Skellysolve A and the extract was freed of solvent to give 155.4 g. (34%) of green semisolid, which was refluxed with 5% ethanolic potassium hydroxide to obtain 135 g. of mixed acids as a green semisolid and 35 g. of yellow, waxy, unsaponifiable fraction. A solution of the acids in 1350 ml. of acetone was kept overnight at −45°, the separated white solid filtered and discarded, and the filtrate evaporated to dryness, leaving 63 g. of greenish yellow liquid. This was refluxed for 3 hr. with 200 ml. of methanol saturated with hydrogen chloride, freed of solvent, and the residue was dissolved in ether, washed successively with 10% sodium carbonate and water, and dried over sodium sulfate. Removal of solvent and distillation of the residual oil (63.4 g.) gave the following 3 fractions: (1) 33.2 g. of pale yellow oil, b.p. 153–170° (0.3 mm.); (2) 9.8 g. of pale yellow oil, b.p. 170–180° (0.3 mm.); (3) 3.0 g. of yellow oil, b.p. 180–185° (0.3 mm.). Fractions 2 and 3 were each dissolved separately in a solution of 10 g. of potassium hydroxide, 3 ml. of water, and 100 ml. of 95% ethanol, and the mixtures were refluxed for 2 hr., diluted with several volumes of water, extracted once with ether, acidified to congo red with 5% hydrochloric acid, and extracted with several portions of ether. The ether solutions were washed with water, dried, and freed of solvent, yielding 7.8 g. and 3.0 g. of viscous orange oil from fractions 2 and 3, respectively. These oils (7.2 g. and 2.4 g.) were chromatographed in 1-g. batches on 80 g. of silicic acid (Merck) prewashed with 150 ml. of 70% ethyl acetate in isooctane and 200 ml. of isooctane. The columns were each eluted with 400 ml. of 10% ethyl acetate in isooctane followed by 400 ml. of 25% ethyl acetate in isooctane. Removal of solvent from the latter eluates gave the product as 4.3 g. of pale yellow oil ($n^{25.5}$D 1.4708), and crystals from fraction 2, and 1.5 g. of identical material from fraction 3.

Anal. Calcd. for $C_{18}H_{34}O_3$: C, 72.43; H, 11.48. Found: C, 71.34; H, 10.98.

***cis*-12-Octadecene-1,9-diol.**—To a stirred solution of 2 g. of lithium aluminum hydride in 75 ml. of anhydrous ether was added slowly, with cooling, a solution of 5.1 g. of 9-hydroxy-*cis*-12-octadecenoic acid in 60 ml. of anhydrous ether. After addition was complete (0.75 hr.), the mixture was treated carefully with 50 ml. of water followed by 75 ml. of 10% sulfuric acid. The separated ether layer was washed with water, dried over sodium sulfate, and freed of solvent, leaving 4.8 g. (100%) of the diol as a gas chromatographically pure pale yellow oil, n^{25}D 1.4718, that solidified after standing for 1 month at room temperature. A small amount was crystallized from pentane–acetone (1:1) and washed with hexane, m.p. 53–54°.

Anal. Calcd. for $C_{18}H_{36}O_2$: C, 75.99; H, 12.76. Found: C, 76.38; H, 12.78.

1,9-Diacetoxy-*cis*-12-octadecene.—To a solution of 4.7 g. of the diol and 4 ml. of dry pyridine in 25 ml. of anhydrous benzene was added dropwise (12 drops/min.), with stirring and ice cooling, a solution of 4 g. of acetyl chloride in 15 ml. of benzene. The mixture was refluxed on a steam bath for 2 hr., cooled, washed successively with dilute hydrochloric acid, dilute potassium hydroxide, and water, and dried over sodium sulfate. Removal of the solvent left 5.76 g. (95%) of yellow, mobile liquid; a portion (5.04 g.) of this was distilled to give the gas chromatographically pure diester (4.1 g.) as a pale yellow, mobile liquid, b.p. 176–177° (0.1 mm.), n^{25}D 1.4520.

