carotene has the tendency to partially overlap with the pigment. (About 200 mg. of phytofluene may be handled on a 24 × 4.8 cm. alumina column.) Somewhat greater becomes the difference in the adsorbabilities of phytofluene and α-carotene when alumina–calcium hydroxide mixtures are used. The phytofluene zone is then markedly broader and the overlapping is of lesser extent. Phytofluene spreads out still more on pure calcium hydroxide and at the same time a differentiation of some stereoisomers may be observed. (We recommend that not more than 100 mg. of substance be placed on a 28 × 8 cm. calcium hydroxide column.) The separation of phytofluene from some members of the stereoisomeric α-carotene set is difficult.

In mixed chromatograms, using calcium hydroxide and petroleum ether, the following sequence was observed from top to bottom: vitamin A, phytofluene, anhydrovitamin A, and isoanhydrovitamin A; the phytofluene zone was flanked by broad, non-fluorescing interzones. Compared with the bluish-white fluorescence of the vitamin A section and with the orange-yellow fluorescence of the anhydro compounds, the phytofluene zone appeared definitely greenish in ultraviolet light.

Summary

The isolation of an oily, colorless, in ultraviolet light strongly fluorescing polyene hydrocarbon (possibly $C_{40}H_{64}$) from commercial tomato paste is described. The compound is photo- and air-sensitive and shows an unusually high adsorption affinity. Some of its spectral and structural characteristics are discussed as well as its role in the bio-synthesis of carotenoid pigments.

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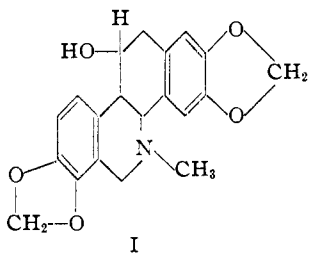
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

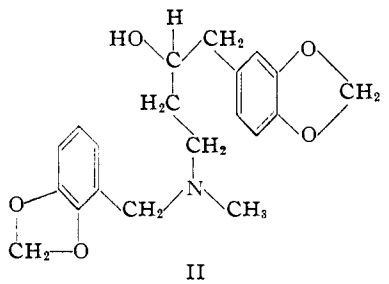
The Synthesis of Some Tertiary Amino Alcohols Related to Chelidonine

BY C. R. NOLLER AND P. D. KNEELAND

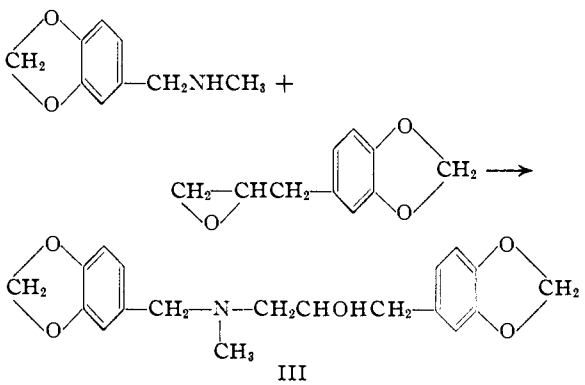
Chelidonine is an alkaloid occurring in celandine (*Chelidonium majus*),[1] and has pharmacological properties resembling those of papaverine.[2] The currently accepted structural formula for chelidonine (I) was proposed by Bruchausen and Bersch.[3] In view of the fact that compounds related to papaverine, but having the nitrogen in an acyclic portion of the molecule, may have antispasmodic properties less than, equal to, or greater than that of papaverine,[4] it was considered desirable to synthesize similar analogs of chelidonine and to determine their pharmacological action. Compound II can be thought of as arising from chelidonine by the breaking of two bonds of the alicyclic rings. Moreover, the product of reaction of safrole oxide with piperonylmethylamine, III, differs from II only in having one less methylene group between the amino group and the hydroxyl group, and a different linkage for one of the methylenedioxyphenyl groups.



I
Chelidonine



II



III

Accordingly the compounds listed in Table I were synthesized by analogous reactions. Their pharmacological action was tested in the laboratory of Dr. P. J. Hanzlik of the Department of Pharmacology, Stanford University Medical School, who states that they show no antispasmodic action, but instead a fairly consistent stimulating action on smooth muscle of different organs. Furthermore, the compounds on intravenous injection depressed the heart sufficiently to be practically useless for therapeutic purposes. The constitution assigned to the compounds is based on the constitution of the reaction product of benzylethylene oxide and ammonia.[5]

(1) Henry, "Plant Alkaloids," P. Blakiston's Son and Company, Philadelphia, Penn., 1939, p. 173.

(2) Hanzlik, *J. Pharmacol.*, **7**, 99 (1915); **18**, 63 (1921); **33**, 387 (1928).

(3) Bruchausen and Bersch, *Ber.*, **63**, 2520 (1930); **64**, 947 (1931).

(4) Rosenmund and co-workers, *ibid.*, **72**, 19, 2161 (1939); Wagner-Jauregg, Arnold and Born, *ibid.*, **72**, 1551 (1939).

(5) Castro and Noller, THIS JOURNAL, **68**, 203 (1946).

