3-Mercapto-2-(mercaptomethyl)propionic Acid (3).—3-Bromo-2-(bromomethyl)propionic acid (1, 18.0 g, 73.2 mmoles) was dissolved in a cold (0–5°), stirred solution of $NaHCO_3$ (6.15 g, 73.2 mmoles) in water (100 ml). The solution was allowed to warm to 25°, and Na_3SPO_3 (26.4 g, 0.147 mole) was added in portions during 15 min with the temperature maintained at less than 35°. Stirring at 25–30° was continued for 5 hr. (All Na_3SPO_3 dissolved during the first hour.) After the solution had been refrigerated overnight, the apparatus was purged with N_2, concentrated hydrochloric acid (38 ml) was added, and the solution was heated at 90–95° for 10 min while **3** separated as a colorless oil. The stirred mixture, still under N_2, was chilled (ice–water bath) and seeded.[7] Rapid crystallization ensued, and the solid was collected (under N_2) and dried *in vacuo* (NaOH pellets). The filtrate was extracted three times with ether (100-ml portions). Evaporation of the dried ($MgSO_4$) ether solution left a viscous oil (2.8 g), which was combined with the dried solid (8.3 g) filtered from the reaction mixture. The crude material was extracted three times with boiling cyclohexane (250-ml portions), and the combined cyclohexane extract was filtered while hot. The filtrate was concentrated under reduced pressure (water pump, rotary evaporator) to about 100 ml. The concentrated mixture, from which **3** had separated as an oil, was seeded; and the oil crystallized readily. The collected and dried solid, mp 53–60°, amounted to 58% yield (6.49 g) of partially purified **3**. Concentration of the filtrate gave a small additional amount (1.00 g) of lower melting material. The two crops were combined and sublimed *in vacuo* (0.1–0.3 mm, bath temperature 45–50°) in an apparatus in which seed crystals of **3** had been implanted on the collection surface. The crystalline solid removed from the collection surface was stirred briefly with cyclohexane (100 ml), collected under N_2, and dried *in vacuo* to give pure **3**: mp 58–61°,[8] 50% yield (5.58 g); σ^{KBr} (major bands) 2575 (SH), 1705 (CO), 1430, 1355, 1305, 1285, 1240, 1190, 920, 640 cm^{-1}.

Anal.[9] Calcd for $C_4H_8O_2S_2$: C, 31.56; H, 5.30; S, 42.13. Found: C, 31.61; H, 5.36; S, 42.57.

Registry No.—**3**, 7634-96-0.

Acknowledgment.—The authors appreciate the technical assistance of Mr. Carl R. Stringfellow, Jr.

(7) A sample of **3** with mp 57–60°[8] was obtained from a small-scale, trial run. Isolation involved extraction with ether, short-path distillation *in vacuo*, and recrystallization of partially crystallized distillate from cyclohexane.

(8) Reported melting points for **3** are 60–61°[2b] and 57–60°.[3]

(9) Thiol assay by the iodometric method is apparently not applicable to **3**; erratic, high results were obtained.

Identity of Cryptophlamic Acid with Erythrophlamic Acid[1]

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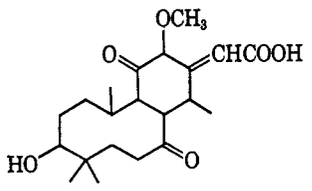
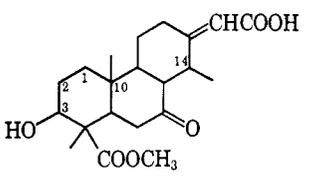
Cryptophlamic acid (I)[2] is the name assigned to an acid derived from a mixture of *Erythrophleum* alkaloids. We believe that cryptophlamic acid is the same as erythrophlamic acid (II)[3–5] and that both the name and the proposed structure I should be dropped from the literature.



