institute of Technology. Melting points were determined on a hot-stage microscope and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 237 instrument; only selected high-intensity bands are listed. Ultraviolet spectra were obtained on a Cary Model 14 recording spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer. Chemical shifts are given in parts per million downfield from tetramethylsilane as internal standard; coupling constants (J) are given in cycles per second. The abbreviations s, d, t, q, and m indicate singlet, doublet, triplet, quartet, and multiplet, respectively. The nmr data are given by listing the chemical shift, number of protons, multiplicity, and coupling constants. Thin layer chromatography (tlc) was used routinely for monitoring reactions and chromatographic separations.

Vilsmeier Condensation with 3-Methylfuran.—A three-necked flask charged with 8.15 g (110 mmoles) of dimethylformamide was cooled in an ice bath and 8.5 g (55 mmoles) of phosphorus oxychloride was added with stirring over a period of 0.5 hr and the mixture kept at 0° for 20 min. 3-Methylfuran[8] (4.1 g, 50 mmoles) was added at such a rate that the temperature did not rise above 15°. The mixture was kept at 0° for 1 hr and then at room temperature for an additional hr. The solution was poured into 100 ml of water and crushed ice, neutralized with sodium carbonate, extracted with ether twice, washed with water, dried over sodium sulfate, evaporated, and the product distilled. A mixture of aldehydes (3 g), bp 78–80° (15 mm), was obtained in 55% yield. Vapor phase chromatography using a 10% Carbowax 12-ft column at 140° revealed two compounds in a ratio of 17:3 with retention times of 7.3 and 9.2 min. An nmr spectrum (CCl_4) showed the two aldehydes in the same ratio: 3-methyl-2-furfuraldehyde (85%) had signals at 2.33 (3 H s), 6.39 (1 H d, J = 1.8), 7.52 (1 H d, J = 1.8), 9.73 (1 H s); 4-methyl-2-furfuraldehyde (15%) had signals at 2.07 (3 H s), 7.00 (1 H s), 7.42 (1 H s), 9.55 (1 H s).

1,3-Butanedione-1-(3-methyl-2-furyl) (6).—To a stirred mixture of 24 g (1 mole) of sodium hydride (washed from mineral oil) in 100 ml of dry ether was added at room temperature 70 g (0.5 mole) of methyl 3-methyl-2-furoate[8] (**3**) in 100 ml of ether and then, dropwise, 58 g (1 mole) of acetone in 100 ml of ether at such a rate that the temperature remained between 27 and 30°. A slow stream of nitrogen was passed through the apparatus and the mixture was stirred for 1 hr, boiled for 2 hr and then allowed to stand at room temperature overnight. Excess sodium hydride was destroyed by the dropwise addition of 25 ml of ethyl alcohol. The mixture was stirred for 30 min, cooled in an ice bath, and 400 ml of 20% sulfuric acid at 0° was added and the mixture stirred for 30 min. The ether extract was washed six times with aqueous sodium bicarbonate, and six times with 10% sodium hydroxide solution at 0°. The sodium hydroxide extracts, after acidification at 0° with 15% HCl, were extracted with ether twice, washed with aqueous sodium bicarbonate and with water, and dried over sodium sulfate. A yellow oil (49.1 g) was obtained after distillation, bp 88–92° (1 mm), yield 59%. A sample purified through the copper salt, $n^{25}D$ 1.5735, had uv absorption (isooctane) at 311 mμ (ε 19,800); the nmr (CCl_4) spectrum of the enol form had signals at 2.06 (3 H s), 2.38 (3 H s), 6.00 (1 H s), 6.30 (1 H d, J = 1.8), 7.34 (1 H d, J = 1.8), 15.30 (1 H s); the nmr spectrum of the diketone form had signals at 2.18 (3 H s), 2.38 (3 H s), 3.80 (2 H s), 6.30 (1 H d, J = 1.8), 7.34 (1 H d, J = 1.8). Infrared absorptions in CCl_4 were at 1725 (w), 1600 (very broad), 1480, 1400 cm^{-1}.

Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 64.78; H, 5.90.

Butan-1-one-3-methyl-3-hydroxy-1-(3-methyl-2-furyl) (9).—A solution of 47 g (0.283 mole) of 1,3-butanedione-1-(3-methyl-2-furyl) in 200 ml of ether was added dropwise to a stirred, ice-cold solution of methylmagnesium iodide prepared from 14.4 g (0.59 mole) of magnesium and 87.3 g (0.59 mole) of methyl iodide in 250 ml of ether, at such a rate that the temperature remained below 5°. After addition, a slow stream of nitrogen was passed through the apparatus, the temperature maintained at 0° for 2 hr and the mixture was stirred overnight at room temperature. The reaction product was cautiously poured on 500 ml of 20% HCl and crushed ice, extracted with ether twice, washed with aqueous sodium bicarbonate, water, dried over sodium sulfate and evaporated. The residue was distilled giving a main fraction, bp 83–90° (1 mm), 33.5 g, 65% yield. The nmr (CCl_4) spectrum gave signals at 1.23 (6 H s), 2.36 (4 H s), 2.93 (2 H s), 6.35 (1 H d, J = 1.8), 7.38 (1 H d, J = 1.8). Infrared absorptions in CCl_4 were at 3500, 1655, 1640, 1580 cm^{-1}.

Dehydroelsholtzione (2). A.—Butan-1-one-3-methyl-3-hydroxy-1-(3-methyl-2-furyl) (32 g, 0.176 mole) in 120 ml of benzene was refluxed for 2 hr in a flask fitted with a water separator. The solution was cooled, extracted with ether, washed with aqueous sodium bicarbonate, water, dried over sodium sulfate and the solvent removed *in vacuo*. The residue was distilled and the main fraction, bp 70–75° (1 mm), fractionated through a Vigreux column giving 23.9 g (yield 83%) of pure ketone: bp 78° (1 mm); $n^{25}D$ 1.5403; uv (isooctane) 284 mμ (ε 16,200), 291.5 mμ (ε 17,200); nmr (CCl_4), 1.93 (3 H s), 2.21 (3 H s), 2.37 (3 H s), 6.28 (1 H d, J = 1.8), 6.68 (1 H m), 7.28 (1 H d, J = 1.8). The infrared spectrum was identical with that published in ref 3.

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 72.89; H, 7.28.

Synthetic dehydroelsholtzione gave a deep red 2,4-dinitrophenylhydrazone: mp 163° (lit.[3] mp 163–164°); ultraviolet absorption ($CHCl_3$) 407 mμ (ε 27,400) [lit.[3] 406 mμ (ε 27,700)].

B.—A solution of Grignard reagent prepared from magnesium (2.55 g) and 1-bromo-2-methyl-1-propene[9] (13.5 g) in tetrahydrofuran (50 ml) was slowly added to a solution of 3-methyl-2-furoylchloride (13 g) in 50 ml of tetrahydrofuran cooled to −40°. The mixture was maintained at this temperature for 1 hr and was then allowed to remain at 0° overnight. Work-up in the conventional manner gave an oil which was distilled and the fraction with bp 77–85° (1 mm) was chromatographed on silicic acid. Distillation of the appropriate fractions gave dehydroelsholtzione (**2**) 1.85 g (12% yield), bp 78° (1 mm), whose spectral properties were identical with those of material prepared as described under A.

3-Methyl-2-furoic acid (4) was prepared according to Burness,[8] mp 135–136° (lit.[8] mp 134–135°).

3-Methyl-2-chloromercurifuran (11).—To a solution of 3-methyl-2-furoic acid (6 g) and sodium hydroxide (1.9 g) in water (120 ml) was added mercuric chloride (13 g) in water (220 ml). The mixture was allowed to stand with occasional agitation for 4 hr at room temperature. The resulting precipitate was filtered off and the filtrate refluxed until the evolution of carbon dioxide was complete. After cooling, the mercurial was filtered off and added to the former precipitate which was then recrystallized from alcohol to give the required product (13 g, 86%) as colorless needles, mp 143–144°.

