[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Synthetic Analogs of Oxytocic Drugs. I. Phenethyl β-Alanine Derivatives[1]

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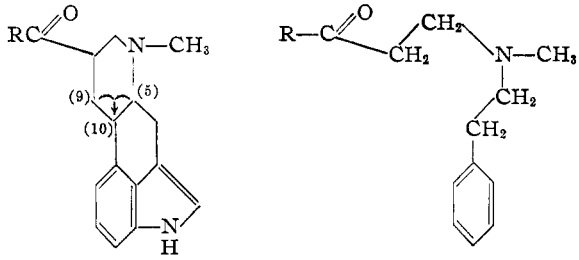
The important natural oxytocic drug ergonovine (ergometrine, ergobasine) has been assigned the structure I (R = $NHCH(CH_3)CH_2OH$[3]) in which the dotted lines indicate the existing uncertainty[4] as to the location of the double bond which is known to shift from the 5-10 to the 9-10 position in transformations between the lysergic and isolysergic acid families of the ergot alkaloids. The contributions of the various portions of the molecule to its physiological activity are not known, although some information is available.

The other ergot alkaloids, in which the group R is replaced by complex cyclic structures, manifest very different physiological behavior, not essentially of an oxytocic character. Stoll and Hofmann[5] have prepared a number of ergonovine analogs and homologs in which 2-amino-1-propanol was replaced by other alkanolamines. A number of these were approximately as active as ergonovine as was α-lysergic acid diethylamide. In contrast to this last finding, Smith and Timmis[6] reported that both ergine and iso-ergine (I, R = NH_2) had only vestigial activity. It does not appear that other derivatives of lysergic acid have been tested. The double bond is apparently not of critical importance since Kharasch[7] has claimed therapeutic efficacy for a dihydro-compound. On the other hand, the presence of the double bond in an unfavorable position (as in the isolysergic acid family) abolishes activity.



I II

Inspection of Formulas I and II shows that lysergic acid (I, R = OH) may be regarded as an N-methyl-N-phenethyl-β-alanine. It is therefore possible to consider a phenethyl-β-alanine alkanolamide as an open-chain model of ergonovine.

A number of phenethyl-β-alanine esters were prepared from N-methylphenethylamines with the intention of transforming them into ethanolamides. While this transformation proved to be unexpectedly tedious and expensive some of the esters themselves showed marked oxytocic activity in laboratory animals. Since the two ethanolamides that have been prepared (compounds IV and XVIII in Table I) appeared to be no more active than the corresponding esters most of our attention was given to the preparation of the latter. It had been hoped that activity could be correlated with structural features. This has been possible only in a general sense. The maximum activity so far observed in this series (5–10% of that shown by ergonovine per unit weight) is manifested by those compounds having two ether substitutions on the phenyl ring. Possibly such substitution of a polar nature may be equivalent roughly to the indole nitrogen in the natural compounds (which would not be cationic under physiological conditions). The activity of the monoalkoxy compounds is perhaps one-tenth that of the di-alkoxy, and the unsubstituted compound (I in Table I) appears inactive. Within the above mentioned classes little differentiation is possible. Differences of less than 100% in potency probably could not be detected by the methods available and the question whether true ergonovine-like action will be manifested in human beings remains to be settled.[8] The secondary amine (XX) and the quaternary salt (XXIV) corresponding to one of the most potent compounds (XXII) showed the same order of activity. The size of the ester alkyl was not critical. On the other hand, the phenolic compounds (II, VI and XIX) were completely inactive. All of these substances showed rather low (in some cases extremely low) toxicities and minimal physiological action of non-oxytocic nature.

The iodinated compounds (VII and VIII) were prepared in the hope that they would partake of the physiological inertness of the parent compound (VI) and would be of interest as radiopaques. Iodination was found, however, to have increased toxicity very considerably.

