[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Synthetic Analogs of Oxytocic Drugs. III. Homologs of the Phenethyl β-Alanine Type[1]

BY RICHARD BALTZLY AND ARTHUR P. PHILLIPS

Oxytocic activity having been observed in certain N-phenethyl-β-alanine esters[2] it seemed desirable to examine the effect of varying the length of the chains (a) between the ring and the amino nitrogen, and (b) between the amino group and the ester grouping. To this end were first prepared four phenethyl derivatives of glycine and α-alanine, Compounds I–IV, none of which proved of physiological interest. The β-alanine homolog of IV is quite active wherefore it is apparent that at least two carbons must intervene between the amino and carbalkoxyl groups.

The reverse operation, increase of the distance between amino and ester functions, produced no comparable change in physiological activity. Compounds VIII and IX were not significantly less potent than their β-alanine equivalents. Evidently there is no critical upper limit in this distance.

The variation of chain length between the amino groups and the ring was not studied in comparable detail since amines with more than two carbons in this chain were less accessible. Three substituted benzyl β-alanine esters, V–VII, were prepared and found to be inactive. At the same time alterations in the nitrogen substituent were made without affecting this result.

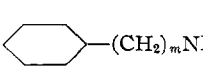
The compounds prepared and their analytical data are presented in Table I. Compounds V–VII were formed from the appropriate secondary amines and methyl acrylate as described in the first paper of this series.[2] The other amino esters were obtained by reaction of the required secondary amine with the appropriate halo ester. The yields by this method were in the range of 30–50% based on pure product. Compound II was prepared by heating I with ethanolamine.

Experimental[2a]

N-Methyl-N-homoveratryl Glycine Ethyl Ester (IV).—Nine grams of ethyl chloroacetate and 14.5 g. of N-methylhomoveratrylamine were refluxed together in absolute ethanol for five hours and the alcohol was then evaporated *in vacuo*. The residual sirup was dissolved in water, basified with sodium carbonate and the bases were taken into ether. After drying over potassium carbonate the bases were distilled at 11 mm. a fraction (4.3 g.) boiling at 192° being selected for further examination. This was dissolved in absolute ethanol, acidified with ethanolic hydrogen chloride and crystallized by addition of ether.

N-Methyl-N-(ξ-carbethoxyhexyl)-homoveratrylamine (IX).—Six hundredths mole of N-methylhomoveratrylamine (12.5 g.) was refluxed in 40 cc. of ethanol with 15 g. of ethyl ξ-bromoheptoate[3] for sixty hours. The alcohol was evaporated and the residual material was dissolved in water. The solution was basified with sodium hydroxide solution and the liberated bases were taken into ether and dried over potassium carbonate. The dry ethereal solution was then treated with portions (1–2 g.) of phenyl isocyanate until the odor of that substance persisted. The excess isocyanate was destroyed with alcohol, the urea filtered off, and the tertiary amine taken into water by extraction with dilute hydrochloric acid. The base was then liberated again, taken into ether, dried and precipitated by addition of ethanolic hydrogen chloride.