TABLE I

AMINO ALCOHOL HYDROCHLORIDES FROM BENZYLETHYLENE OXIDES AND BENZYLMETHYLAMINES

Compound, $RCH_2N(CH_3)CH_2CHOHCH_2R'\cdot HCl$	M. p., °C.	Molecular formula	Analyses,[c] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Chlorine Calcd.	Chlorine Found
R = Phenyl, R' = 3,4-Methylenedioxyphenyl	131–133[a]	$C_{18}H_{22}ClNO_3$	64.37	64.15 64.10	6.61	6.61 6.67	10.57	10.40
R and R' = 3,4-Methylenedioxyphenyl	152–154[a]	$C_{19}H_{22}ClNO_5$	60.08	60.19 60.29	5.84	5.84 5.75	9.33	9.21
R = 3,4-Dimethoxyphenyl, R' = 3,4-Methylenedioxyphenyl	148.4–149.4[b]	$C_{20}H_{26}ClNO_5$	60.67	60.64 60.64	6.62	6.70 6.74	8.96	8.84 8.76
R = Phenyl, R' = 3,4-Dimethoxyphenyl	150.4–151.4[b]	$C_{19}H_{25}ClNO_3$	64.85	64.83 64.90	7.45	7.47 7.40	10.08	9.89
R = 3,4-Methylenedioxyphenyl, R' = 3,4-Dimethoxyphenyl	151.9–154.1[b]	$C_{20}H_{26}ClNO_5$	60.67	60.67 60.72	6.62	6.79 6.76	8.96	8.82
R and R' = 3,4-Dimethoxyphenyl	165.8–167.4[a]	$C_{21}H_{30}ClNO_5$	61.23	61.13 61.02	7.34	7.32 7.40	8.61	8.35

[a] Crystallized from isopropyl alcohol. [b] Crystallized from ethyl alcohol–ether mixture. [c] Carbon–hydrogen analyses by Dr. E. W. D. Huffman, Denver, Colo.; chlorine analyses by Mr. A. J. Castro.

Experimental

Benzylmethylamines.—To a solution of 0.5 mole of the aromatic aldehyde in 0.5 mole of 33% aqueous methylamine and 150 cc. of 95% alcohol was added 0.5 g. of platinum oxide, and the mixture was shaken with hydrogen under an initial gage pressure of 45 pounds. Absorption of hydrogen usually stopped at about 90% of the calculated amount after four hours, although occasionally the catalyst required three to four hours to be reduced, and twenty-five to thirty hours was required for complete reduction. After removal of the catalyst and solvent, an equal volume of water was added, and then 100 cc. of 6 *N* hydrochloric acid, and the solution extracted with three 75-cc. portions of benzene. The aqueous layer was made alkaline by the addition of 150 cc. of 6 *N* sodium hydroxide solution, the oil separated, and the aqueous layer extracted with three 50-cc. portions of benzene. The benzene was removed and the residual oil distilled at reduced pressure. The yields of amines having the indicated boiling ranges were as follows: benzylmethylamine,[6] b. p. 68–70° at 9 mm., 82%; (3,4-methylenedioxybenzyl)-methylamine,[7] b. p. 118–122° at 7 mm., 89%; (3,4-dimethoxybenzyl)-methylamine,[8] b. p. 142–147° at 9 mm., 80%.

Benzylethylene Oxides.—A solution of 0.2 mole of safrole or methyleugenol in 320 cc. of cold chloroform containing 0.2 mole of perbenzoic acid was allowed to stand at 10° until all of the perbenzoic acid had reacted (approximately three days). The solution was freed of benzoic acid by extracting with 10% aqueous sodium hydroxide, and the chloroform layer was washed thoroughly with water and dried over anhydrous sodium sulfate. Removal of the solvent and fractional distillation under reduced pressure gave the following yields of oxides having the indicated boiling ranges: safrole oxide,[9] b. p. 116–118° at 4 mm., 55–63%; methyleugenol oxide,[9] b. p. 190–195° at 10 mm., 50–52%. Some of the starting material always was recovered, and based on the amount reacted, the yields were 80–85% of the calculated amounts.

Amino Alcohols.—In a 25 × 200 mm. test-tube was placed 0.1 mole of the oxide, and 0.1 mole of the secondary amine and sufficient water was stirred into the mixture so that a 2-cm. layer remained during the stirring. The mixture was allowed to stand for three days at room temperature, reëmulsification with the water being brought about by stirring each morning and evening. The excess water was decanted, the remaining water removed by distillation under reduced pressure, and the residue distilled at a pressure of less than 1 mm. The fractions boiling over a 10° range amounted to 85–90% of the calculated amounts.

The free bases were thick viscous oils and were converted to the hydrochlorides by dissolving in a minimum volume of absolute ether, cooling in an ice-bath, and adding a cold saturated solution of dry hydrogen chloride in absolute ether until precipitation was complete. At this stage the hydrochlorides were very hygroscopic and in the subsequent purification were exposed to air as little as possible, and all solvents were kept strictly anhydrous. The mixture was allowed to warm to room temperature, and the precipitate became pasty. The ether was decanted and as much more as possible worked out of the paste with a spatula. Addition of acetone, dried over anhydrous potassium carbonate, first dissolved the paste and then caused precipitation of the hydrochloride in a granular form which was not too hygroscopic to be filtered. The hydrochlorides were recrystallized from either anhydrous isopropyl alcohol, or from a mixture of absolute ethyl alcohol and ether until pure, as indicated by halogen analyses.[10] Decomposition points and analyses for the individual products are given in Table I.

Summary

A number of amino alcohols that may be considered to be related to the alkaloid, chelidonine, have been synthesized by the reaction of benzylethylene oxides with benzylmethylamines. In contrast to chelidonine, which has an antispasmodic action, these amino alcohols have a stimulating action on smooth muscle. Moreover, they are too toxic for therapeutic use.

STANFORD UNIVERSITY, CALIF. RECEIVED JULY 2, 1945

(6) Emde, *Arch. Pharm.*, **247**, 304 (1909).

(7) Andree, *Ber.*, **35**, 420 (1902).

(8) Tiffeneau, *Bull. soc. chim.*, [4] **9**, 928 (1911).

(9) Forneau and Tiffeneau, *Compt. rend.*, **141**, 662 (1906).

(10) The authors are indebted to Mr. A. J. Castro, who purified the products for analysis and analyzed them for chlorine.