2. Picrasmin and isoquassin are identical.
3. Quassin is a molecular complex containing isoquassin and neoquassin in approximately equal amounts.
4. Neoquassin ($C_{22}H_{30}O_6$) is a hydroxy compound and isoquassin ($C_{22}H_{28}O_6$) is the corresponding ketone.

URBANA, ILLINOIS RECEIVED JULY 25, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

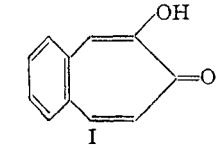
4,5-Benztropolone and Related Compounds[1]

BY D. STANLEY TARBELL,* GEORGE P. SCOTT AND ALEXANDER D. KEMP

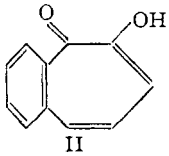
The evidence that has been presented for the occurrence of the seven-membered "tropolone" ring[2] in colchicine,[3] the thujaplicins[4] and purpurogallin[5] has made the problem of synthesizing examples of this interesting ring system an attractive one. Model tropolones have obvious value in elucidating the properties of colchicine, and possess in addition considerable intrinsic chemical interest.

The present paper reports the synthesis of 4,5-benztropolone (I) and some of its derivatives, by a method which promises to be of general application. Preparation of an isomer of I, 3,4-benztropolone, by a different method, has been reported recently by Cook.[6]

Our approach to the benztropolone was suggested by work of Thiele,[7] who showed that *o*-phthalaldehyde condensed with a carbonyl compound such as methyl ethyl ketone or acetonedicarboxylic ester to yield derivatives of benzocycloheptadienone III. In some cases, the product of the condensation was the acylhydrindone IV, which differed from the seven-ring ketone type (III) by its enolic character, and by the presence of the elements of water.



I



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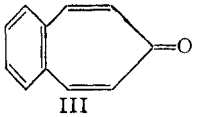
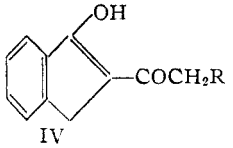
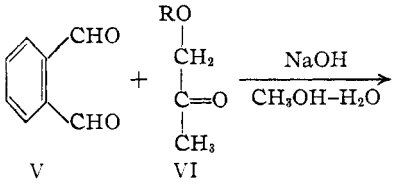


III

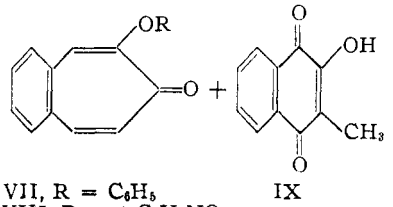


IV

We have found that Thiele's reaction can be applied to aryloxyacetones and to hydroxyacetone itself, to yield 4,5-benztropolone and its aryl ethers. The latter (VII and VIII) were obtained readily, and were assigned the benztropolone structure on the basis of analysis, absence of enolic properties and formation of carbonyl derivatives. The last fact is noteworthy, because colchicine does not form carbonyl derivatives. Furthermore, the infrared spectra of VII and VIII were quite similar to that of I, indicating analogous structures.



V VI



VII, R = C_6H_5 IX
VIII, R = *p*-$C_6H_4NO_2$
I, R = H

The condensation of phthalaldehyde with hydroxyacetone itself led to an unexpected result; two products were obtained in about equal amount, one with the composition $C_{11}H_8O_2$, corresponding to the desired benztropolone I, and the other apparently containing one more atom of oxygen, $C_{11}H_8O_3$.

The properties of the latter, such as its melting point, bright yellow color and the formation of intensely red solutions in alkali or bicarbonate, suggested that it was phthiocol (IX),[8] and this was confirmed by the melting point of the monoacetate, and by a mixed melting point of the compound and its monoacetate with known synthetic samples.[9] The absorption curves for the synthetic phthiocol and that derived from the condensation were identical. The formation of phthiocol may be plausibly explained by the following steps, although experimental evidence is not yet available to support this mechanism.

* Harvard University Ph.D. 1937.

(1) Aided by a grant from the National Institutes of Health; presented at the Atlantic City Meeting of the American Chemical Society, September 21, 1949.

(2) Dewar, *Nature*, **155**, 141, 479 (1945).

