lowing the solution to cool resulted in the formation of a clear gel which was converted by the method above to an extremely bitter white powder which darkened above 200° melting with decomposition at 230–240°.

The salt was dried in a vacuum desiccator containing sulfuric acid for several days or *in vacuo* at 150° for one hour.

Anal. Calcd. for $C_{15}H_{15}ClN_2$: C, 69.63; H, 5.83; Cl, 13.71; N, 10.83. Found: C, 69.44; H, 5.95; Cl, 13.66; 13.70; N, 10.88.

This compound absorbed atmospheric moisture rapidly, taking up one molar equivalent of water.

Anal. Calcd. for $C_{15}H_{17}ClN_2O$: N, 10.12. Found: N, 10.05.

The absorption spectrum of N-(2-anilinoethyl)-formanilide in 0.1 *N* sodium hydroxide is indicated in Fig. 3. The transformation of this compound into 1,3-diphenyl-2-imidazolinium chloride is indicated by the change in the absorption spectrum in acidic solution as indicated in Fig. 3. This change in absorption spectrum is very rapid in strongly acidic solutions, and the reverse change takes place rapidly in strongly basic solutions; however, at intermediate *p*H ranges the rate of the transformations from one form to the other occurs more slowly. The rate of the transformation from the basic form to the acid form and the reverse is indicated in Table VI.

TABLE VI

EFFECT OF *p*H ON THE RATE OF INTERCONVERSIONS OF N-(2-ANILINOETHYL)-FORMANILIDE AND 1,3-DIPHENYL-2-IMIDAZOLINIUM CHLORIDE

	Optical density,[a] 312 mμ					
	N-(2-Anilinoethyl)-formanilide[b]			1,3-Diphenyl-2-imidazolinium chloride[c]		
Time	*p*H 3	*p*H 4	*p*H 4.5	*p*H 5	*p*H 6	*p*H 7
2 min.	0.109	...	0.013	...	0.555	0.539
5	.202	0.051	.023	0.541	.509	.459
10	.316	.088	.036	.537	.479	.356
20	.431	.120	.062	.518	.411	.181
1 hr.	.517	.308	.139	.507	.268	.049
2	.516	...	...	.501	.129	.011
20	.514	.451	.301	...	...	...

[a] At 10 γ per cc. of compound. [b] Compound (200 γ per cc.) in alcohol was added to 0.2 *M* phosphate buffer at indicated *p*H. [c] Compound (100 γ per cc.) in 0.1 *N* hydrochloric acid in 50% alcohol was added to 0.2 *M* phosphate buffer at indicated *p*H.

AUSTIN, TEXAS RECEIVED JANUARY 29, 1951

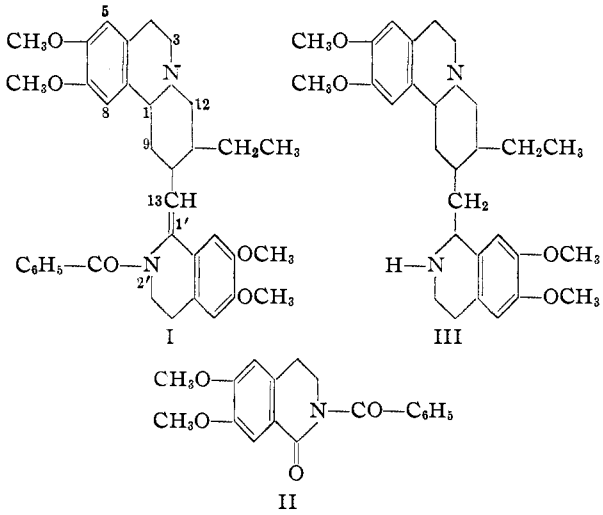
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF KANSAS]

Studies on Emetine. II. Synthesis of N-Benzoylcorydaldine

BY MELVIN I. MOYER[1] AND WILLIAM E. MCEWEN

1-(β-3′,4′-Dimethoxyphenylethylamino)-6,7-dimethoxy-3,4-dihydroisoquinoline (V) was prepared by applying a Bischler–Napieralski reaction to *s*-bis-(β-3,4-dimethoxyphenylethyl)-urea (IV). A reaction of V with benzoyl chloride and aqueous sodium hydroxide solution afforded N-benzoylcorydaldine (II). The substituted urea (IV) was obtained by a reaction of ethyl acetonedicarboxylate with β-3,4-dimethoxyphenylethylamine. Some similar reactions involving β-phenylethylamine are also described.