Anal. Calcd. for $C_{22}H_{40}O_4$: C, 71.69; H, 10.94. Found: C, 71.38; H, 11.18.

An additional 1.15 g. of 95% pure diester was obtained by combining the undistilled portion with the distillation residue and chromatographing the mixture on 80 g. of prewashed silicic acid. The column was eluted with 400 ml. of isooctane followed by 400 ml. of 5% ethyl acetate in isooctane. Removal of solvent from the latter eluate left the diester.

9-Acetoxy-*cis*-12-octadecen-1-ol (II).—A solution of 5.0 g. of the previously mentioned diester, 1 g. of potassium hydroxide, 2 ml. of water, and 20 ml. of 95% ethanol was refluxed on the steam bath for 1.5 hr., then diluted with several volumes of water and extracted with ether. The ether solution was washed with water, dried, and evaporated to dryness; the residue (4.1 g., 93%) distilled as a colorless oil, b.p. 184° (0.4 mm.), n^{25}D 1.4621, that was shown by gas chromatography to consist of 80% II and 20% 1,9-diol.

Anal. Calcd. for $C_{20}H_{38}O_3$: C, 73.56; H, 11.74. Found: C, 73.10; H, 11.84.

Ricinelaidyl Alcohol.—To 50 g. of ricinoleyl alcohol, maintained at 60°, was added with rapid stirring 3.4 ml. of 2 *M* sodium nitrite solution and 2.2 ml. of 40% nitric acid. Heating and stirring was continued for 3 hr., after which the reaction mixture was poured into 500 ml. of water contained in a separatory funnel. The ricinelaidyl alcohol was extracted with ether, which was washed free of acid with water, and dried over sodium sulfate. Removal of the solvent left 50 g. of a yellow oil that solidified completely at room temperature. It was dissolved in 10 volumes of pentane–acetone (1:1), allowed to crystallize overnight at −5°, and the colorless solid (25.5 g.) was recrystallized from hexane, m.p. 51.5° (lit.[3] m.p. 53.0–53.4°).

Anal. Calcd. for $C_{18}H_{36}O_2$: C, 75.99; H, 12.76. Found: C, 76.77; H, 12.79.

1,12-Diacetoxy-*trans*-9-octadecene.—This was prepared in 92% yield from 47.3 g. of ricinelaidyl alcohol and 30 g. of acetyl chloride by the procedure already given. A colorless, mobile liquid, b.p. 181° (0.4 mm.), n^{26}D 1.4497, was obtained (lit.[3] b.p. 166–167° at 0.085 mm.).

Anal. Calcd. for $C_{22}H_{40}O_4$: C, 71.69; H, 10.94. Found: C, 72.00; H, 11.09.

12-Acetoxy-*trans*-9-octadecen-1-ol (*trans*-Gyplure).—The product obtained in 92% yield by selective saponification of the diacetoxy compound was distilled to give a colorless, somewhat viscous liquid, b.p. 167–168° (0.1 mm.), n^{26}D 1.4579. A portion (703 mg.) of this liquid was chromatographed on 80 g. of silicic acid (prewashed as previously described), and eluted with 400 ml. of 5% ethyl acetate in isooctane followed by 400 ml. of 10% ethyl acetate in isooctane. The latter eluate yielded 486 mg. (69% of the distilled product) of gas chromatographically pure product.

Anal. Calcd. for $C_{20}H_{38}O_3$: C, 73.56; H, 11.74. Found: C, 74.21; H, 11.14.

