

Experimental

Peracetic Acid Oxidations.—To 0.1 mole of compound to be oxidized dissolved in 100 cc. of acetonitrile was added with cooling an equal volume of acetonitrile solution of peracetic acid (prepared from either 40 or 70% peracetic acid). Cooling was continued for approximately thirty minutes after which the reaction mixture was allowed to stand at 25° for twenty-four hours. The mixture was concentrated under reduced pressure and under 40°, diluted with water and extracted with chloroform. Benzoic acids were removed from the chloroform by extraction with aqueous sodium bicarbonate solution; benzoic acid was separated from the *p*-nitro derivative by dissolving the former in petroleum solvents. The sulfonic acids were isolated as potassium salts from alcohol. Neutral esters or thioisulfonates remained in the chloroform after bicarbonate extraction.

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The Structure of Verbenalin

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Since our work on the glucoside verbenalin was in progress when the recent paper by Karrer and Salomon² came to our attention, it appears desirable to report a part of our results at this time. We have isolated verbenalin from an American species, *Verbena stricta*, by a new and simplified procedure. Our analytical data for the glucoside are in agreement with Cheymol's formula, C₁₇H₂₄O₁₀,³ but the optical rotation differs.

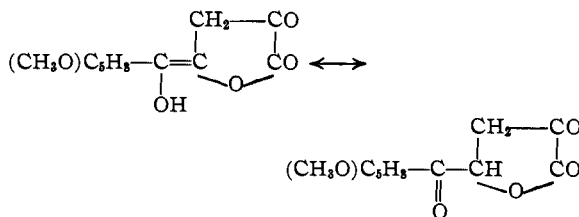
We have observed the same properties of verbenalin as reported by previous investigators, namely, a positive iodoform test, reduction of Fehling solution, and ammoniacal silver nitrate, no coloration with ferric chloride, and failure to yield carbonyl derivatives. Its saponification equivalent is lower than the theoretical value for one lactone group, indicating the presence of some other alkali-labile groups. The compound absorbs approximately one mole of bromine on titration but liberates it slowly on standing, which might indicate the presence of a labile enol group.

In contrast to Karrer's report,² verbenalin was reduced smoothly in the presence of Adams catalyst, absorbing two moles of hydrogen to yield a crystalline tetrahydroverbenalin, C₁₇H₂₈O₁₀, which gives no iodoform test nor color with ferric chloride, does not reduce Fehling solution, but does reduce ammoniacal silver nitrate. Our hydrogenated product, m. p. 173–174.5°, may be an isomer of the one, m. p. 195–196°, obtained with platinized Raney nickel, by Karrer.²

Emulsin hydrolysis of verbenalin at 23–25° and pH 4.3–4.6 produces the aglucone, verbenalol, C₁₁H₁₄O₅, in maximum yields of approximately 60%. Analytical data for this aglucone agree with that of Cheymol and Karrer except for

optical rotation. Verbenalol gives a positive iodoform test, reduces Fehling solution as well as hot aqueous copper acetate and ammoniacal silver nitrate; and, contrary to Karrer's observation, it gives immediately a strong violet color reaction with ferric chloride. Upon bromine titration it absorbs one mole of halogen which it liberates slowly on standing. Verbenalol also yields a di-2,4-dinitrophenylhydrazone, indicating the presence of two carbonyl groups; and on treatment with diazomethane yields an oily product which is not colored by ferric chloride; hence the presence of an enolic group in verbenalol must be assumed.

Emulsin hydrolysis of tetrahydroverbenalin produces tetrahydroverbenalol, C₁₁H₁₈O₅, (yield 60%), the m. p. of which, 123–124°, is considerably higher than that of Karrer's sample (102°), which was isolated from a mixture of reduction products of verbenalin.² Tetrahydroverbenalol gives no iodoform reaction nor coloration with ferric chloride; it does not reduce Fehling solution, but does reduce ammoniacal silver nitrate. It is indifferent to carbonyl reagents but yields a diacetate. The negative reaction with periodic acid² excludes the presence of an α -glycol grouping in its structure. The structure



for verbenalol appears to explain all of the data thus far available on the compound and its tetrahydro derivative. The sugar contained in the naturally occurring glucoside, which has been identified as glucose,³ may well be linked to the enolic hydroxyl group. Less probable is a structure containing the sugar in an α -enol lactone since it would fail to explain the positive iodoform test for the glucoside. Further work on oxidative degradation to clarify the structure of the C₅H₈ group and to confirm the above formula is in progress.

