[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLLEGE OF PHARMACY, UNIVERSITY OF ILLINOIS]

Synthetic Oxytocics. Derivatives of N-2-Naphthylglycine and N-2-Naphthyl-β-alanine[1,2]

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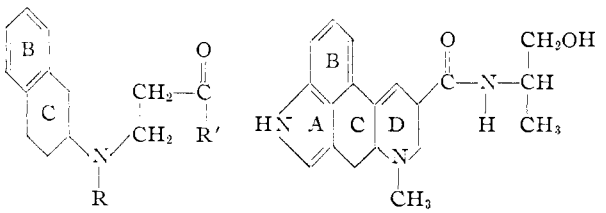
The methyl or ethyl esters, the amides and the N,N-diethylamides of N-2-naphthylglycine, N-methyl-N-2-naphthylglycine, N-2-naphthyl-β-alanine and N-methyl-N-2-naphthyl-β-alanine were prepared and tested for oxytocic activity. Appreciable oxytocic activity was shown only by the ethyl ester and the N,N-diethylamide of N-methyl-N-2-napthyl-β-alanine.

Of the many organic compounds prepared and tested for oxytocic activity, some of the most active are the N-2-(1,2,3,4-tetrahydronaphthyl)-glycine and β-alanine (I) derivatives prepared by Bovet.[3] These may be considered as modified fragments of the ergonovine (II) molecule.



I II

R = CH_3 or H

R′ = CH_3O, C_2H_5O, NH_2, $N(C_2H_5)_2$

Since it has been shown by Stoll[4] that the double bond in ring D of ergonovine contributes markedly to its oxytocic activity, it was therefore of interest to investigate an analogous series of compounds in which ring C is aromatic. Such a series of compounds, analogous to Bovet's N-2-(1,2,3,4-tetrahydronaphthyl)-β-alanine and glycine derivatives, would afford a means of studying further the effects of unsaturation upon oxytocic activity. Therefore, the methyl or ethyl esters, the amides and the diethylamides of N-2-naphthylglycine, N-methyl-N-2-naphthylglycine, N-2-naphthyl-β-alanine and N-methyl-N-2-naphthyl-β-alanine were prepared and tested for oxytocic activity.

These compounds were prepared by the three reactions

$$2\text{-}C_{10}H_7NHR + XCH_2COR' \longrightarrow 2\text{-}C_{10}H_7NRCH_2COR' + HX \quad (A)$$

$$2\text{-}C_{10}H_7NHR + CH_2{=}CHCOR' \longrightarrow 2\text{-}C_{10}H_7NRCH_2CH_2COR' \quad (B)$$

$$2\text{-}C_{10}H_7NRCH_2CH_2COOCH_3 + NH_3 \longrightarrow 2\text{-}C_{10}H_7NRCH_2CH_2CONH_2 + HOCH_3 \quad (C)$$

R = H or CH_3; R′ = OCH_3, OC_2H_5, NH_2 or $N(C_2H_5)_2$; X = halogen

The N-2-naphthylglycine and N-methyl-N-2-naphthylglycine derivatives were prepared by reaction A, following the procedure of Bischoff and Hausdoerfer[5] in which the reactants were heated for several hours in the presence of anhydrous sodium carbonate. Use of a solvent or substitution of pyridine or triethylamine for the anhydrous sodium carbonate gave lower yields of the desired products.

Since the reaction of 2-naphthylamine or N-methyl-2-naphthylamine with ethyl 3-bromopropionate gave only very low yields of the ethyl esters of N-2-naphthyl-β-alanine and N-methyl-N-2-naphthyl-β-alanine, they were prepared by adding corresponding amines to ethyl or methyl acrylate (reaction B). Unfortunately, similar additions of these amines to acrylamide and N,N-diethylacrylamide resulted in only traces of the desired compounds. Therefore, the unsubstituted amides of N-2-naphthyl-β-alanine and N-methyl-N-2-naphthyl-β-alanine were prepared by the ammonolysis of the methyl esters (reaction C) while the N,N-diethylamides were obtained from the proper amine and N,N-diethyl-3-bromopropionamide by reaction A.

With the exception of the ethyl esters of both N-2-naphthylglycine and N-methyl-N-2-naphthylglycine and the derivatives of N-2-naphthyl-N-methyl-β-alanine, all of the compounds prepared formed crystalline hydrochlorides (Table II).