Basically Substituted Derivatives of 4-Hydroxy-2,3,6-trimethoxy-5H-benzocyclohepten-5-one

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Received December 6, 1963

Since the proposal of the tropolone ring system by Dewar in 1945,[1] a great number of compounds containing the tropolone and tropone structures were prepared and some of these compounds were tested for their chemotherapeutic activity. We prepared several substituted benzotropones (Table I) for evaluation of their pharmacodynamic properties. The starting material for the synthesis of these compounds, 4-hydroxy-2,3,6-trimethoxy-5H-benzocyclohepten-5-one[2] (A, formula in Table I where R = H and R′ = OCH_3), was obtained by oxidation of pyrogallol to the substituted benzotropolone, purpurogallin,[3] followed by treatment of the latter with dimethyl sulfate. Compounds **1–3** of Table I were obtained by the addition of A to an equivalent of sodium isopropoxide in isopropyl alcohol followed by the appropriate basically substituted alkyl chloride. Compounds **4–8** were prepared by heating A with an excess of the appropriate alkylenediamine in toluene or xylene for about 24 hr. The products were isolated and purified in the form of oxalic acid salts.

(1) For review articles on the subject see T. Nozoe in "Nonbenzenoid Aromatic Compounds," D. Ginsburg, Ed., Interscience Publishers, Inc., New York, N. Y., 1959, p. 339, and P. L. Pauson, *Chem. Rev.*, **55**, 9 (1955).

(2) J. A. Barltrop and J. S. Nicholson, *J. Chem. Soc.*, 116 (1948).

(3) T. W. Evans and W. M. Dehn, *J. Am. Chem. Soc.*, **52**, 3647 (1930).

The compounds of Table I were tested for effects on the cardiovascular and central nervous systems of laboratory animals. Following the intravenous administration of a 2 mg./kg. dose of these compounds to dogs anesthetized with urethane (2 g./kg.), **1** produced a 35% decrease of the mean arterial blood pressure lasting more than 70 min., **2** caused a 24% decrease of pressure for more than 30 min., and **3–8** produced no significant decrease at this concentration. Compounds **1–3** (50 mg./kg., i.p.) showed no apparent effect on the central nervous system of the rat, whereas **4–8** caused tremors at the following doses: **4**, 100 mg./kg.; **5** and **7**, 10 mg./kg.; **6** and **8**, 50 mg./kg. No tremors were observed when 25 or 50 mg./kg. of oxalic acid was administered to the rat. In one test, an attempt to reverse the tremors caused by **7** with benzotropine was not successful, indicating that the tremors caused by this class of compounds differ from those produced by 1,4-dipyrrolidino-2-butyne.[4]

Experimental[5]

4-(2-Diethylaminoethoxy)-2,3,6-trimethoxy-5H-benzocyclohepten-5-one Hydrogen Oxalate (2).—A warm solution of 6.9 g. (0.3 g.-atom) of sodium in 700 ml. of isopropyl alcohol was treated with a suspension of 78.5 g. (0.3 mole) of 4-hydroxy-2,3,6-trimethoxy-5H-benzocyclohepten-5-one[2] in 1 l. of hot isopropyl alcohol. This mixture was heated to reflux temperature, cooled to room temperature, treated with 52.0 g. (0.38 mole) of 2-diethylaminoethyl chloride, and then refluxed for 3 hr. The solvent was removed under reduced pressure and the cooled residue was treated with 300 ml. of water and 300 ml. of ether. Filtration of the resulting emulsion gave 14.0 g. of unreacted 4-hydroxy-2,3,6-trimethoxy-5H-benzocyclohepten-5-one. The filtrate was extracted 3 times with 500 ml. of ether and the combined ether phase dried over magnesium sulfate. The mixture was treated with Darco, filtered, and the filtrate treated with a solution of 22 g. (0.24 mole) of oxalic acid in ether to give a semicrystalline salt. The mother liquor was decanted and the product was triturated with 50 ml. of acetonitrile to give 79.5 g. of yellow product, m.p. 131–135°. This material was dissolved in 150 ml. of hot acetonitrile, treated with Darco, and filtered to give 63.5 g. (59% based on unrecovered starting material) of pale yellow product, m.p. 141–143°; λ_{max}^{Nujol} 6.0 μ (C=O).