I



II

Cryptophlamic acid was obtained[2] from "erythrophleine sulfate,"[6] a commercial mixture of sulfate salts of the total alkaloids from *Erythrophleum guineense*. We have now shown that erythrophlamic acid (II) can be isolated from the same starting material by following a procedure similar to the one used for cryptophlamic acid (I). The physical properties of the erythrophlamic acid isolated from "erythrophleine," the properties recorded in the literature for erythrophlamic acid, and the properties given for cryptophlamic acid[2] correspond closely. The same is true of a series of derivatives. Comparison of the pertinent data (see the Experimental Section) will suggest strongly that cryptophlamic acid is, in fact, erythrophlamic acid.

Two results complicated the identification. In the cryptophlamic series, ozonolysis of methyl cryptophlamate (VII) is described as giving rise to product VIII (mp 165–167°). In the revised erythrophlamic formulation, this material should be the tricyclic diketone IV; yet, it is clearly not the same as the tricyclic diketone (mp 211–212°) of the same structure previously obtained from the ozonolysis of methyl erythrophlamate.[4] In our hands, ozonolysis of methyl erythrophlamate (III) gave tricyclic diketone IV (mp 167–168°), the same as that found in the cryptophlamic series and again different from that expected for the erythrophlamic series. The problem was resolved when the lower melting material turned out to be an epimer of the higher melting form. Exposure to alkali transformed the 167–168° compound (IV) to the 211–212° compound (V). Evidently, compound V described before[4] had isomerized during its isolation. Similar inversions have been encountered in closely related structures.[7]

The action of phosphorus pentachloride on ozonolysis product VIII = IV presented another problem. Structure VIII in the cryptophlamic formulation carried a *gem*-dimethyl grouping next to secondary hydroxyl. Phosphorus pentachloride would be expected to dehydrate and rearrange this system to the isopropylidene system as in IX;[8] ozonolysis would then give compound X. When this recognized two-stage sequence was applied to the cryptophlamic ozonolysis product, anticipated product X, mp 201–203°, was actually obtained.[2] This result was disconcerting, since rationalization of the transformation on the basis of erythrophlamic formulation IV would be difficult. Accordingly, the process was reexamined, with

(1) This work was supported by the National Heart Institute, U. S. Public Health Service, under Grant HE-04141.

(2) B. Tursch and E. Tursch, *Anais Assoc. Brasil. Quim.*, **21**, Numero Espec., 23 (1962); *Chem. Abstr.*, **61**, 691 (1964).

(3) V. P. Arya and B. G. Engel, *Helv. Chim. Acta*, **44**, 1650 (1961).

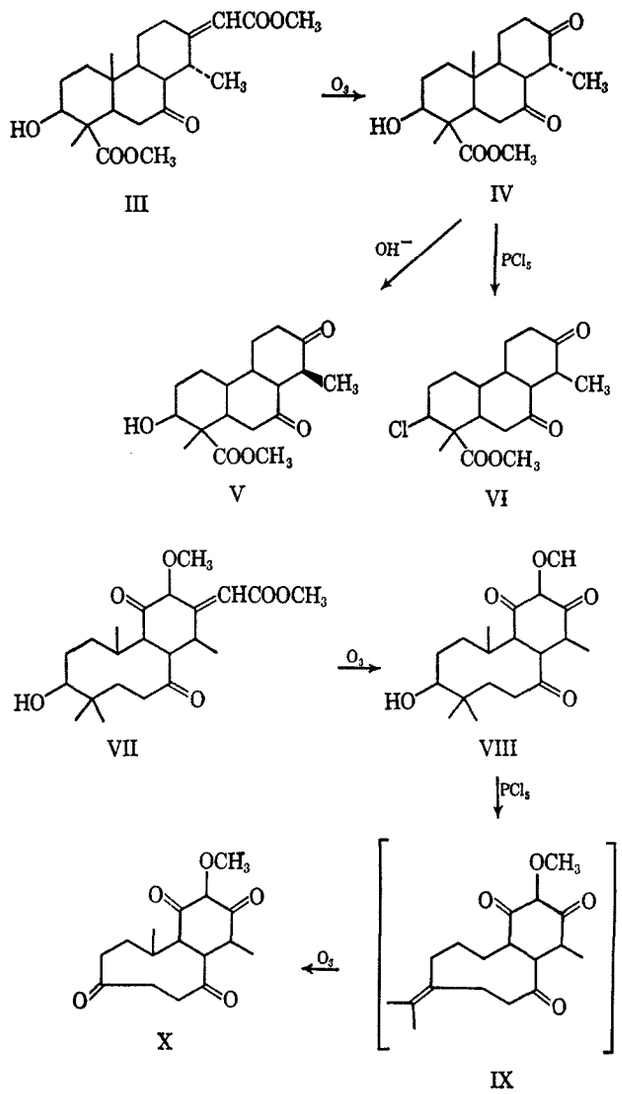
(4) V. P. Arya, *J. Indian Chem. Soc.*, **38**, 829 (1961).