Perphthalic acid oxidation or ozonolysis of N-benzoyl-O-methylpsychotrine (I) has been reported to yield a product, the elementary analysis of which is reasonably consistent with the formula of N-benzoylcorydaldine (II).[2] This result, in conjunction with the fact that reduction of O-methylpsychotrine affords both emetine (III) and a diastereoisomer, isoemetine,[2,3] has been advanced as evidence for the position of the non-aromatic double bond in O-methylpsychotrine.[4] In view of this, it seemed desirable to verify the isolation of II by synthesizing it independently and comparing its properties with those of the degradation product.



I III

II

Cyclization of *s*-bis-(β-3,4-dimethoxyphenylethyl)-urea (IV) according to the Bischler–Napieralski procedure afforded 1-(β-3′,4′-dimethoxyphenylethylamino) - 6,7 - dimethoxy - 3,4 - dihydroisoquinoline (V). Reaction of this with benzoyl chloride and aqueous sodium hydroxide solution gave N-benzoylcorydaldine (II). Its physical properties were in agreement with those reported for the product obtained by oxidative cleavage of N-benzoyl-O-methylpsychotrine (I).[2] Thus the position of the extra double bond in O-methylpsychotrine is probably confirmed.[5] In a similar reaction involving V, benzenesulfonyl chloride and aqueous alkali, a product was obtained, the elementary analysis and properties of which are consistent for N-benzenesulfonylcorydaldine.[6] Although Mohunta and Ray have reported that various 1-arylamino-6,7-dimethoxy-3,4-dihydroisoquinolines (VI) are resistant to hydrolytic reagents,[7] it is not surprising that the conditions employed

(1) U. S. Public Health Service fellow, predoctorate, National Heart Institute, June 5, 1950, to June 4, 1951.

(2) P. Karrer, C. H. Eugster and O. Ruttner, *Helv. Chim. Acta*, **31**, 1219 (1948).

(3) F. L. Pyman, *J. Chem. Soc.*, **111**, 419 (1917).

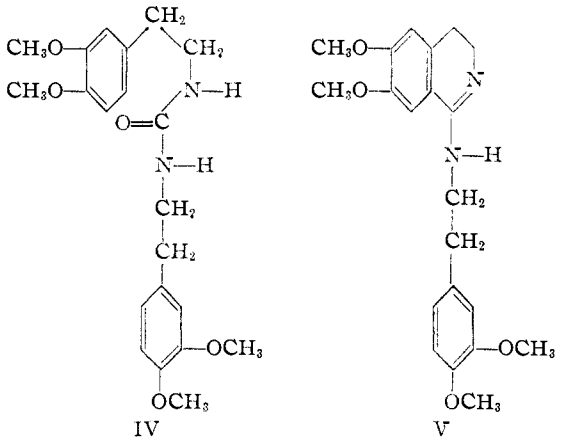
(4) In O-methylpsychotrine itself, the extra double bond may be located at C-13, C-1′, at C-1′, N-2′, or the substance may be an equilibrium mixture of the two isomers.

(5) The total synthesis of *d,l*-rubremetinium bromide has recently been reported. An intermediate product in the synthesis was either *d,l*-O-methylpsychotrine or one of its diastereoisomers. A. R. Battersby and H. T. Openshaw, *Experientia*, **VI**, 378 (1950).

(6) *Cf.* H. J. Barber, *J. Chem. Soc.*, 101 (1943).

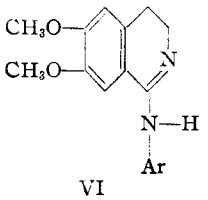
(7) L. Mohunta and J. N. Ray, *ibid.*, 1263 (1934).

by us led to the cleavage of V. It is to be expected that prior formation of an acyldihydroisoquinolinium cation would expedite attack by the hydroxide ion at the 1-position of the ring.



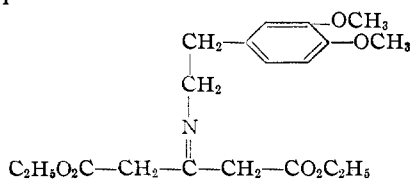
IV

V



VI

Although *s*-bis-(β-3,4-dimethoxyphenylethyl)-urea (IV) has been obtained previously by the decomposition of β-3,4-dimethoxyphenylpropionyl azide in a xylene solution containing water,[7] we prepared IV in a different manner. Heating a mixture of ethyl acetonedicarboxylate and β-3,4-dimethoxyphenylethylamine, with distillation of the volatile by-products, afforded IV in good yield.[8] β-Phenylethylamine reacted similarly with ethyl acetonedicarboxylate to give the known[9] *s*-bis-(β-phenylethyl)-urea. At lower temperatures, β-3,4-dimethoxyphenylethylamine and ethyl acetonedicarboxylate gave only the simple condensation product, ethyl β-(homoveratrylimino)-glutarate (VII). β-Phenylethylamine and ethyl acetonedicarboxylate reacted in a different manner at lower temperatures, and the results are described in the experimental section.