(3) (a) Arnstein, Tarbell, Scott and Huang, THIS JOURNAL, **71**, 2448 (1949); (b) Scott and Tarbell, *ibid.*, **72**, 240 (1949).

(4) Erdtman and Gripenberg, *Acta Chim. Scand.*, **2**, 625 (1948), and following papers.

(5) Haworth, Moore and Pauson, *J. Chem. Soc.*, 1045 (1948).

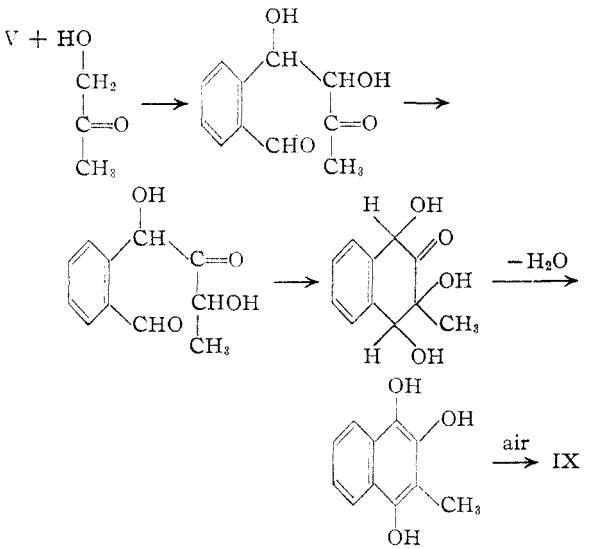
(6) Cook and Somerville, *Nature*, **163**, 410 (1949). We have adopted the numbering system used by these authors.

(7) Thiele and Schneider, *Ann.*, **369**, 287 (1909); Thiele and Weitz, *ibid.*, **377**, 1 (1910).

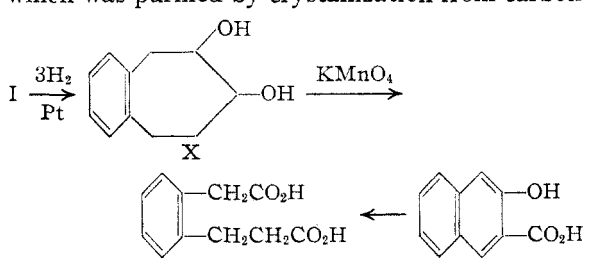
(8) Anderson and Newman, *J. Biol. Chem.*, **103**, 405 (1933).

(9) Creighton and Anderson, *ibid.*, **130**, 429 (1939).

The first step is considered to be an aldol condensation, followed by a shift of the carbonyl group, possibly through the enediol, with a subsequent second aldol condensation and loss of water. The naphthohydroquinone would undoubtedly air-oxidize to phthiocol in the basic solution.[9a]



The compound $C_{11}H_8O_2$ was of course of greater interest than phthiocol; it gave a positive ferric chloride test, was soluble in potassium hydroxide but not in sodium hydroxide, gave a monoacetate, and gave a negative Schiff test, thus ruling out the possibility that it was a hydroxynaphthaldehyde. Catalytic reduction with Adams catalyst yielded a crystalline diol X, which was purified by crystallization from carbon



tetrachloride, or, much more satisfactorily, by chromatography, and the diol readily formed a crystalline diacetate. The diol consumed somewhat over one mole of periodate, and apparently the oxidation product, which gave a strong Schiff test, was further oxidized slowly by periodate; from the oxidation solution was obtained a small amount of dinitrophenylhydrazone which had the nitrogen content calculated for the dinitrophenylhydrazone of 3,4-dihydronaphthaldehyde-1, (*cf.* ref. 3a).

The structure of X, and hence of the benztropolone I, was proved conclusively by oxidation with aqueous permanganate; this gave a good yield of benzene-*o*-aceticpropionic acid (XI), which was shown to be identical with an authentic sample of this compound prepared by sodium–amyl alcohol reduction of 2-hydroxy-3-naphthoic acid.[10]

The synthesis is being extended to other tropolone derivatives.