(5) B. G. Engel, R. Tondeur, and L. Ruzicka, *Rec. Trav. Chim.*, **69**, 396 (1950).

(6) B. K. Blount, H. T. Openshaw, and A. R. Todd, *J. Chem. Soc.*, 286 (1940). The starting material used in this earlier work was obtained from E. Merck, Darmstadt.

(7) See R. B. Turner, O. Buchardt, E. Herzog, R. B. Morin, A. Riebel and J. M. Sanders, *J. Am. Chem. Soc.*, **88**, 1766 (1966), and references cited therein.

(8) For examples in the terpene field, see O. Jeger, *Progr. Chem. Org. Nat. Prod.*, **7**, 1 (1950); G. Ourisson, P. Crabbé, and O. Rodig, "Tetracyclic Triterpenes," Holden-Day, Inc., San Francisco, Calif., 1961, p 37. Also *cf.* J. Freid and E. F. Sabo, *J. Am. Chem. Soc.*, **84**, 4356 (1962); N. W. Atwater, *ibid.*, **82**, 2847 (1960).



authentic erythrophlamic tricyclic diketane IV taken as substrate. We found that phosphorus pentachloride effected no retropinacol rearrangement; instead, the hydroxyl group in IV was replaced with chlorine to give derivative VI, mp 204–205°.[9] This compound, obtained *without* ozonolysis, proved to be the same as compound X, obtained *after* ozonolysis. Thus, the ozonolysis step in the earlier work[2] had nothing to do with the formation of the product isolated. The fact that the carbon and hydrogen content for formulation X (C, 65.29; H, 7.53) is close to that for formulation VI (C, 64.28; H, 7.67) undoubtedly contributed to the earlier acceptance of incorrect structure X.

Accordingly, the evidence weighs against cryptophlamic acid as a new compound and points to its identity with erythrophlamic acid. Structure I appears to be no longer supported or required by the facts.

Experimental Section[10]

Methyl Erythrophlamate (III) from "Erythrophleine Sulfate."—Boiling a mixture of the sulfate[6] with 5% aqueous sodium hydroxide for 3–5 hr gave a homogeneous, yellow solution. The organic acids were precipitated with hydrochloric acid, collected, and treated in methanol–ether solvent with diazomethane. The mixed organic acids could also be obtained by hydrolyzing "erythrophleine sulfate" with boiling 2 *N* hydrochloric acid. Methyl erythrophlamate was isolated by a lengthy chromatographic procedure using alumina with several eluting solvents. Infrared spectroscopy as well as thin layer chromatography served conveniently to guide the separation. The fractions rich in methyl erythrophlamate were combined and recrystallized three times from heptane–methylene chloride to give product III, mp 177–178°. The sample for analysis was sublimed *in vacuo* to give material with mp 176–177°.

Anal. Calcd for $C_{22}H_{32}O_6$ (III): C, 67.32; H, 8.22. Found: C, 67.24; H, 8.17.