Anal. Calcd for C_5H_5OHgCl: C, 18.92; H, 1.59. Found: C, 18.98; H, 1.70.

2,2′-Di-3-methylfurylmercury (12).—3-Methyl-2-chloromercurifuran (6.3 g) was added to a solution of sodium thiosulfate (10 g) in water (40 ml). After stirring for 2 hr at room temperature, the reaction mixture was added to ether (20 ml). The ether layer was washed with water and dried and the solvent removed. The crude product was recrystallized from

(10) Method of H. Gilman and G. F. Wright, *J. Amer. Chem. Soc.*, **55**, 3302 (1933).

(11) We are indebted to Professor G. Whitesides, M. I. T., for useful advice on this reaction.

(12) H. Staudinger, W. Kreis, and W. Schilt, *Helv. Chim. Acta*, **5**, 750 (1922).

acetone–water to give 3.5 g (97%) of pure material. A sample for analysis was chromatographed on aluminum oxide (Woelm, neutral, activity grade II) and eluted with ether to afford colorless crystals: mp 54.5–55°; ir (CCl_4), 1575, 1480, 1460, 1390, 1150, 1060, 890, 730 cm^{-1}; nmr (CCl_4), 2.20 (6 H s), 6.41 (2 H d, J = 2), 7.53 (2 H d, J = 2).

Anal. Calcd for $C_{10}H_{10}O_2Hg$: C, 33.08; H, 2.77. Found: C, 32.83; H, 2.76.

3-Methyl-2-(3-methylbutene-2)furan (Rosefuran) (1).—2,2′-Di(3-methylfuryl)mercury (**12**) (5.50 g) in absolute ether (10 ml) was dropped, during 1 hr, into a suspension (−20°) of lithium sand (0.36 g, >50% excess) in ether (10 ml). After the addition was complete the reaction mixture was stirred at −20° for 1 hr. This mixture was then allowed to warm to room temperature and was then stirred for an additional 30 min. The solution of the organolithium compound was forced by helium pressure through a sintered glass disk into a second reaction vessel kept at −20°. 1-Bromo-3-methylbutene (4.50 g) in absolute ether (6 ml) was added through a dropping funnel in the course of 30 min. After the reaction mixture had reached room temperature it was poured into ice cold 15% ethanolic potassium hydroxide (20 ml). The ether was carefully distilled off, and after the mixture had been allowed to reflux for 1.5 hr the hydrolysis of unreacted bromide was complete. To the cold reaction mixture was added ether (30 ml) and the ether solution was washed with water until neutral and free of ethanol. After the solvent had been removed *in vacuo* the residue was distilled giving 1.64 g (36% yield) of rosefuran (**1**): bp 39–40° (1.0 mm); ir absorptions, 1675, 1625, 1510, 1460, 1380, 1160, 1090, 900, 860, 730 cm^{-1}; nmr ($CDCl_3$), 1.74 (6 H d, J = 1), 1.98 (3 H s), 3.31 (2 H d, J = 7.5), 5.34 (1 H t of heptet, J = 7.5, J' = 1), 6.22 (1 H d, J = 2), 7.28 (1 H d, J = 2), mass spectrum, M^+ 150, intense peak at 135.

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.99; H, 9.45.

Registry No.—**1**, 15186-51-3; **2**, 6138-88-1; **6**, 15135-45-2; **9**, 15135-46-3; **11**, 15136-36-4; **12**, 15136-37-5.

Acknowledgment.—We are indebted to Firmenich et Co., Geneva for generous financial support.