Experimental

Physical properties and analytical figures for the phenethyl-β-alanine derivatives are presented in Table I. Analytical results were at times rather unsatisfactory. In general, the most serious error in analysis of amine salts results from difficulty in drying. The present series of compounds presents all the usual complications in drying

(1) The work reported here is a part of a project undertaken in collaboration with a pharmacological group in these Laboratories who will report separately on the pharmacology of the substances described in this paper.

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(3) Craig, Shedlovsky, Gould and Jacobs, *J. Biol. Chem.*, **125**, 289 (1938).

(4) Adams and Mahan, THIS JOURNAL, **64**, 2588 (1942).

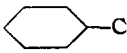
(5) Stoll and Hofmann, *Helv. Chim. Acta*, **26**, 944 (1943).

(6) Smith and Timmis, *J. Chem. Soc.*, 1440 (1936).

(7) Kharasch, U. S. Patent 2,086,559.

(8) The physiological action of ergonovine in rabbits and dogs is qualitatively different from that in human beings. These substances behave much like ergonovine with laboratory animals.

TABLE I

SALTS OF N-METHYL-N-PHENETHYL-β-ALANINE DERIVATIVES  —$CH_2CH_2NMeCH_2CH_2CORHX$

Compound	Phenethyl substitutions	R	HX	Crystallizing solvent[b] and crystal habit[a]	M. p., °C.[c]	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
I	None	OEt	HBr	AE	134–135	$C_{14}H_{22}BrNO_2$	53.13	53.32	7.02	6.97
II	2-OH	OEt	HCl	AE[f]	155.5–156.5	$C_{14}H_{22}ClNO_3$	58.42	58.65	7.71	7.71
III	2-OMe	OEt	HCl	Æ[g]	98–98.5	$C_{15}H_{24}ClNO_3$	59.69	59.76	8.02	8.31
IV	2-OMe	$NHCH_2CH_2OH$	$(HOOC)_2$	Ac. Aq. E.[h]	128–129	$C_{17}H_{26}N_2O_7$	55.10	55.41	7.08	7.39
V	3-OEt	OEt	HCl	AE	101.5	$C_{16}H_{26}ClNO_3$	60.84	60.76	8.30	8.74
VI	4-OH	OEt	HCl	AE	136	$C_{14}H_{22}ClNO_3$	58.42	58.06	7.71	7.60
VII	4-OH, 3,5-I_2	OH	None	Aq	154 (dec.)	$C_{12}H_{15}I_2NO_3$	30.32	30.24	3.18	3.75
VIII	4-OH, 3 5-I_2	OEt	HCl	A Æ E	154 (dec.)	$C_{14}H_{20}ClI_2NO_3$	31.14	31.27	3.74	3.81
IX	4-OMe	OMe	HCl	Ac[g]	139.5–140.5	$C_{14}H_{22}ClNO_3$	58.42	58.19	7.71	8.00
X	4-OMe, 3-Br	OMe	HCl	Ac E	134–135	$C_{14}H_{21}BrClNO_3$	45.82	46.09	5.77	5.70
XI	4-OMe, 3-Br	OEt	HCl	Ac E	85–88	$C_{15}H_{23}BrClNO_3$	47.28	47.60	6.09	6.01
XII	4-OMe, β-Me	OEt	HCl	AE	109	$C_{16}H_{26}ClNO_3$	60.84	60.62	8.30	8.39
XIII	2,3-$(OMe)_2$	OEt	$(HOOC)_2$	Ac[h]	138.5	$C_{18}H_{27}NO_8$	56.08	56.25	7.07	7.37
XIV	2-OEt, 3-OMe	OEt	HCl	Æ	91–92	$C_{17}H_{28}ClNO_3$	59.03	59.10	8.16	8.28
XV	2,4-$(OMe)_2$	OEt	$(HOOC)_2$	Ac[h]	120.5–121	$C_{18}H_{27}NO_8$	56.08	55.94	7.07	7.15
XVI	2,5-$(OMe)_2$	OMe	HCl	M Ac E	108–109	$C_{15}H_{24}ClNO_4$	56.69	57.00	7.61	7.83
XVII	2,5-$(OM)_2$	OEt	HCl	Æ E[f]	105.5–106.5	$C_{16}H_{26}ClNO_4$	57.91	58.14	7.90	8.17
XVIII	2,5-$(OMe)_2$	$NHCH_2CH_2OH$	$(HOOC)_2$	Ac Aq E[i]	153–153.5	$C_{18}H_{28}N_2O_8$	53.98	54.02	7.05	7.48
XIX	3,4-$(OH)_2$	OEt	HCl	A Ac E	96–97.5	$C_{14}H_{22}ClNO_4$	55.34	55.30	7.31	7.42
XX	3,4-$(OMe)_2$[d]	OMe	HCl	Ac[j]	121–122	$C_{14}H_{22}ClNO_4$	55.34	55.30	7.31	7.54
XXI	3,4-$(OMe)_2$	OMe	HCl	Ac E	120–122	$C_{15}H_{24}ClNO_4$	56.68	56.28	7.62	7.62
XXII	3,4-$(OMe)_2$	OEt	HCl	A Ac E[k]	139–139.5	$C_{16}H_{26}ClNO_4$	57.91	57.94	7.90	8.04
XXIII	3,4-$(OMe)_2$	OEt	HBr	A E	118	$C_{16}H_{26}BrNO_4$	51.07	50.79	6.97	7.11
XXIV	3,4-$(OMe)_2$[e]	OEt	I	A Æ E	113–115	$C_{17}H_{28}INO_4$	46.66	46.96	6.45	6.89
XXV	3,4-$(OMe)_2$,6-Br	OMe	HCl	Ac E	138–139	$C_{15}H_{23}BrClNO_4$	45.38	45.55	5.84	6.15
XXVI	3,4-$(OEt)_2$	OMe	HCl	Ac E	111–112	$C_{17}H_{28}ClNO_4$	59.01	59.03	8.16	7.92
XXVII	3,4-$(OEt)_2$	OEt	HCl	Ac E	133–134	$C_{18}H_{30}ClNO_4$	60.04	60.18	8.41	8.27
XXVIII	3,4-$(OEt)_2$	$OC_5H_{11}(n)$	HCl	Ac E	124–125	$C_{21}H_{36}ClNO_4$	62.72	62.47	9.03	8.87
XXIX	3,4-O-CH_2-O	OEt	$(HOOC)_2$	Ac Aq[h]	146.5–147	$C_{17}H_{23}NO_8$	55.27	55.46	6.28	6.49