Experimental

Isolation of Verbenalin.—2-Kg. portions of dried, powdered *V. stricta* (collected near Madison, Wis.) were extracted with ether for two weeks in a Soxhlet apparatus. Verbenalin separated from the solution in the extraction flask, was filtered, washed with ether-acetone (1:1) and then dry acetone which removed most of the coloring and gummy matter. It was then decolorized with charcoal in alcohol and purified by several recrystallizations from alcohol and alcohol-ethyl acetate when colorless rhombic plates, m. p. 182–183° (dec.)⁴ were obtained; yields averaged 0.85%; $[\alpha]_D^{25} -171$ to 172° (water); -165 to 166° (alcohol).

Anal. Calcd. for C₁₇H₂₄O₁₀: C, 52.57; H, 6.18; OCH₃, 7.99; mol. wt., 388; sapon. equiv., 388. Found: C,

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(2) P. Karrer and H. Salomon, *Helv. Chim. Acta*, **29**, 1544 (1946).

(3) J. Cheymol, *Bull. Soc. Chim.*, **5**, 633, 642 (1938).

(4) All melting points given are corrected.

52.36; H, 6.05; OCH₃, 8.33, 8.05; mol. wt. (Rast), 395, 398; sapon. equiv., 246, 242.

Isolation of Verbenalol.—Verbenalin (2 g.) was dissolved in 100 ml. of water containing 2.5 g. of crude emulsin, 25 ml. of citrate buffer (pH 4.5) added, and allowed to stand at 24° for one week. From the mixture which had turned dark brown, the aglucone was extracted continuously with ether, the yellow ether extract washed with water, dried, and concentrated to 5 ml. Crystalline verbenalol which separated on standing was recrystallized from ethyl acetate, acetone and alcohol to yield colorless rods, m. p. 133–134° (dec.); yield, 0.7 g. (58%); $[\alpha]^{24}_D$ –20 to 21° (alcohol). When a drop of freshly prepared ferric chloride solution was added to a solution of 5 mg. of pure verbenalol in 1 ml. of water an immediate strong violet color was produced.

Anal. Calcd. for C₁₁H₁₄O₅: C, 58.40; H, 6.19; OCH₃, 13.71; mol. wt., 226; sapon. equiv., 226. Found: C, 58.54, 58.56; H, 6.14, 6.10; OCH₃, 14.73, 14.14; mol. wt. (Rast), 220, 216; sapon. equiv., 161, 155.

Verbenalol-2,4-dinitrophenylhydrazone.—2,4-Dinitrophenylhydrazine (0.25 g.) was dissolved in 25 ml. of warm absolute methanol, 0.25 g. of verbenalol added, and the solution refluxed on the steam-bath for one-half hour and allowed to cool. The microscopic crystals which separated (0.2 g.) were recrystallized from methanol to yield reddish-brown crystals, m. p. 179° (dec.).

Anal. Calcd. for C₂₃H₂₂O₁₁N₈: N, 19.11. Found: N, 19.83, 19.87.

Action of Bromine on Verbenalol.—Verbenalol (0.1143 g.) was dissolved in 50 ml. of chloroform, 25 ml. of 0.05 N bromine and 5 ml. of hydrochloric acid added, the mixture shaken and kept in the dark for two hours with shaking from time to time. Then 1.0 g. of potassium iodide was added and the liberated iodine titrated with 0.05 N thiosulfate. Upon standing after the end-point was reached the mixture continued to liberate iodine slowly.

Anal. Calcd. (for one mole of bromine absorbed): 20.22 ml. of 0.05 N Br. Found: 20.74 ml.

Methylation of Verbenalol.—To an absolute methanol solution of verbenalol (1.0 g. in 5 ml.) was added an ether solution (100 ml.) of diazomethane prepared from 10 g. of nitrosomethylurea. After keeping in the refrigerator for one week, incomplete methylation was indicated and the methylation was repeated on the residue with two additional portions of diazomethane prepared from 10-g. portions of nitrosomethylurea. The viscous brown residue obtained upon slow evaporation of the ether gave no coloration with ferric chloride but could not be crystallized. It was distilled at 175–180° (0.002 mm.).

Anal. Calcd. for C₁₀H₁₀O₃(OCH₃)₂: OCH₃, 25.83. Found: OCH₃, 22.22, 23.00.