Our methyl erythrophlamate showed $[\alpha]D$ −41° (*c* 2, chloroform), −66° (*c* 1.7, ethanol), and −1.2° (*c* 0.2, absolute ethanol) with the third value regarded with considerable reservation. Methyl erythrophlamate in deuteriochloroform showed nmr signals at 0.82 (singlet), 1.02 and 1.12 (doublet), and 1.39 (singlet) ppm downfield from tetramethylsilane. As required by structure III, the number of protons in the doublet was half the sum of both singlets. The two peaks at 3.69 and 3.72 ppm are assigned to the two carbomethoxy methyl groups. Whether the signal for the proton at position 3 comes here too was not determined. Methyl erythrophlamate has been described before[4,5] with mp 175–176° or 177–179° and with $[\alpha]^{21}D$ −67° (*c* 0.5, 95% alcohol) and $[\alpha]^{17}D$ −65 ± 2° (*c* 1.2, 95% alcohol). The same pattern of nmr peaks has been observed elsewhere.[11]

The methyl ester of cryptophlamic acid is described[2] as melting at 177–178° and showing $[\alpha]D$ −41.7° (*c* 1.7, methanol[12]). The nmr spectrum shows peaks corresponding to two methyl groups as singlets and to two methyl groups as doublets. We cannot explain these nmr results except to suggest impurities in the sample. The recorded peaks for methyl cryptophlamate at 0.72 and 1.27 ppm[12] might reasonably correspond to the above-mentioned 0.82 and 1.39 peaks.

Erythrophlamic Acid (II).—Methyl erythrophlamate (0.15 g) in 20 ml of methanol plus 20 ml of 2 *N* potassium hydroxide was boiled for 2 hr. The resulting organic acid was isolated and crystallized from aqueous acetone (aqueous alcohol as well as heptane–methylene chloride are also suitable solvents) to give erythrophlamic acid II, mp 223–224° (evacuated capillary) and $[\alpha]D$ −60° (*c* 2.6, alcohol).

Anal. Calcd for $C_{21}H_{30}O_6$: C, 66.64; H, 7.99. Found: C, 66.33; H, 7.79.

Erythrophlamic acid appears in the literature[4,5] with mp 218–220° dec (evacuated capillary) and with $[\alpha]^{20}D$ −62° and −63 ± 2° (*c ca.* 1, 95% alcohol). Cryptophlamic acid is given[2] with mp 221–223° and $[\alpha]D$ −59.2° (*c* 1, methanol[12]).

Acetate of Methyl Erythrophlamate (Acetate of III).—A solution of methyl erythrophlamate (0.19 g) in pyridine (2 ml) that had been freshly distilled from barium oxide was mixed with freshly distilled acetic anhydride (2 ml). After about 1 day at room temperature, 15 ml of water was added. The isolated product, after a single crystallization from aqueous methanol, afforded the acetate of methyl erythrophlamate, mp 160–161°, in 88% yield. Two additional crystallizations gave needles with mp 161–162° and $[\alpha]D$ −62° (*c* 3, ethanol) and −53° (*c* 2, chloroform).

Anal. Calcd for $C_{24}H_{34}O_7$: C, 66.34; H, 7.89. Found: C, 66.28; H, 7.82.

The same derivative has been reported before with mp 173 and 171°, and with $[\alpha]^{22}D$ −59 ± 4° (*c* 0.5, alcohol) and −59° (*c* 1, chloroform).[4,5] The acetate of methyl cryptophlamate is described[2] with mp 158–159° and $[\alpha]D$ +14.3° (*c* 1.4, chloroform[12]). The optical rotation here must be in error.

Diketonic Product from Oxidation of Methyl Erythrophlamate with Chromic Oxide (III, with Carbonyl in Place of Hydroxyl).—This compound appears in the literature[3,4] with mp 130–131° or 133–134° and with $\lambda_{max}^{95\% EtOH}$ 221 mμ (log ε 4.27) and λ_{max} 222 mμ (log ε 4.10). The corresponding cryptophlamic derivative is given with mp 132.5–133.5° and λ_{max} 220 mμ (log ε 4.3).[2]

Methyl Dihydroerythrophlamate (III, with the Ethylenic Bond Saturated).—Hydrogenation of methyl erythrophlamate (III) in absolute alcohol with 10% palladium-on-carbon catalyst

(9) G. G. Allan [*Chem. Ind.* (London), 1497 (1965)] reported a similar process in a structurally related compound.

(10) Melting points are uncorrected. Elementary analyses were performed by Massachusetts Institute of Technology Microchemical Laboratory, Cambridge, Mass., and by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

(11) V. P. Arya, *J. Sci. Ind. Res.* (India), **21B**, 381 (1962); *Chem. Abstr.*, **57**, 15161 (1962).