The hydrochlorides and the free bases of those compounds not forming crystalline hydrochlorides were tested for oxytocic activity on the isolated guinea pig uterus. Appreciable oxytocic activity was shown only by the ethyl ester and the N,N-diethylamide of N-methyl-N-2-naphthyl-β-alanine, which gave measurable and reproducible contractions of the guinea pig uterus in concentrations as low as 0.2 mg. per liter. Since these compounds appear to possess the same order of activity as the corresponding tetrahydronaphthyl-β-alanine derivatives, it would appear that the degree of unsaturation in the naphthalene rings is not closely related to oxytocic activity.

Experimental

Reaction A. N-Methyl-N-2-naphthylglycinamide.—The following experiment illustrates the preparation of N-2-naphthylglycine and N-2-naphthyl-β-alanine derivatives by the reaction of 2-naphthylamine or N-methyl-2-naphthylamine[6] with chloroacetic or 3-bromopropionic acid derivatives.

A mixture of 17.9 g. (0.10 mole) of N-methyl-2-naphthylamine, 9.4 g. (0.10 mole) of chloroacetamide and 10.6 g. (0.10 mole) of anhydrous sodium carbonate was heated at 140 to 150° for 8 hours. The reaction mixture was cooled and the resulting solid recrystallized from ethyl alcohol; yield 11.6 g. (54%), m.p. 194–196°.

When the final product was a liquid, the reaction mixture, after being freed from inorganic materials by extraction with water, was distilled under reduced pressure. In the case of the N,N-diethylamide of N-methyl-N-2-naphthyl-

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(2) Abstracted in part from a thesis submitted by Kenneth J. Liska to the faculty of the Univ. of Ill. in partial fulfillment of the requirements for the degree of Master of Science.

(3) G. B. Marini-Betollo, S. Chiavarelli and D. Bovet, *Gazz. chim. ital.*, **80**, 281 (1950).

(4) A. Stoll and A. Hofmann, *Helv. Chim. Acta*, **26**, 2070 (1943); **29**, 635 (1946).

(5) C. A. Bischoff and A. Hausdoerfer, *Ber.*, **25**, 2296 (1892).

(6) R. Pschorr and W. Karo, *ibid.*, **39**, 3141 (1906).

TABLE I

DERIVATIVES OF N-2-NAPHTHYLGLYCINE AND N-2-NAPHTHYL-β-ALANINE, 2-$C_{10}H_7NR(CH_2)_nCOR'$

R	R'	n	Method of prepn.	M.p., or b.p. °C. (uncor.)	Yield, %	Molecular formula	Nitrogen, % Calcd.	Found
H	OC_2H_5	1	A	88–89	71	$C_{14}H_{15}O_2N$[a]		
H	NH_2	1	A	164–166	50	$C_{12}H_{12}ON_2$[b]		
H	$N(C_2H_5)_2$	1	A	136–138	55	$C_{16}H_{20}ON_2$	10.93	10.88
CH_3	OC_2H_5	1	A	165–170 (2 mm.)[c]	30	$C_{15}H_{17}O_2N$	5.76	5.61
CH_3	NH_2	1	A	194–196	54	$C_{13}H_{14}ON_2$	13.02	12.76
CH_3	$N(C_2H_5)_2$	1	A	.....	31	$C_{17}H_{22}ON_2$[d]		
H	OC_2H_5	2	A	50–51	19	$C_{15}H_{17}O_2N$	5.76	5.75
H	OCH_3	2	B	68–70	42	$C_{14}H_{15}O_2N$	6.11	6.15
H	NH_2	2	C	105–106	37	$C_{13}H_{14}ON_2$	13.03	13.11
H	$N(C_2H_5)_2$	2	A	83–85	41	$C_{17}H_{22}ON_2$	10.37	10.28
CH_3	OC_2H_5	2	B	156–162 (0.3 mm.)[c]	53	$C_{16}H_{19}O_2N$	5.44	5.50
CH_3	OCH_3	2	B	153–156 (0.5 mm.)[c]	44	$C_{15}H_{17}O_2N$	5.76	5.86
CH_3	NH_2	2	C	115–117	20	$C_{14}H_{16}ON_2$	12.27	12.50
CH_3	$N(C_2H_5)_2$	2	A	205–210 (1 mm.)[c]	34	$C_{18}H_{24}ON_2$	9.84	9.68

[a] Ref. 5. [b] A. L. Lumiere and F. Perrin, *Bull. soc. chim. France*, **29**, 967 (1903). [c] Boiling points. [d] Isolated only as the hydrochloride.