[a] Crystal habit noted only when macroscopically characteristic. [b] A = absolute ethanol, Ac = acetone, Aq = water. Æ = ethyl acetate. M = methanol, E = ether. [c] Melting points uncorrected. [d] Des-N-methyl. [e] Methiodide from base of XXII. [f] Plates. [g] Prisms. [h] Needles. [i] Flat needles. [j] Fine-meshed needles. [k] Needle-prisms.

with the additional disadvantage that β-alanine esters have some tendency to split off acrylic esters.

The general stability of β-alanine derivatives under varying conditions has not been studied thoroughly. We are at present in a position to offer only incidental observations. The salts, as crystalline solids, are not noticeably unstable—only two of the melting points listed in Table I appeared to be accompanied by decomposition. On the other hand, the odor of acrylic esters is usually noticeable when a bottle containing one of these salts is opened. One or two compounds, on standing several years in stoppered bottles, were observed to liquefy and this has been attributed to decomposition. Despite the above, the demethylation reactions leading to the formation of II, VI, and XIX resulted in satisfactory yields. Further, the ester-exchange reactions leading to the formation of XI, XXVII and XXVIII were effectively quantitative and hence could not have been accompanied by significant decomposition. The stability of the free bases appears to be less than that of the salts. Compounds IX and XXI (as bases) were distilled *in vacuo* of 1–5 mm. The boiling points varied from 140–170° and there was obviously considerable decomposition.

