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Potential Ergot Substitutes: Esters and Amides of *beta*-Amino Acids*

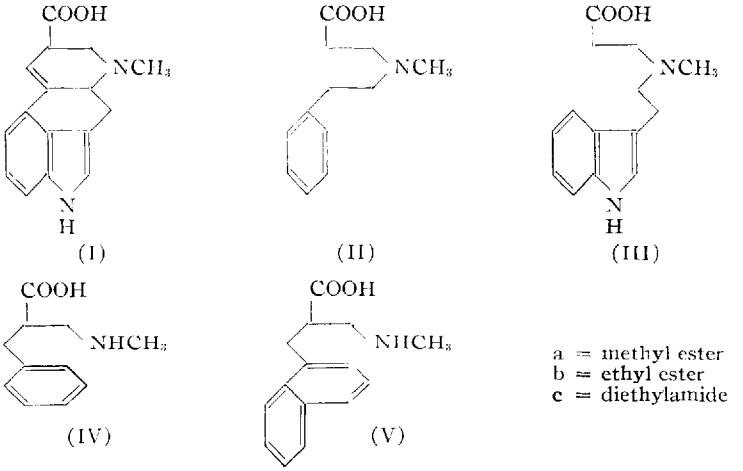
By P. E. NORRIS and F. F. BLICKE

Six esters and amides of derivatives of β-alanine which are related to lysergic acid have been prepared and tested for oxytocic activity. None of these products possess a significant oxytocic activity. A method for the preparation of N-methyltryptamine is described.

ERGOT has been used in medicine for many years as an oxytocic drug. Of the six pharmacologically active alkaloids which are found in ergot, the most important clinically is lysergic acid (I);[1] ergonovine, the 2-(1-hydroxy)-propylamide, is the simplest of these alkaloids.

The purpose of this investigation was to synthesize amides and also esters of compounds (II–V) which represent fragments of the lysergic acid molecule in the hope that some of these products might possess oxytocic activity.

Various modified fragments of the lysergic acid molecule have been synthesized previously; it was claimed that some of the compounds are



ergonovine. The high cost, the uncertainties of an agricultural source, and the low yields of the alkaloids are disadvantages which make it desirable to discover a synthetic substitute for ergot or, particularly, for ergonovine. All of the ergot alkaloids are substituted amides of active oxytocics (1–7). Baltzly, Dvorkovitz, and Phillips (3) found, during the course of an extensive investigation of derivatives of phenylethyl-β-alanine, that in laboratory animals, the esters of several of the compounds prepared possess oxytocic activity equal to that of the ethanolamide of the same compound.

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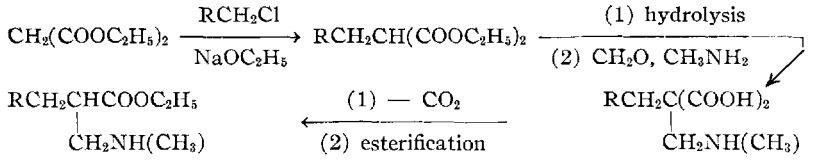
[1] Stoll, A., Hofmann, A., and Troxler, F., *Helv. Chim. Acta*, **32**, 506(1949); Stoll, A., *Chem. Rev.*, **47**, 197(1950).

The methyl ester and the diethylamide of compound II were prepared by the condensation of N-methylphenylethylamine with methyl acrylate and N,N-diethylacrylamide, respectively, and were isolated as hydrobromides. The methyl ester and the diethylamide of III were obtained in the same manner except that N-methyltryptamine was substituted for N-methylphenylethylamine. In the latter case the diethylamide was purified by chromatography with an alumina column; a stable oxalate salt was obtained for use in pharmacological tests. The required N-methyltryptamine was obtained by the following procedure: 3-indoleacetonitrile→ tryptamine → N-formyltryptamine → N-methyltryptamine.

Ethyl esters of compounds IV and V were prepared by the alkylation of malonic ester with either benzyl chloride or α-chloromethylnaphthalene, followed by hydrolysis of the esters, isolation of the substituted malonic acids, Mannich reactions of the acids with formaldehyde and methylamine, decarboxylation, and then re-esterification of the remaining carboxyl group.