TABLE II

HYDROCHLORIDES OF 2-$C_{10}H_7NR(CH_2)_nCOR'$

R	R'	n	M.p., °C.	Formula	Chlorine, % Calcd.	Found	Nitrogen, % Calcd.	Found
H	NH_2	1	190–192	$C_{12}H_{13}ON_2Cl$	14.98	15.12	11.83	11.67
H	$N(C_2H_5)_2$	1	162–164	$C_{16}H_{21}ON_2Cl$	12.10	12.33	9.57	9.41
CH_3	NH_2	1	210–212	$C_{13}H_{15}ON_2Cl$	14.14	14.06	11.17	11.08
CH_3	$N(C_2H_5)_2$	1	160–162	$C_{17}H_{23}ON_2Cl$	11.59	11.63	9.13	9.32
H	OC_2H_5	2	167–169	$C_{15}H_{18}O_2NCl$	12.67	12.67	5.01	4.82
H	OCH_3	2	123–125	$C_{14}H_{16}O_2NCl$	13.34	13.33	5.27	5.13
H	NH_2	2	164–166	$C_{13}H_{15}ON_2Cl$	14.14	14.15	11.18	11.06
H	$N(C_2H_5)_2$	2	155–157	$C_{17}H_{23}ON_2Cl$	11.55	11.83	9.13	9.12

glycine, the reaction mixture was extracted with absolute alcohol, and the resulting solution treated with anhydrous hydrogen chloride. The hydrochloride precipitated upon the addition of anhydrous ether. Hydrochlorides of the purified bases were prepared in a similar manner and were recrystallized from absolute alcohol by the addition of anhydrous ether.

Reaction B. N-Methyl-N-2-naphthyl-β-alanine Methyl Ester.—The following experiment will illustrate the preparation of N-2-naphthyl-β-alanine esters by the addition of 2-naphthylamine or N-methyl-2-naphthylamine to ethyl or methyl acrylate.

A mixture of 27.8 g. (0.18 mole) of N-methyl-2-naphthylamine, 17.7 g. (0.18 mole) of ethyl acrylate and 5 cc. of glacial acetic acid was refluxed for 20 hours. The cooled reaction mixture, after being washed twice with 50 cc. of saturated sodium bicarbonate solution and once with 50 cc. of water, was dissolved in ether and dried over anhydrous sodium sulfate. After removal of the ether, the residue was distilled under reduced pressure. It yielded 24.5 g. (53%) of a viscous yellow oil which distilled at 156–162° (0.3 mm.).

Reaction C. N-2-Naphthyl-β-alanamide.—The following experiment illustrates the preparation of N-2-naphthyl-β-alanamide and N-methyl-N-2-naphthyl-β-alanamide by the ammonolysis of the corresponding methyl esters. To 2.2 g. (0.01 mole) of the methyl ester of N-2-naphthyl-β-alanine was added 150 cc. of 28% ammonium hydroxide, and the resulting mixture allowed to stand with only occasional shaking for 7 days. The aqueous layer was then decanted and the lower oily layer washed with small portions of a mixture of 1 part ether and 2 parts petroleum ether until solid. This amorphous solid after recrystallization from the ether–petroleum ether mixture yielded 0.9 g. (37%) of a white crystalline solid which melted at 105–106°.

***N,N*-Diethyl-3-bromopropionamide.**—To 27.7 g. (0.16 mole) of 3-bromopropionyl chloride, previously chilled to 0°, was added dropwise a solution of 23.7 g. (0.32 mole) of diethylamine in 150 cc. of anhydrous ether. The precipitated diethylamine hydrochloride was removed by filtration and washed with several portions of dry ether which were added to the filtrate. After removal of the ether by distillation, the residue was distilled under reduced pressure, yielding 24.4 g. (72%) of a colorless oil which boiled at 95 to 97° (3.0 mm.).

Anal. Calcd. for $C_7H_{14}ONBr$: N, 6.73. Found: N, 6.74.

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