Experimental[11]

Condensation of Phthalaldehyde with Hydroxyacetone.—Phthalaldehyde[12] (8.5 g.) and freshly prepared hydroxyacetone[13] (4.7 g.) dissolved in 1 l. of methanol were treated with a solution of sodium hydroxide (2.8 g.) in 40 cc. of methanol, the base being added slowly with stirring. After a short time, a yellowish color appeared, which rapidly changed to an intense red. After standing at room temperature for three days, the solution was evaporated at 60–70° under reduced pressure to a volume of about 100 cc. Water (350 cc.) was added, and the solution filtered to remove a small quantity of solid (0.14 g.). The filtrate was extracted four times with ether, the *p*H brought to about 5 with sulfuric acid, and the solid which formed was collected; m. p. 115–145°, wt., 2.7 g. This substance was dissolved in 50 cc. of chloroform, and extracted with thirteen 25-cc. portions of 7% sodium bicarbonate, at which point the alkaline extract was only slightly colored. The chloroform solution was washed twice with water, dried and the solvent removed; the residue (0.75 g.) yielded, after crystallization from ethanol, 0.5 g. of tan crystals, m. p. 155–157°. Two further crystallizations followed by sublimation at 1 mm. gave the analytical sample, light yellow in color, m. p. 159.5–160.5°.

Anal. Calcd. for $C_{11}H_8O_2$ (I): C, 76.74; H, 4.68. Found: C, 76.36; H, 4.97.

The compound gives a negative Schiff test, is readily soluble in 5% potassium hydroxide but not in potassium bicarbonate, giving a strongly yellow solution. With 5% sodium hydroxide, the solid compound turns yellow, and gives a pale yellow solution, but the solid does not dissolve appreciably. Addition of sodium hydroxide to a solution of the material in potassium hydroxide produces a yellow precipitate. The original compound dissolves in concentrated hydrochloric acid, giving a yellow solution, but the material is liberated apparently unchanged on dilution with water.

The acetyl derivative was prepared by allowing 95 mg. of I to stand for twenty-four hours at room temperature in 5 cc. of pyridine with 1.5 cc. of acetic anhydride, and then heating for an hour on the steam-bath. The mixture was poured into 3% hydrochloric acid, extracted with ether, the ether extracts washed with cold dilute alkali, and the solvent dried and removed. The residual oil crystallized, and after recrystallization from ethyl acetate–hexane, yielded 49 mg. of white crystals, m. p. 103–104°. The m. p. was unchanged by sublimation at 1 mm.

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.97; H, 4.71. Found: C, 72.73; H, 4.56.

Phthiocol (IX).—The red bicarbonate washings from the chloroform solution mentioned above were acidified with 10% sulfuric acid. The fine yellow precipitate which formed was taken up by extraction with three portions of chloroform; evaporation yielded a bright yellow solid (1.25 g.), which, after two recrystallizations from

(9a) We are indebted to Drs. R. B. Carlin and J. F. Bunnett for interesting discussions of this mechanism.

(10) Einhorn and Lumsden, *Ann.*, **286**, 268 (1895); Fry and Fieser, THIS JOURNAL, **62**, 3489 (1940). We are indebted to Dr. Duane L. Hufford for preparation of the authentic sample and determination of the mixed m. p.

(11) All m. p's. corrected; analyses by Mrs. G. Sauvage and Micro-Tech Laboratory.

(12) Prepared by the method of Thiele and Gunther, *Ann.*, **347**, 106 (1906), and purified by distillation and recrystallization from hexane, m. p. 57–58°; the reported value is 56–56.5°.

(13) "Organic Syntheses," Coll. Vol. II, p. 5.

alcohol, followed by a vacuum sublimation, melted at 174–175°. The carbon and hydrogen analysis agreed well with that calculated for phthiocol. The mixed m. p. of a sample of this material with an authentic sample of phthiocol was not depressed, and neither was the mixed m. p. of the monoacetate. The ultraviolet absorption spectrum of the material was identical with that of the synthetic sample of phthiocol in the range 240–350 mμ except for a very slight deviation in the shape of the band near 280 mμ.

Condensation of Phthalaldehyde with Phenoxyacetone (VII).—Phthalaldehyde (5.0 g.) and phenoxyacetone (5.6 g.) were dissolved in methanol and the solution diluted with 750 cc. of water; sodium hydroxide (1.0 g.) in 30 cc. of 50% methanol was then added slowly with stirring. The solution was allowed to stand for five days at room temperature, and 4.6 g. of cream-colored solid was collected by filtration, which after crystallization from ethanol, yielded 3.63 g. of white needles, m. p. 134–135°. The analytical sample, m. p. 136–137° was obtained by vacuum sublimation.