VII

Acknowledgment.—This work was supported in part by a grant from the Office of Naval Research.

(8) We did not set out to prepare the substituted urea by this method. Rather, we desired the di-homoveratrylamide of acetonedicarboxylic acid for use in another connection. Other workers have prepared corresponding diamides by reaction of ethyl acetonedicarboxylate with amines. *Cf.* E. Besthorn and E. Garben, *Ber.*, **33**, 3439 (1900); K. G. Naik, *J. Chem. Soc.*, **119**, 1231 (1921). The cleavage of a β-keto ester by an amine to give a substituted urea is a known reaction, however. See R. M. Roberts and M. B. Edwards, THIS JOURNAL, **72**, 5537 (1950), for examples and earlier references.

(9) T. Curtius and H. Jordan, *J. prakt. Chem.*, [2] **64**, 297 (1901).

Experimental[10]

***s*-Bis-(β-3,4-dimethoxyphenylethyl)-urea (IV).**—On mixing 50.0 g. (0.25 mole) of ethyl acetonedicarboxylate with 134.5 g. (0.75 mole) of β-3,4-dimethoxyphenylethylamine, heat was evolved, and a colorless solid formed. The reaction flask was attached to a Todd column, and the mixture was refluxed until 26 cc. of liquid had distilled over at 70–78°. On cooling, the residue in the distilling flask solidified to a tough gum. This was crystallized from absolute ethanol, yielding 63.7 g. (63%) of the crude urea. After several recrystallizations from ethanol, colorless leaflets were obtained, m.p. 151–152° (Mohunta and Ray[7] report a m.p. of 152°).

Anal. Calcd. for $C_{21}H_{28}N_2O_5$: C, 64.92; H, 7.26; N, 7.21. Found: C, 64.95; H, 7.03; N, 7.23.

1-(β-3′,4′-Dimethoxyphenylethylamino)-6,7-dimethoxy-3,4-dihydroisoquinoline Phosphate Dihydrate.—To a solution of 15.0 g. (0.0385 mole) of *s*-bis-(β-3,4-dimethoxyphenylethyl)-urea in 250 cc. of anhydrous xylene was added 23 g. of phosphorus pentoxide, and the mixture was refluxed for 90 minutes. The condenser was reversed, and 200 cc. of xylene was distilled in the course of 45 minutes. To the residue was added 250 cc. of water, and the mixture was steam distilled until all the xylene had been removed. The aqueous residue was diluted to 300 cc., heated to boiling, and about 3 g. of tarry material was removed by filtration. The orange-colored aqueous filtrate deposited 11.5 g. (59%) of light tan salt on standing overnight. This was recrystallized from 200 cc. of water (decolorizing charcoal), yielding 6.7 g. of colorless crystals, m.p. 269–270°. A further recrystallization raised the m.p. to 271.0–272.5°.

Anal. Calcd. for $C_{21}H_{26}N_2O_4 \cdot H_3PO_4 \cdot 2H_2O$: C, 49.97; H, 6.60; N, 5.55; P, 6.15; H_2O, 7.2. Found for an air-dried sample: C, 50.35; H, 6.57; N, 6.26; P, 6.14; loss in weight on drying *in vacuo* at 110°, 6.7, 7.6.

1-(β-3′,4′-Dimethoxyphenylethylamino)-6,7-dimethoxy-3,4-dihydroisoquinoline (V).—A sample of the above phosphate was dissolved in warm water and made basic with sodium hydroxide solution. A clear gum settled out. On digestion of this gum with ether, a colorless solid formed. This was recrystallized from ether, m.p. 134.4–135.2°.

Anal. Calcd. for $C_{21}H_{26}N_2O_4$: C, 68.08; H, 7.08; N, 7.56. Found: C, 67.51; H, 6.92; N, 7.75.