(12) From unpublished records at Boston University.

afforded methyl dihydroerythrophlamate (79%), mp 183–183.5° and $[\alpha]D$ +43° (*c* 0.9, ethanol). Repeated crystallizations from methylene chloride–heptane brought the melting point to 187–188°. As a mull with mineral oil, the dihydro derivative showed absorption peaks at 3448, 1727, 1712, and 1685 cm^{-1}. The analytical sample was sublimed at 175° (0.01 mm).

Anal. Calcd for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69. Found: C, 66.77; H, 8.96.

Methyl dihydroerythrophlamate has been obtained before with mp 175–176° and $[\alpha]^{22}D$ +55° (*c* 1, chloroform).[3]

Diketone from Methyl Dihydroerythrophlamate (III, with Ethylenic Bond Saturated and with Carbonyl in Place of Hydroxyl).—A mixture of 0.68 g of methyl dihydroerythrophlamate, 0.40 g of chromic anhydride, 11 ml of acetic acid, and 4 ml of water was allowed to stand at room temperature for 1 hr. Adding water precipitated the crude product, which after crystallization from methylene chloride–pentane weighed 0.48 g and showed mp 150–151° and $[\alpha]D$ +19° (1.3% in chloroform). The same compound was described before with mp 148–149° and $[\alpha]^{22}D$ +16° (1.6% in chloroform).[3]

Tricyclic Diketone IV by Ozonolysis of Methyl Erythrophlamate (III).—Oxygen containing ozone was bubbled into a −60° solution of methyl erythrophlamate (0.89 g) in methylene dichloride (30 ml). When the solution became blue, the system was flushed with oxygen and then allowed to come to room temperature. Methanol was added, and the mixture after concentration and dilution with water was boiled for 1 hr. The organic product consisted of crude tricyclic diketone IV, which on several recrystallizations from methylene dichloride–heptane melted at 167–168° and showed $[\alpha]D$ +26° (*c* 2, ethanol). This compound (IV) showed no noteworthy absorption in the ultraviolet (200–400 mμ); it did show infrared absorption peaks at 3491, 1717 sh, and 1701 cm^{-1} (mineral oil mull). The sample for analysis was sublimed at 160° (0.01 mm).

Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.54; H, 8.18.

The corresponding derivative (VIII) in the cryptophlamic series is described,[2] with mp 165–167° and $[\alpha]D$ +2.9° (*c* 1, chloroform[12]), and no absorption in the ultraviolet. A large carbonyl absorption peak appears at 1712 cm^{-1}.

Epimer V of Tricyclic Diketone IV.—A methanol solution of tricyclic diketone IV, mp 167–168° (0.46 g in 30 ml), was treated with 15 ml of 2 *N* potassium hydroxide and boiled for 1.5 hr. Water (150 ml) was added, and the mixture was extracted with chloroform. The chloroform extract was washed with water, dried, and evaporated. After three recrystallizations of the residue from methanol containing a little water, the epimerized diketone V emerged in the form of blades, mp 210–211° and $[\alpha]D$ −1.3° (*c* 2.6, chloroform–ethanol). The infrared absorption curve for the epimerized material mulled with mineral oil was similar to, but not identical with, that of the starting material (IV). Peaks appeared at 3497 and 1706–1681 cm^{-1}. The sample for analysis was sublimed at 195° (0.01 mm).

Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.83, 67.57; H, 8.33, 8.24.

Arya obtained this compound, mp 211–212°, directly from the ozonolysis mixture.[4] His compound was stable to 2 hr of boiling in ethanol containing a catalytic amount of aqueous potassium hydroxide.