Anal. Calcd. for $C_{17}H_{12}O_2$ (VII): C, 82.26; H, 4.88. Found: C, 82.35; H, 4.63.

This product was neutral, was slightly soluble in concentrated hydrochloric acid, and gave no color with ferric chloride. The **dinitrophenylhydrazone** was prepared in the usual way, and recrystallized from a mixture of glacial acetic acid and nitrobenzene, followed by recrystallization from a large volume of chloroform; m. p. 254.5–257°.

Anal. Calcd. for $C_{23}H_{16}O_5N_4$: C, 64.33; H, 3.76; N, 13.05. Found: C, 64.14; H, 3.65; N, 12.70.

Condensation of Phthalaldehyde with *p*-Nitrophenoxyacetone (VIII).—Phthalaldehyde (2.0 g.) and *p*-nitrophenoxyacetone[14] (2.9 g.) were dissolved in 300 cc. of methanol and diluted with 175 cc. of water. A solution of 0.5 g. of sodium hydroxide in 200 cc. of 75% methanol was slowly added. After the mixture had stood for one day, 0.78 g. of solid was collected by filtration. Three recrystallizations from methyl ethyl ketone yielded a white product, m. p. 191.5–192.5°.

Anal. Calcd. for $C_{17}H_{11}O_4N$ (VIII): C, 69.68; H, 3.78. Found: C, 69.97: H, 3.79.

1,2-Dihydroxy-4,5-benzocycloheptane (X).—4,5-Benztropolone (I, 406 mg., m. p. 158°) was dissolved in 60 cc. of pure methanol with gentle warming, and added to 40 mg. of prereduced Adams catalyst in 10 cc. of methanol. The hydrogenation was carried out at room temperature and pressure; the uptake was fairly rapid at first, but became slower. The reduction was stopped after three hours, when 172 cc. of hydrogen had been adsorbed; the theoretical amount for 3 moles was 174 cc. The greenish-yellow oil obtained by removal of the catalyst and solvent was dissolved in 10 cc. of benzene, and purified by adsorption on a grade III alumina column. Elution with 600 cc. of benzene removed some fluorescent greasy material. By gradually increasing the percentage of chloroform in the eluent to 100%, nearly pure diol began to come off the column after the passage of 900 cc. of eluent; an additional 600 cc. of chloroform removed all the glycol, and further elution with 95% ethanol did not remove additional material. The pure glycol (110 mg.) was obtained by crystallization from ethyl acetate–hexane as colorless plates, m. p. 114.5–115.5° (sintering from 113°). An analytical sample, prepared by rechromatographing this material followed by crystallization from ethyl acetate–hexane, melted at 116.5–117° (sintering from 113°). The compound was soluble in methanol and ethanol, and somewhat soluble (at least 10 mg./1 cc.) in warm water.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.30; H, 8.22.

The **diacetate** was prepared by acetylating 60.3 mg. of the diol (m. p. 113–115°) with 0.3 cc. of acetic anhydride in 5 cc. of pure pyridine at room temperature for three days. The solvent was removed under reduced pressure on the steam-bath, and the residue (94 mg.) crystallized from ethyl acetate; m. p. 128–128.5°. The analytical sample (25 mg.) prepared by a further crystallization, had the same m. p. after drying five hours in vacuum at 100°.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.71; H, 6.92. Found: C, 68.87; H, 7.10.

Oxidation of the Glycol X: Benzene-*o*-aceticpropionic Acid (XI).—The glycol (69 mg., m. p. 113–115°), dissolved in 10 cc. of distilled water with warming, was treated at 30° with 127 mg. of powdered potassium permanganate (theory for three oxygens, 123 mg.), the addition taking place in small amounts, over a period of an hour. At the end of five hours at 25°, the permanganate color was completely discharged. The solution was made just acid to congo red, sufficient sodium sulfite added to dissolve the manganese dioxide, the solution was saturated with sodium chloride, and extracted ten times with 20-cc. portions of ether. The combined ether solutions were washed five times with 10-cc. portions of cold saturated potassium bicarbonate solution. The combined bicarbonate extracts were acidified, extracted ten times with 25-cc. portions of ether, and from the extracts was obtained, after drying and removal of solvent under vacuum, 67 mg. of the acid, m. p. 127–138°; after three crystallizations from water, 33.5 mg. of thick colorless needles were obtained, m. p. 141–142.5° (some softening from 138.5°). The mixed m. p. with an authentic sample[10] of XI showed no depression.