The phenethyl-β-alanine esters were prepared from the appropriate secondary amines[9] by reaction either with methyl acrylate or with ethyl β-bromopropionate. The former reaction affords the methyl esters in nearly quantitative yield. In the earlier part of this work the desired ethyl esters were obtained from ethyl bromopropionate and compounds I, III, V, XII–XV, XXII, XXIII and XXIV were first prepared in this way. This reaction, however, is relatively unsatisfactory both on its own merits and in comparison with the excellent methyl acrylate procedure. After it was found that higher esters could be obtained readily by ester exchange from the methyl esters, the us of ethyl bromopropionate was discontinued.

Compounds XIII, XV and XXIX were isolated as acid oxalates, the corresponding hydrochlorides proving uncrystallizable.

N-Phenethyl-β-alanine Methyl Esters.—The bases to be transformed were mixed with about two equivalents of methyl acrylate (Eastman Kodak Co. "Practical Grade") in 5–10 volumes of benzene. The solutions were allowed to stand overnight and refluxed thirty to sixty minutes. On cooling, phenyl isocyanate was added in small portions (0.5–1 cc.) until its odor was detectable after standing for ten minutes; usually only 1–2 cc. of phenyl isocyanate was required.[10] Sufficient methanol was then added to combine with excess isocyanate and, after standing about twenty minutes, basic material was extracted with dilute hydrochloric acid. The aqueous solutions were basified with sodium carbonate and the oily bases were taken into ether and dried over potassium carbonate. The ethereal solutions were then run into methanol containing excess hydrogen chloride. In a number of cases the hydrochlorides could be induced to crystallize during this neutralization, never separating as oils or sirups. More often the sirupy layer of hydrochloride had to be worked over considerably before crystallization ensued.

N-Homoveratryl-β-alanine methyl ester hydrochloride (XX) was prepared by hydrogenation of the corresponding N-benzyl derivative with palladized charcoal. The N-benzyl compound, formed by the reaction of the known benzyl homoveratrylamine[11] with methyl acrylate, was

(9) With the exception of the precursor of compound XXV, whose preparation is described, all of these amines were known previously.

(10) This treatment with phenyl isocyanate is probably an unnecessary precaution. In the preparation of analogous substances from β-hydroxyphenethylamines, it appeared better to dispense with this operation, but the products were still obtained in semi-quantitative yields and substantially pure as first isolated.

(11) Buck, THIS JOURNAL, **53**, 2192 (1931).

not obtained analytically pure. Compound XX was also the only isolable product from the reaction of homoveratrylamine with excess methyl acrylate on the steam-bath (homoveratrylamine bis propionic ester had been expected and has subsequently been obtained by variation in reaction conditions).

Ester Exchange Reactions.—The methyl ester hydrochlorides to be transformed were dissolved in 10–20 parts by weight of the appropriate higher alcohol and a considerable amount of alcoholic hydrogen chloride. In the preparation of compound XXVII, 3.5 g. of compound XXVI, 100 cc. of absolute ethanol and 10 g. of ethanolic hydrogen chloride (33% by wt.) were refluxed four hours under a fractionating column, solvent being allowed to distil gradually until the volume was about 10 cc. On cooling and dilution with acetone and ether there was obtained 3.5 g. of product melting at 133–134°. The exchange was effectively quantitative.

The corresponding *n*-amyl ester (XXVIII) was recovered in only 70% yield from the reaction of 5 g. of XXVI 50 cc. of *n*-amyl alcohol and 15 cc. of methanolic hydrogen chloride (reflux time, two days with distillation of about half the amyl alcohol) but, since the amyl ester hydrochloride was pure as first isolated it is to be presumed that transformation had been virtually complete.