N-Benzoylcorydaldine (II).—To a suspension of 0.50 g. of 1-(β-3′,4′-dimethoxyphenylethylamino)-6,7-dimethoxy-3,4-dihydroisoquinoline phosphate dihydrate and 1.0 cc. of benzoyl chloride in 5 cc. of water was added to 10 cc. of 10% sodium hydroxide solution, in small portions with vigorous shaking. Heat was evolved and a light tan gum slowly formed. Crystallization from 50% ethanol afforded 0.10 g. (32%) of crude N-benzoylcorydaldine, m.p. 190–194°. Recrystallization from methanol afforded colorless prisms, m.p. 194–195° (Karrer, Eugster and Ruttner[2] report a m.p. of 195–196° for the product obtained on oxidative cleavage of N-benzoyl-O-methylpsychotrine).

Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.51; N, 4.50. Found: C, 69.23; H, 5.20; N, 4.66.

N-Benzenesulfonylcorydaldine.—To a suspension of 0.30 g. of 1-(β-3′,4′-dimethoxyphenylethylamino)-6,7-dimethoxy-3,4-dihydroisoquinoline phosphate dihydrate in 5 cc. of 10% sodium hydroxide solution was added 0.5 cc. of benzenesulfonyl chloride. The mixture was shaken for ten minutes. After standing several hours, a yellow gum separated, which was washed with water. On crystallization from 80% ethanol, 0.10 g. (49%) of colorless N-benzenesulfonylcorydaldine was obtained, m.p. 191–192.5°. After two additional crystallizations from 80% ethanol, the m.p. was raised to 193.4–194.8°.

Anal. Calcd. for $C_{17}H_{17}NO_5S$: C, 58.77; H, 4.93; N, 4.03; S, 9.22. Found: C, 58.96, 58.73; H, 4.81, 5.15; N, 4.36; S, 9.90.

***s*-Bis-(β-phenylethyl)-urea.**—A mixture of 10.0 g. (0.0495 mole) of ethyl acetonedicarboxylate and 18.0 g. (0.149 mole) of β-phenylethylamine was refluxed in a flask joined to a Todd column. In the course of an hour, 6.2 cc. of a liquid distilled over, b.p. 70–78°. The residual grown gum, after washing with dilute hydrochloric acid and water, was crys-

(10) Analyses by Oakwold Laboratories, Alexandria, Virginia, and by Weiler and Strauss, Oxford, England. All m.p.'s's are corrected.

tallized from ethanol, giving 3.3 g. of crude, yellow-brown *s*-bis-(β-phenylethyl)-urea. After several crystallizations from absolute ethanol, colorless crystals were obtained, m.p. 140–141° (Curtius and Jordan[9] report a m.p. of 138.0–138.5° for a sample crystallized from benzene).

Anal. Calcd. for $C_{17}H_{20}N_2O$: C, 76.06; H, 7.53; N, 10.44. Found: C, 76.18; H, 7.62; N, 10.55.

Ethyl β-(Homoveratrylimino)-glutarate (VII).—On mixing 21.0 cc. of β-3,4-dimethoxyphenylethylamine and 19.0 cc. of ethyl acetonedicarboxylate, heat was evolved, and a colorless solid formed. This was crystallized from absolute ethanol, 37.1 g. of colorless leaflets being obtained, m.p. 68–73°. After several additional crystallizations from absolute ethanol, the m.p. was raised to 79.2–79.8°.

Anal. Calcd. for $C_{19}H_{27}NO_6$: C, 62.47; H, 7.40; N, 3.85. Found: C, 62.84, 62.87; H, 7.38, 7.58; N, 4.02, 4.31.

The use of a 2:1 or 3:1 molar ratio of the amine to the keto-ester gave the same product. Heating the reaction mixture to over 100° resulted in the formation of the same product.

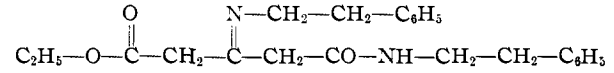
Reaction of β-Phenylethylamine with Ethyl Acetonedicarboxylate at Room Temperature and at 100°.—A mixture of 6.0 g. of β-phenylethylamine and 5.0 g. of ethyl acetonedicarboxylate was heated at 100° for 20 hours in a pressure bottle. The dark red liquid which resulted was dissolved in 300 cc. of ether. The ether solution was washed with dilute hydrochloric acid solution, water, and then dried over anhydrous calcium chloride. On concentrating the ether solution to 50 cc. and cooling, 1.20 g. of colorless solid crystallized. The m.p. varied from 112 to 119°, depending on the solvent from which the substance was crystallized (ether, ligroin, ethanol), and the rate of heating during the m.p. determination.