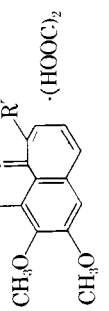
6-(2-Dimethylaminopropylamino)-4-hydroxy-2,3-dimethoxy-5H-benzocyclohepten-5-one Hydrogen Oxalate (7).—A mixture of 50.0 g. (0.19 mole) of 4-hydroxy-2,3,6-trimethoxy-5H-benzocyclohepten-5-one,[2] 350 ml. of 3-diethylaminopropylamine, and 250 ml. of toluene was refluxed for 23 hr. The resulting solution was concentrated under reduced pressure, the residue was dissolved in 200 ml. of xylene, and concentrated under reduced pressure to remove residual 3-diethylaminopropylamine. The residue was dissolved in 1.5 l. of ether; the resulting dark solution was extracted with 400 ml. of water (in 5 portions) and the ether phase was dried over magnesium sulfate, treated with Darco, and filtered. To the filtrate was added an ethereal solution of 25.0 g. of oxalic acid to give an orange-black gum. The latter was triturated with 270 ml. of warm ethanol to give 55 g. of a yellow-brown solid, m.p. 141–146°. Crystallization from 200 ml. of methanol gave 27 g. of yellow-orange solid, m.p. 161–163°. Recrystallization of part of this material (18.5 g.) from 60 ml. of dimethylformamide gave 16 g. (27%) of yellow-orange product, m.p. 161–163°; λ_{max}^{Nujol} 2.95 μ (NH). Carbonyl absorption at 6 μ of this material and A are absent due to hydrogen bonding.

Acknowledgment.—The author is indebted to Dr. Joseph J. Piala and Mr. Jack High for the pharmacological data and to Mr. Joseph Alicino and his associates for the analyses reported herein.

(4) J. Krapcho, A. Szabo, and J. Williams, *J. Med. Chem.*, **6**, 214 (1963).

(5) Melting points were taken in a Thomas-Hoover capillary melting point apparatus and are corrected.

TABLE I



Compd.	R	R′	M.p., °C.[a]	% yield	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Methoxyl, % Calcd.	Methoxyl, % Found
1	$(CH_2)_2N(CH_3)_2$	OCH_3	178–180	17	$C_{20}H_{25}NO_9$	56.73	56.54	5.95	6.06	3.31	3.15	21.99	22.26
2	$(CH_2)_2N(C_2H_5)_2$	OCH_3	141–143	59	$C_{22}H_{29}NO_9$	58.53	58.77	6.47	6.42	3.10	3.22	20.62	20.31
3	$(CH_2)_3N(CH_3)_2$	OCH_3	149–151	47	$C_{21}H_{27}NO_9$	57.66	57.56	6.22	6.43	3.20	3.39	21.28	21.03
4	H	$NH(CH_2)_2N(CH_3)_2$	207–208	46	$C_{19}H_{24}N_2O_8$	55.87	55.83	5.92	6.04	6.86	6.61	15.20	15.03
5	H	$NH(CH_2)_2N(C_2H_5)_2$	190–192	29	$C_{21}H_{28}N_2O_8$	57.79	57.72	6.47	6.52	6.42	6.51	14.22	14.04
6	H	$NH(CH_2)_3N(CH_3)_2$	174–176	24	$C_{20}H_{26}N_2O_8$	56.86	56.75	6.20	6.53	6.63	6.66	14.64	14.23
7	H	$NH(CH_2)_3N(C_2H_5)_2$	161–163	27	$C_{22}H_{30}N_2O_8$	58.65	58.98	6.71	6.88	6.22	6.55	13.78	13.56
8	H	$NH(CH_2)_3NHCH(CH_3)_2$	231–233	17	$C_{19}H_{27}N_2O_6$[b]	61.36	61.45	6.95	6.83	7.16	7.28	15.86	15.76

[a] Crystallization solvents: **1–3**, acetonitrile; **4–8**, dimethylformamide. Color of these compounds: **1–3**, pale yellow; **4–8**, yellow-orange. [b] This salt contains 0.5 mole of oxalic acid.