Periodate Titration of 1,2-Dihydroxy-4,5-benzcycloheptane (X).—The glycol (90.6 mg., 0.509 mmole., m. p. 114.5–115.5°) in a mixture of 2 cc. of absolute alcohol and 8 cc. of distilled water was added to 10 cc. of a solution containing 1.06 mmoles. of periodic acid. A blank solution was prepared in the same manner, omitting only the glycol; the solutions were kept at room temperature and aliquots were titrated from each, using the sodium arsenite method for determination of periodate.[15] After sixteen minutes, the glycol had used 1.28 moles of periodate compared to the blank, and after four hours, 1.64 moles; the end-point faded somewhat in the glycol solutions. Apparently the phenylacetaldehyde derivative formed initially by cleavage of the glycol was further attacked by periodate.

The oxidation solution, which gave a strong Schiff test, was extracted ten times with 10-cc. portions of chloroform, the extracts washed with bicarbonate, from which no acidic material was recovered, and the chloroform solution dried and evaporated. Treatment of an alcoholic solution of the residue with dinitrophenylhydrazine gave an immediate yellow precipitate; this was purified by chromatography on alumina from chloroform; elution with chloroform yielded a small amount of red oil, which was crystallized from ethyl acetate–hexane, m. p. 192–197°. Purification by a second chromatogram yielded orange-yellow crystals, m. p. 198–201° giving a strong depression with 2,4-dinitrophenylhydrazine.

Anal. Calcd. for $C_{17}H_{14}N_4O_4$ (the dinitrophenylhydrazone of 3,4-dihydro-1-naphthaldehyde)[16]: N, 16.53. Found: N, 16.83.

Infrared Spectra.—The spectra of I, VII and VIII in the range 1250–1800 cm.$^{-1}$ were determined in chloroform solution, and showed the following maxima.[3b]

3,4-Benztropolone (I): 1252, 1307, 1353, 1431, 1469, 1538, 1575, 1618, 1635.

Benztropolone Phenyl Ether (VII): 1250, 1297, 1343, 1400, 1420, 1494, 1550, 1605, 1630.

Benztropolone *p*-Nitrophenyl Ether (VIII): 1250, 1290, 1344, 1418, 1455, 1494, 1519, 1558, 1606, 1632.

Summary

Condensation of phthaldehyde with hydroxyacetone yields phthiocol and 4,5-benztropolone, which has been reduced to a glycol; the structure

(14) Tarbell, *J. Org. Chem.*, **7**, 251 (1942).

(15) Jackson, "Organic Reactions," John Wiley & Sons, Inc., New York, N. Y., Vol. II, p. 361.

(16) The dinitrophenylhydrazone of 1-naphthaldehyde itself melts at 254° (Coles and Dodds, THIS JOURNAL, **60**, 853 (1938)).

of the glycol is proved by periodate titration, and by permanganate oxidation to benzene-*o*-acetic-propionic acid. Phthaldehyde condenses with aryloxyacetones to yield aryl ethers of 4,5-benztropolone.

ROCHESTER, NEW YORK RECEIVED OCTOBER 3, 1949

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Amines Related to 2,5-Dimethoxyphenethylamine. V. 2,5-Dihydroxy and 2-Methoxy-5-hydroxy Derivatives[1]

BY RICHARD BALTZLY,* JOHANNES S. BUCK[2] AND WALTER S. IDE

Interest in the 2,5-dialkoxylated type of pressor was first aroused by the study of the properties of 2,5-dimethoxyphenethylmethylamine.[3] This substance was at that time unique as being the only ring-alkoxylated pressor of considerable potency.[4] It was also unusual as possessing considerable activity when given orally. Whereas ordinarily the hydroxy pressors are far more potent than their ethers, 2,5-dihydroxyphenethylmethylamine was of about the same potency as its dimethyl ether and its action was shorter.[4]