Compounds XI, XXVII and XXVIII were first prepared from the corresponding methyl esters by the above procedure. Compounds XVII and XXII were prepared in this fashion when additional material was required. It is to be presumed that any of the compounds actually prepared by the ethyl bromopropionate reaction could be obtained more advantageously through the methyl acrylate method followed by ester exchange.

Preparation of Hydroxyphenethyl-β-alanine Esters.—Compounds II, VI and XIX were formed by the demethylation of the corresponding methyl ethers (III, IX and XXI) with concentrated hydrochloric acid at 160–165° in glass bombs (four hours of heating). On opening the bombs the solutions were evaporated *in vacuo* and the residual solids were re-esterified by refluxing with ethanolic hydrogen chloride.

In the preparation of the diiodo compounds VII and VIII, the initial product of the demethylation of IX (presumably the acid corresponding to VI) was dissolved in ammonium hydroxide solution and iodinated by addition of a solution of iodine in dioxane.[12] When the disappearance of iodine had become very slow, the solution was evaporated *in vacuo* to small volume. Compound VII (probably a zwitter-ion) crystallized during this evaporation and was purified by crystallization from water. Compound VIII was formed by esterification of VII with ethanolic hydrogen chloride.

Preparation of the Ethanolamides.—When the β-alanine esters III and XVI were refluxed with excess ethanolamine compounds IV and XVIII were isolated from the reaction mixtures in poor yield and with difficulty. The analogous reaction with phenethyl glycine esters is very satisfactory and it is apparent that the present process involves decomposition of some sort. From one reaction between ethanolamine and XVI, run in methanol, a picrate was isolated corresponding to about one-third of the starting material. This picrate proved to be that of 2,5-dimethoxyphenethylmethylamine which must have been formed by loss of methyl acrylate from XVI. The methyl acrylate released may have combined with ethanolamine.

Somewhat better results were obtained by the method of Stoll[5]: Ester → hydrazide → azide → ethanolamide. This gave XVIII in about 25% yield. A major difficulty in the application of Stoll's procedure to substances of this type is found in the physical properties of the azide. Stoll's procedure was especially devised for the transformation of lysergic acid hydrazide into alkanolamides of lysergic acid. According to Stoll the azide of lysergic acid can be precipitated from aqueous solution by bicarbonate. The azides corresponding to compounds III and XVI are very soluble in water and salt solutions and are poorly and incompletely extracted therefrom by ether. Furthermore, the extractions prolong the operation which is probably undesirable.

The Bromophenethyl Derivatives.—Compound X resulted from the reaction of methyl acrylate with N-methyl-3-bromohomoanisylamine. This secondary amine had been prepared previously[13] by bromination of N-methylhomoanisylamine dissolved in hydrochloric acid. It had been assumed that substitution took place in the 3-position. This has now been confirmed by oxidation (with alkaline permanganate solution) to 3-bromo-4-methoxybenzoic acid. Compound XI was obtained from X by ester exchange.

N-Methyl-6-bromo-3,4-dimethoxyphenethylamine.—Bromination of N-methylhomoveratrylamine hydrochloride in aqueous solution proceeded smoothly. After one mol of bromine had been absorbed, the solution was basified, the amine taken into ether, dried over potassium carbonate and transformed to the hydrochloride which crystallized from ethanol–ethyl acetate–ether mixtures; m. p., 152–3°. *Anal.* Calcd. for $C_{11}H_{17}BrClNO_2$: C, 42.49; H, 5.52. Found: C, 42.48; H, 5.28. Substitution was shown to have been in the 6-position by oxidation (permanganate) to the known 6-bromoveratric acid (m. p., 184–185°).

Reaction of the base with methyl acrylate afforded XXV.

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Summary

1. A number of esters of substituted phenethyl-β-alanines have been prepared.

2. Some of these substances show oxytocic activity in laboratory animals.

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(12) *Cf.* Harington, *Biochem. J.*, **21**, 180 (1927).

(13) Buck, Baltzly and Ardis, THIS JOURNAL, **66**, 311 (1944).