Anal. Calcd. for $C_{23}H_{28}N_2O_3$[11]: C, 72.60; H, 7.42; N, 7.36. Found: C, 72.85, 72.84; H, 7.39, 7.18; N, 7.80.

The same product was obtained by allowing a mixture of 10.0 g. of the keto-ester and 18.0 g. of the amine to stand at room temperature for 11 days, 12.3 g. of crude product being obtained.

Bischler–Napieralski Reaction of *s*-Bis-(β-phenylethyl)-urea.—To a solution of 6.0 g. of *s*-bis-(β-phenylethyl)-urea in 100 cc. of dry xylene was added 15.0 g. of phosphorus pentoxide, and the mixture was refluxed for four hours. After cooling, the xylene layer was decanted and the residue washed with water, leaving about 5 g. of dark, viscous material. On mixing this with 20 cc. of ethanol, 0.90 g. of colorless solid was obtained, m.p. 237–240°. Its properties were similar to those of 1-(β-3′,4′-dimethoxyphenylethylamine)-6,7-dimethoxy-3,4-dihydroisoquinoline phosphate dihydrate, but no attempt was made to further characterize the material.

(11) Probable structure:



LAWRENCE, KANSAS RECEIVED JANUARY 5, 1951

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE MOUNT SINAI HOSPITAL]

Betaine Hydrazone of Aminochromes[1]

BY HARRY SOBOTKA AND JOHN AUSTIN

A number of cyclic oxidation products of the adrenochrome type have been prepared from epinephrine homologs: epinochrome, 2-iodoepinochrome and 2-carbethoxyepinochrome. The following water-soluble betaine hydrazones of aminochromes have been prepared: the trimethylammoniumacethydrazones of adrenochrome, epinochrome, 2-carbethoxyepinochrome, and the piperidiniumacethydrazone of adrenochrome. The 2-iodoaminochromes are deiodized during this condensation reaction.

A few years ago, Oster and Sobotka[2] discovered the antipressor action of adrenochrome derivatives. The great instability of the earlier preparations of adrenochrome itself and the limited solubility in water of this substance and of its 2-iodo- and 2-bromo- derivatives, which we had studied in our original experiments, impeded the therapeutic application of our observations. Attempts at a complete synthesis of more water-soluble derivatives led to the preparation of 5,6-methylenedihydroxindoxylic acid, to be described in another communication, but were given up because of the difficulties inherent in the polyfunctional nature of the desired product. This research was resumed after the end of the war with the idea of preparing water-soluble adrenochrome derivatives by condensation with water-soluble reagents for carbonyl such as the betaine hydrazides of Girard.

The preparation and isolation of adrenochrome has been facilitated by Veer[3a] and by Buchnea,[3b] who oxidized adrenaline with silver oxide (in 50% excess) in dilute methanol–formic acid solution. We have improved the yield and purity of the reaction product by operating in two stages, as described in the Experimental Part. By this procedure, we have prepared L-adrenochrome from L-epinephrine and DL-adrenochrome from DL-epinephrine. The corresponding cyclic oxidation product which we have obtained from epinine, we have designated as epinochrome. We have also prepared β-(3,4-dihydroxyphenyl)-N-methylalanine (= N-methyl-"dopa"). From its ethyl ester we have prepared by oxidation with silver oxide a solution of 2-carbethoxyepinochrome. We have also improved the preparation of 2-iodo- and 2-bromoadrenochrome and have synthesized the new 2-iodoepinochrome.

The class of cyclic oxidation products with two oxygen functions in positions 5 and 6 of a dihydroindole system and including variants in the heterocyclic moiety has been tentatively designated as "aminochromes," especially as the uncertainty of the orthoquinoid structure makes a systematic nomenclature appear premature. The formulation of adrenochrome as a 5,6-orthoquinone of 1-methyl-3-hydroxydihydroindole is not in full accord with all its chemical properties; an isomeric formulation has been considered by Harley-Mason,[4] which accounts well for the limitation of reactivity to one carbonyl group in condensations with carbonyl

(1) This work was carried out under a grant from the Life Insurance Medical Research Fund.

(2) Oster and Sobotka, *J. Pharm. Exp. Ther.*, **78**, 100 (1943).

(3) (a) Veer, *Rec. trav. chim.*, **61**, 638 (1942); (b) Office of Publication Board, U. S. Dept. of Commerce, Report No. 47 (1945).

(4) Harley-Mason, *Experientia*, **4**, 307 (1948); *J. Chem. Soc.*, 1276 (1950).