Greenheart Alkaloids. III. Sepeerine (Ocoteamine) and Demerarine[1,2]

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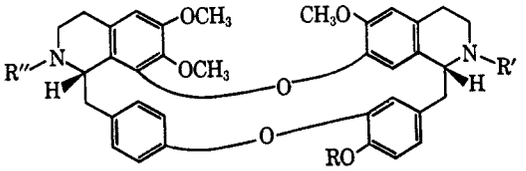
Received April 14, 1967

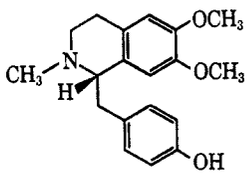
The seven alkaloids which had been isolated from the ether-soluble alkaloids of greenheart bark (*Ocotea rodiaei*) had properties pointing to biscoclaurine structures. Three of these alkaloids, rodiasine, norrodiasine, and dirosine, appeared to have one diphenyl ether linkage[1] and such a structure has recently been determined for rodiasine.[3] The four other alkaloids, ocoteamine, otocamine, demerarine, and ocodemerine, appeared to have two diphenyl ether linkages.[1] The latter alkaloids each had one secondary amino group and ocoteamine and demerarine each had one free phenolic group.

Ocoteamine has an infrared spectrum very similar to that of oxyacanthine (I), a phenolic alkaloid with no secondary amino groups. Methylation with formaldehyde and formic acid gave N-methylocoteamine whose hydrochloride was indistinguishable from that of oxyacanthine (based on infrared spectral comparisons, specific rotations, and distribution coefficients in acetate buffer–chloroform). Ocoteamine is thus a de-N-methyloxyacanthine (II or III).



	R	R′	R″	
I	H	CH_3	CH_3	oxyacanthine
II	H	H	CH_3	ocoteamine, sepeerine
III	H	CH_3	H	
IV	CH_3	H	CH_3	dimethyldaphnoline
V	CH_3	CH_3	H	hydroepistephanine-A

Methylation of the phenolic group of ocoteamine with diazomethane should give O-methylocoteamine of structure IV or V. The hydrochloride of O-methylocoteamine differed from that of authentic hydroepistephanine-A (V)[4] (in specific rotation, distribution coefficient, and R_f in paper chromatography). O-Methylocoteamine, therefore, had to be the same as O,O-dimethyldaphnoline (O,O-dimethyltrilobamine, IV)[5,6] and the specific rotation of the hydrochloride was indeed the same as that reported in the literature. The structure of O-methylocoteamine (IV) was further confirmed by reductive cleavage with sodium in liquid ammonia. This cleavage gave armepavine (VI), which can be obtained from a structure such as IV, but not from V.



VI

Ocoteamine therefore has structure II and is identical with sepeerine, which Grundon and McGarvey isolated from Greenheart.[7] Ocoteamine has a higher melting point (222.5° *vs.* 199°), but the specific rotations are the same and the infrared spectra are practically indistinguishable. The name ocoteamine should therefore be superseded by sepeerine.

Turning now to demerarine, this alkaloid has several properties closely resembling those of ocoteamine. These include the molecular composition, the distribution coefficients in acetate buffer and chloroform, the R_f values in multibuffer chromatography, the infrared spectrum of the phenolic peak,

(1) Part II: P. J. Hearst, *J. Org. Chem.*, **29**, 466 (1964).

(2) Presented in part at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept 1963.

(3) M. F. Grundon and J. E. B. McGarvey, *J. Chem. Soc., Sect. C*, 1082 (1966).

(4) M. Tomita and Y. Watanabe, *Pharm. Bull.* (*Tokyo*), **4**, 124 (1956); and H. Furukawa, *Yakugaku Zasshi*, **86** (3), 253 (1966).

(5) Y. Inubushi, *Pharm. Bull.* (Tokyo), **3**, 384 (1955).

(6) I. R. C. Bick, P. S. Clezy, and M. J. Vernengo, *J. Chem. Soc.*, 4928 (1960).

(7) M. F. Grundon and J. E. B. McGarvey, *ibid.*, 2739 (1960); 2077 (1962).