R = phenyl or α-naphthyl

The yields from this method are very poor and the products are unusually difficult to purify, due to the fact that the products from the Mannich reactions tend to dissociate spontaneously into a substituted acrylic acid, carbon dioxide, and methylamine. In fact, this process has been used as a preparative method to obtain α-substituted acrylic acids (8).

Pharmacologic data indicated that none of the esters or amides of compounds II–V which were prepared possess a significant oxytocic action when compared to the clinically used oxytocics. However, the diethylamide of N-methyl-N-[β′-(3-indolyl)-ethyl]-β-alanine (IIIc) appeared to have an oxytocic activity approximately ten times stronger than that of the diethylamide of N-methyl-N-(β′-phenylethyl)-β-alanine (IIc).

EXPERIMENTAL

Methyl Ester of N-Methyl-N-(β′-phenylethyl)-β-alanine Hydrobromide (IIa).—This compound was prepared by the general method of Baltzly, *et al.* (3). The hydrobromide was recrystallized from absolute alcohol-ether and melted at 145–147°; yield, 4.5 Gm. (50%).

Anal.—Calcd. for $C_{13}H_{20}O_2NBr$: N, 4.63; Br, 26.44. Found: N, 4.49; Br, 26.01.

N,N-Diethylacrylamide.—To freshly distilled acrylyl chloride[2] (20.4 Gm.) in 150 cc. of benzene, cooled in an ice-bath, there was added dropwise 23.8 Gm. of diethylamine. Diethylamine hydrochloride precipitated. After two hours at room temperature, the mixture was filtered and the filtrate was fractionated; yield, 20 Gm. (70%); b. p. 82–88° (9 mm.); reported (11) b. p. 95° (19 mm.); n_D^{25} 1.4670; reported (11) n_D^{25} 1.4672.

Diethylamide of N-Methyl-N-(β′-phenylethyl)-β-alanine Hydrobromide (IIc).—A solution of 3.5 Gm. of N-methylphenylethylamine and 7 Gm. of N,N-diethylacrylamide in 100 cc. of benzene was refluxed for fifteen hours. An ethereal solution of hydrogen bromide was added dropwise to the cooled solution until the mixture remained cloudy. Upon refrigeration, an oily layer separated, and after a day or two, crystals formed on the walls of the flask. The oily layer was seeded with a few crystals and refrigeration was continued. The solid after recrystallization from benzene melted at 69–73°; yield, 5 Gm. (80%).

Anal.—Calcd. for $C_{16}H_{27}ON_2Br$: N, 8.16; Br, 23.27. Found: N, 7.86; Br, 23.04.

Tryptamine.—A solution of 7.6 Gm. (0.2 mole) of lithium aluminum hydride in 300 cc. of dry ether was prepared in a three-necked flask equipped with a stirrer, reflux condenser, and dropping funnel. To the stirred solution was added dropwise a solution of 15.6 Gm. (0.1 mole) of indoleacetonitrile[3] in 120 cc. of dry ether. The addition required about one and one-half hours. The mixture was refluxed for one-half hour and then cooled. Fifty cubic centimeters of water was added dropwise, followed by 75 cc. of 10% sodium hydroxide solution. The ether layer was separated and the aqueous gel was extracted with ether. The combined ether extracts were dried over magnesium sulfate and the ether was removed immediately by distillation under reduced pressure. The oily residue was distilled and the fraction which boiled at 155–160° (0.5 mm.) or at 130–135° (0.05 mm.) was retained. The distillate solidified and was recrystallized from benzene; m. p. 113–115°; reported (12) m. p. 114–115°. The hydrochloride, recrystallized from alcohol-ether melted at 245–247°; reported (12) m. p. 248–249°. The picrate melted at 242–244°; reported (12) m. p. 242–243°.

N-Formyltryptamine.—A mixture of 6.0 Gm. (0.037 mole) of tryptamine and 1.9 Gm. (0.042 mole) of formamide was heated in an oil bath (125–130°) for four hours and stirred frequently.

[2] Acrylyl chloride was obtained from acrylic acid by the method of Rehberg, Dixon, and Fisher (9). Acrylic acid was prepared from α-chloropropionic acid by the procedure of Moureu, Murat, and Tampier (10).