Chloro Derivative VI from Tricyclic Diketone IV.—A mixture of 116 mg of tricyclic diketone IV, mp 167.5–168°, and 15 ml of hexane (distilled from sodium) in a carefully dried flask protected from moisture was stirred for 0.5 hr. Phosphorus pentachloride (71 mg) was added portionwise to the mixture, which still contained some undissolved starting material. After 2.5 hr of stirring at room temperature, the mixture was poured into 100 ml of water. The organic phase was removed, and the aqueous layer was extracted with several portions of methylene dichloride. The combined organic phases were rinsed with water, dried, and warmed to remove solvents. The white, crystalline residue, which according to thin layer chromatography consisted of four components including much starting material, was resolved by column chromatography over Merck acid-washed alumina. Material eluted with benzene was crystallized twice from methylene chloride–hexane to give chloro derivative VI, mp 199–200°. The chloro compound showed a very weak absorption maximum at 209 mμ (in ethanol); it showed two peaks in the carbonyl region (1720 and 1710 cm^{-1}) but none in the hydroxyl region. The nmr spectrum taken in deuteriochloroform is consistent with formulation VI. Signals appeared at 0.88 (three-proton singlet for the 10 methyl), 0.98 and 1.08 (three-proton doublet for the 14 methyl), 1.33 (three-proton singlet for the 4 methyl), 2.20 (multiplet), 3.74 (three-proton singlet for the ester methyl, and 4.75 ppm (one-proton triplet for the hydrogen at position 3). Further crystallization of the chloro derivative from ether–methylene chloride raised the melting point to 204–205°.

Anal. Calcd for $C_{19}H_{27}ClO_4$: C, 64.28; H, 7.67; Cl, 10.00. Found: C, 64.66; H, 8.03; Cl, 10.28.

The corresponding tetraketone (VIII) according to the cryptophlamic formulation is described with mp 201–203° and with no absorption in the ultraviolet.[2] A sample of the cryptophlamic compound X (= VI) obtained by using phosphorus pentachloride followed by ozonolysis was available for direct comparison. A mixture of the cryptophlamic derivative (mp 199–201°) with the above chloro derivative (mp 204–205°) melted at 201.5–203°. The infrared absorption spectra of the two materials as mineral oil mulls were superposable. Thin layer chromatographic comparisons were performed using silica gel as adsorbent and cyclohexane–ethyl acetate (3:2, v/v) as developing solvent. The R_f values for the two materials were the same.

Registry No.—I, 5989-63-9; erythrophlamic acid, 510-99-6; III, 7703-50-6; III acetate, 7695-41-2; III (carbonyl in place of hydroxyl), 7695-42-3; III (ethylenic bond saturated), 7695-43-4; III (ethylenic bond saturated, carbonyl in place of hydroxy), 7703-51-7; IV, 7695-44-5; V, 7695-44-5; VI, 7695-45-6.

Diazomethane–Fluoroboric Acid Treatment of Some Corticoids

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This laboratory has reported[1] on the synthesis of triamcinolone 16-methyl ether 21-acetate (**1a**) *via* diazomethane–fluoroboric acid treatment[2] of the 21-acetate **1b**. As by-products in this preparation there was obtained an unknown compound isomeric to **1a**, designated as "compound II." Furthermore, it was implied that carbonate treatment of this unknown isomer also gave a new compound ("compound V") which contained, surprisingly, two methyl ether groupings. Subsequent analysis has shown that compound II possesses the structure 16α-acetoxy-9α-fluoro-11β,-17α-dihydroxy-21-methoxypregna-1,4-diene-3,20-dione (**1e**), and compound V possesses the structure 9α-fluoro-11β,17α-dihydroxy-16α,21-dimethoxypregna-1,4-diene-3,20-dione (**1g**). The explanation of these findings resides simply in the unexpected observation that the starting material, triamcinoline 21-acetate (**1b**), was impure, and was contaminated with triamcinoline 16-acetate (**1c**) and triamcinolone itself (**1d**). Repetition of the diazomethane–fluoroboric acid treatment on *rigorously* purified **1b** [partition chromatography on Celite[3] with a cyclohexane–dioxane–water (65:35:8) system] gave only the 16-methyl ether (**1a**).

(1) M. Heller, S. M. Stolar, and S. Bernstein, *J. Org. Chem.*, **27**, 328 (1962).

(2) M. Neeman, M. C. Caserio, J. D. Roberts, and W. S. Johnson, *Tetrahedron*, **6**, 36 (1959).

(3) Celite is Johns-Manville's registered trademark for diatomaceous earth.