Hydrogenation of Verbenalin.—5.01 g. of verbenalin was dissolved in 60 ml. of water, 1.0 g. of platinum oxide catalyst added, and shaken for five hours at room temperature in a bomb at a beginning pressure of 45 lb. p. s. i. The net pressure fall was approximately equivalent to two moles of hydrogen.⁵ In another experiment 5.5 g. of verbenalin, dissolved in 250 ml. of absolute alcohol, was shaken with hydrogen in the presence of 1.0 g. of platinum oxide catalyst at room temperature and atmospheric pressure. The absorption of hydrogen proceeded smoothly during a period of eleven hours, the net amount (620 cc. at 0°, 760 mm.) corresponding very closely to two moles. From the latter hydrogenation mixture the catalyst was centrifuged off, the clear supernatant solution concentrated to 5 ml. and diluted with 50 ml. of chloroform, when the crude, amorphous product separated (4.5 g., m. p. 158–170°). Recrystallizations from ethyl acetate yielded colorless, glistening plates of tetrahydroverbenalin (2.8 g.), m. p. 173–174.5°. Tetrahydroverbenalin gave no color with ferric chloride, no iodoform test, did not reduce Fehling solution, but gave a beautiful silver mirror with ammoniacal silver nitrate.

(5) We are indebted to Prof. Homer Adkins for this hydrogenation.

Anal. Calcd. for C₁₇H₂₈O₁₆: C, 52.04; H, 7.14; OCH₃, 7.91. Found: C, 52.48; H, 6.91; OCH₃, 8.12.

Tetrahydroverbenalol.—A mixture of tetrahydroverbenalin (2.0 g. in 75 ml. of water), crude emulsin (2.0 g.) and 20 ml. of citrate buffer (pH 4.5) was allowed to stand at room temperature for one week and the dark brown mixture then extracted continuously with ether. The residue, upon evaporation of the ether and crystallization from ethyl acetate and then acetone, yielded colorless plates of tetrahydroverbenalol, m. p. 123.5–124°; yield, 0.7 g. (60%). Tetrahydroverbenalol gave no color with ferric chloride, no iodoform test, did not reduce Fehling solution, but gave a beautiful silver mirror with ammoniacal silver nitrate. Its solution in aqueous alkali remained colorless during forty-eight hours and upon acidification the original tetrahydroverbenalol could be recovered.

Anal. Calcd. for C₁₁H₁₈O₅: C, 57.39; H, 7.83; OCH₃, 13.48. Found: C, 57.69, 57.54; H, 7.89, 7.85; OCH₃, 13.84.

Acetylation of Tetrahydroverbenalol.—A solution of tetrahydroverbenalol (0.28 g.) in 2.2 ml. of acetic anhydride and 0.3 ml. of pyridine was refluxed for two hours and poured into iced water. The separated solid was extracted with ether, and the ether extract evaporated to yield colorless crystals, which crystallized from ethyl acetate and then acetone in colorless plates (0.28 g.), m. p. 109–109.5°.

Anal. Calcd. for C₁₁H₁₆O₃(OCOCH₃)₂: sapon. equiv., 105.3. Found: sapon. equiv., 103.3, 99.3.

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Triphenylmethyl Derivatives of Diphenylamine

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The reaction of triphenylchloromethane (trityl chloride) with diphenylamine in boiling benzene was reported by Wieland and others¹ to yield *p*-trityldiphenylamine. Campbell,² working in this Laboratory, found that the reaction when conducted in the presence of aluminum chloride went to completion to form not only the mono-trityl derivative but also a high melting by-product. To this he assigned the structure *p*-anilino-*p*'-diphenylmethyldiphenyl. More recent work has shown that Campbell's assignment of structure was based in part on an incorrect analysis for carbon. Our analyses now show that the empirical formula for this compound is C₅₀H₃₉N corresponding to the composition of a ditrityldiphenylamine. The reaction of the compound with phenol in the presence of zinc chloride formed *p*-tritylphenol. Based on this reaction and the known tendency of aromatic amines to tritylate in the para-position,³ it is inferred that the C₅₀H₃₉N compound is *p,p*'-ditrityldiphenylamine. This inference is supported by the strong infrared absorption band at 2.9 microns which was found for the ditrityl as well as for the mono-trityl derivative. This band is characteristic of the >NH group.

(1) Wieland and others, *Ber.*, **52**, 893 (1919).

(2) U. S. Patent 1,902,115, March 21, 1933; U. S. Patent 1,950,079, Mar. 14, 1934; Compare Groggins "Unit Processes in Organic Synthesis," McGraw-Hill, Inc., New York, N. Y., 1947, p. 747.

(3) (a) Iddles and Hussey, *This Journal*, **63**, 2768 (1941); (b) Witten and Reid, *ibid.*, **69**, 973 (1947).