TABLE I

SALTS OF PHENALKYLAMINO ACID DERIVATIVES 

Compound	Ring substituents	m	R	n	R′	HX	M. p., °C.[a]	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
I	None	2	CH_3	1	OEt	HCl	219–220[f]	$C_{13}H_{20}ClNO_2$	60.56	60.58	7.83	7.76
II	None	2	CH_3	1	$NHCH_2CH_2OH$	HCl	106–107[b]	$C_{12}H_{21}ClN_2O_2$	57.23	57.47	7.77	7.93
III	None	2	CH_3	1[c]	OEt	HBr	120	$C_{14}H_{22}BrNO_2$	53.13	52.75	7.01	7.16
IV	3,4-$(MeO)_2$	2	CH_3	1	OEt	HCl	164.5	$C_{15}H_{24}ClNO_4$	56.65	56.40	7.61	7.59
V	4-MeO-3-Br	1	C_2H_5	2	OMe	$(COOH)_2$	126–127	$C_{16}H_{22}BrNO_7$	45.69	45.57	5.28	5.43
VI	3,4-$(MeO)_2$	1	CH_3	2	OMe	HCl	136.5[b]	$C_{14}H_{22}ClNO_4$	55.34	55.18	7.31	7.66
VII	3,4-$(MeO)_2$	1	n-C_4H_9	2	OMe	$(COOH)_2$	126–127	$C_{19}H_{29}NO_8$	57.11	57.00	7.32	7.26
VIII	2,5-$(MeO)_2$	2	CH_3	3	OMe	HCl	105–108	$C_{15}H_{26}ClNO_4$	57.89	57.94	7.90	8.22
IX	3,4-$(MeO)_2$	2	CH_3	6	OEt	HCl	118–120	$C_{20}H_{34}ClNO_4$	61.89	61.54	8.84	8.97
						Intermediates						
X	4-MeO-$C_6H_4CH_2NHC_2H_5$·HCl						180–180.5[d]	$C_{10}H_{16}ClNO$	59.53	59.61	8.00	7.93
XI	4-MeO-3-Br-$C_6H_3CH_2NHC_2H_5$·HBr						214[d]	$C_{10}H_{15}Br_2NO$	36.93	37.36	4.66	4.90
XII	3,4-$(MeO)_2C_6H_3CH_2NHCH_3$·HCl						207[d]	$C_{10}H_{16}ClNO_2$	55.15	54.82	7.41	7.56
XIII	3,4-$(MeO)_2C_6H_3CH_2NHC_4H_9$-$n$·HCl						128–129[e]	$C_{13}H_{22}ClNO_2$	60.08	60.19	8.54	8.61

[a] Melting points below 200° are corrected. [b] Needles. [c] $(CH_2)_n$ = —CH(CH_3)—. [d] Plates. [e] Fine felted needles. This compound comes down as very minute crystals, almost as a gel. [f] v. Braun and Wirz, *Ber.*, **60**, 102 (1927), prepared the base and described the hydrochloride as oily.

N-Methyl-N-phenethylglycine Ethanolamide (II).—Eleven grams (0.05 mole) of N-methyl-N-phenethyl glycine ethyl ester and 30 g. (0.5 mole) of ethanolamine was

(1) The work here reported is part of a program carried out in collaboration with a pharmacological group in these laboratories.

(2) Baltzly, Dvorkovitz and Phillips, THIS JOURNAL, **71**, 1162 (1949).

(2a) Since the preparations fall into definite classes and were fairly uniform, a few type procedures are given.

(3) Barger, Robinson and Smith, *J. Chem. Soc.*, 718 (1937).

heated under reflux with a thermometer in the liquid. Heating was applied by a metal-bath. The material, at first in layers, became homogeneous at about 90°. The temperature of the liquid when it began to boil was 154° (b. p. of ethanolamine, 172°) and this temperature fell during twenty minutes to 144° where it remained during forty-five minutes more of gentle refluxing. The contents of the flask was then distilled at 16 mm.; 22 g. of ethanolamine came over at 82°. The residue, which was not extracted from aqueous solution by ether, was acidified with hydrochloric acid (12 cc. of concentrated acid), iced and treated with 10 g. of sodium nitrite and 5 cc. more of concentrated hydrochloric acid. After standing an hour, the solution was evaporated *in vacuo*, dissolved in a minimum of water and basified with 20% sodium hydroxide solution. Repeated extraction with ether removed a sirupy base leaving most of the color behind. The ethereal extracts were dried over potassium carbonate and poured into an excess of ethanolic hydrogen chloride solution. A sirupy layer separated and crystallized slowly. The yield of purified material was 7 g.

The salts described in Table I had no unusual solubilities but the lower melting members were most advantageously recrystallized from acetone with a trace of the esterifying alcohol and with addition of sufficient ether to saturate the solution to the liquid phase. The acid oxalates, V and VII, were prepared because the hydrochlorides could not be induced to crystallize. The hydrobromide III was obtained directly from the reaction mixture in which it was formed.