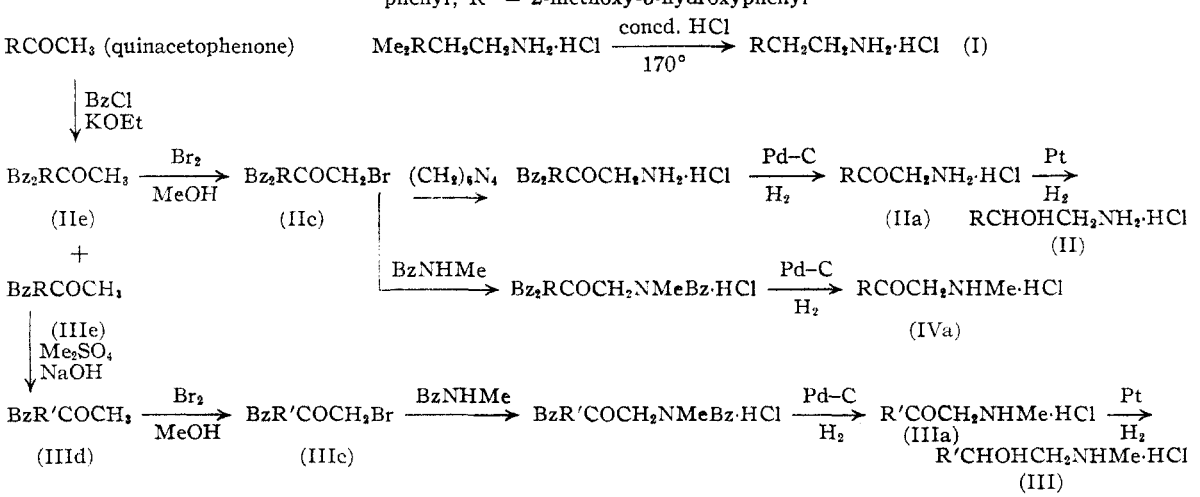
When a more extended series of 2,5-dialkoxyphenethylamines[5] had been prepared, comparison was sought between two other members and their demethylated analogs. Demethylation of 2,5-dimethoxyphenethylamine and of β-(2,5-dimethoxyphenyl)-isopropylamine afforded the corresponding dihydroxy compounds of which only the first could be obtained crystalline. Both were tested, the latter as a solution of the crude preparation, and gave results similar to those previously reported by Hjort[4] although 2,5-dihydroxyphenethylamine[5a] was somewhat superior to its N-methyl derivative and resembled closely the dimethoxy pressors. Oral activity was, however, largely absent.

It later became apparent that optimal activity was to be expected only with an hydroxyl group in the side chain.[6] We decided to attempt preparation of further 2,5-dihydroxy types, but as extreme experimental difficulties were anticipated (since these are derivatives of hydroquinone) it seemed best to prepare a few specimens for test and only to complete the series if preliminary results gave promise that the effort would be rewarded.

The scheme of synthesis followed is outlined in Chart I. Use of quinacetophenone as starting material gave access also to derivatives of the 2-methoxy-5-hydroxy type and operations in that series were carried out in parallel. Observations from various laboratories, confirmed and summarized by Hjort[4] had been to the effect that in pressors a *m*-hydroxyl group was especially bene-

CHART I

The Roman numerals refer to new substances isolated in pure form: R = 2,5-dihydroxyphenyl; Me_2R = 2,5-dimethoxyphenyl; Bz_2R = 2,5-dibenzyloxyphenyl; BzR = 2-hydroxy-5-benzyloxyphenyl; BzR′ = 2-methoxy-5-benzyloxyphenyl; R′ = 2-methoxy-5-hydroxyphenyl



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* Harvard University Ph.D. 1931.

(1) This work is part of a joint research carried out in collaboration with a pharmacological group in these laboratories.

(2) Present address: Sterling-Winthrop Research Institute, Rensselaer, New York.

(3) Buck, THIS JOURNAL, **54**, 3661 (1932).

(4) Hjort, *J. Pharmacol. Exptl. Therapeut.*, **52**, 101 (1934).

(5) Baltzly and Buck, THIS JOURNAL, **62**, 161 (1940).

(5a) Neuberger (*Biochem. J.*, **43**, 606 (1948)) has recently reported this substance. His characterization (m. p. 169–170°) is in reasonable agreement with ours.

(6) Hjort, Randall and de Beer, *J. Pharmacol. Exptl. Therapeut.*, **92**, 283 (1948).