Intermediates.—The secondary amines leading to compounds I, III, IV and IX, phenethylmethylamine and homoveratrylmethylamine are familiar. The precursor of VIII, N-methyl-2,5-dimethoxyphenethylamine was described by Buck.[4] The intermediates for compounds V–VII are shown in Table I. Veratrylmethylamine (XII),[5] veratrylbutylamine (XIII) and anisylethylamine (X) were prepared by hydrogenation of the corresponding Schiff bases in acetic acid with Adams catalyst; the yields were 75–80%. N-Methyl-4-methoxy-3-bromobenzylamine (XI) was prepared by brominating X in aqueous solution as its hydrobromide; the yield of recrystallized hydrobromide was 76%.

Acknowledgment.—The microanalyses here reported were performed by Messrs. Walter S. Ide and Samuel Blackman to whom we wish to express our gratitude.

Summary

A group of N-phenethyl glycine and N-benzyl-β-alanine derivatives as well as two higher homologs have been prepared for study of their oxytocic properties.

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

(5) Tiffeneau, *Bull. soc. chim.*, [4] **9**, 930 (1911), has characterized the base and its hydroiodide.

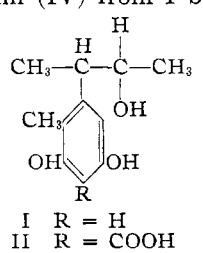
TUCKAHOE 7, NEW YORK RECEIVED MAY 17, 1949

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

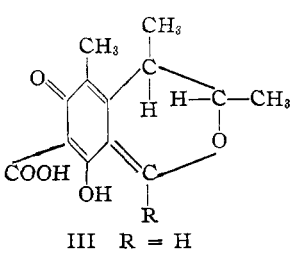
The Synthesis of Dihydrocitrinin and Citrinin

BY H. H. WARREN, GREGG DOUGHERTY AND EVERETT S. WALLIS

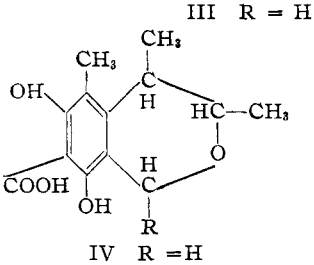
The synthesis of citrinin by Cartwright, *et al.*,[1] from the phenolic degradation product A (I), and the synthesis of the racemic form of A corroborates the structure, III, for citrinin advanced by Brown and co-workers.[2] In this Laboratory we have accomplished the synthesis of dihydrocitrinin (IV) from I by the cyclization of the carboxylic acid derivative, II, with methylal. The dihydrocitrinin thus prepared (m. p. 169.5–170.5° dec.) was readily converted to citrinin by oxidation with bromine in accordance with a method essentially the same as that recently published by Schwenk, Schubert and Stahl.[3]



I R = H
II R = COOH



III R = H



IV R = H

Preliminary observations from investigations now in progress on the synthesis of homologs and analogs of dihydrocitrinin and of citrinin for the purpose of determining the effect of variation in structure on physiological activity indicate that the cyclization is of general applicability for the preparation of derivatives of III and IV where R is methyl, ethyl, benzyl, etc., or substituted radicals of various structures. The results of these experiments will be described in a later paper.

Experimental Part

Compound A.—Citrinin was hydrolyzed with ammonium hydroxide according to the method of Schwenk.[3] Compound A was obtained in excellent yields. Recrystallization from hot chloroform gave a pure product of m. p. 128–130°.

Carboxylic Acid Derivative of Compound A.—The method used was similar to that described by Cartwright.[1] A mixture of 0.50 g. of compound A, 1.00 g. of potassium bicarbonate and 1.00 g. of glycerol was heated under an atmosphere of carbon dioxide in an oil-bath at 150° for five hours. After cooling, the material was dissolved in twice its volume of water and was extracted four times with ether to remove glycerol. Careful acidification of the

(1) Cartwright, Robertson and Whalley, *Nature*, **163**, 94 (1949).

(2) Brown, Cartwright, Robertson and Whalley, *ibid.*, **162**, 72 (1948); see also Frye, Wallis and Dougherty, *J. Org. Chem.*, **14**, 397 (1949).

(3) Schwenk, Schubert and Stahl, *Arch. Biochem.*, **20**, 220 (1949).