[3] Prepared from indole by the method of Majima and Hoshino (12).

The product boiled at 195–205° (0.02 mm.); reported (13) b. p. 190–200° (0.04 mm.). The yield of viscous oil was 6.2 Gm. (86%).[4]

N-Methyltryptamine.—N-Formyltryptamine, 13.3 Gm., was reduced with 5.5 Gm. of lithium aluminum hydride by the procedure described above. The oily product crystallized from an ethereal solution which was cooled in a dry ice-acetone bath. The N-methyltryptamine melted at 85–87°; reported (14) m. p. 89–90°; yield, 10.5 Gm. (86%). The picrate, recrystallized from methanol-ethanol, melted at 186–188°; reported (14) m. p. 190–191°. The hydrochloride, recrystallized from alcohol-ether, melted at 175–176°; reported (15) m. p. 180°. The hydrobromide, recrystallized from alcohol-ether, melted at 156–158°.

Methyl Ester of N-Methyl-N-[β′-(3-indolyl)-ethyl]-β-alanine Hydrochloride (IIIa).—A mixture of 1.74 Gm. of N-methyltryptamine, 1.74 Gm. of methyl acrylate, and 30 cc. of benzene was allowed to remain at room temperature for twelve hours and then was refluxed for one hour. The benzene solution was cooled and an ethereal solution of hydrogen bromide was added dropwise, until no more precipitate formed. The liquid was decanted from the gummy precipitate and the latter was recrystallized from alcohol-ether. The product melted at 110–112°; yield, 2 Gm. (60%).

Anal.—Calcd. for $C_{16}H_{21}O_2N_2Br$: C, 52.78; H, 6.20; N, 8.21; Br, 23.4. Found: C, 52.81; H, 6.23; N, 8.33; Br, 23.6.

Diethylamide of N-Methyl-N-[β′-(3-indolyl)-ethyl]-β-alanine Oxalate (IIIc).—A solution of 1.74 Gm. of N-methyltryptamine, 2.54 Gm. of N,N-diethylacrylamide, and 6 drops of Triton "B" in 60 cc. of benzene was refluxed for eight hours. The solution was cooled and then was poured over a column of alumina (¾ in. x 23 in.) which had been previously moistened with benzene. The column was eluted with a 2% methanol-in-benzene solution. Ten-cubic centimeter portions were collected in tared beakers and then were evaporated to dryness. A graphic comparison of the cubic centimeters collected with the milligrams of residue produced a curve with two peaks. The first peak was found to represent the excess of starting material and the second peak to represent the product. Four of the residues, which were the bulk of the material represented by the second peak, were combined. An attempt to "distill evaporatively" the viscous syrup (0.5 to 1.0 mm.) by the use of a sublimation apparatus was unsuccessful. The hydrobromide could not be induced to crystallize. The syrup was dissolved in ether and treated with a 2% ethereal solution of oxalic acid. The acid oxalate was crystallized from absolute alcohol-ether and melted at 133–136°; yield, 1.5 Gm. (50%).

Anal.—Calcd. for $C_{20}H_{29}O_5N_3$: C, 61.36; H, 7.46; N, 10.73. Found: C, 61.22; H, 7.61; N, 10.48.

α-Benzyl-α-methylaminomethylmalonic Acid.—This compound was prepared by the general method of Mannich and Ganz (8). Both formaldehyde (37%) and methylamine (40%) were used in the form of aqueous solutions. As soon as the exothermic reaction subsided, the solid product precipitated. After several hours at room temperature the mixture was filtered; if a longer time elapsed the precipitated material became oily. The crude product melted at 125–130° (dec.); reported (8) m. p. 150° (dec.) for recrystallized material.

Ethyl Ester of N-Methyl-α-benzyl-β-alanine Hydrochloride (IVb).—The preceding compound was placed in a centrifuge tube and heated in an oil bath which was maintained at temperatures between 125 and 130°. The solid melted and was stirred occasionally with a glass rod. The evolved gases were basic. After fifteen minutes the viscous oil was cooled and dissolved in alcoholic hydrogen chloride. The solution was allowed to remain at room temperature for fifteen hours and was then concentrated to a syrup in a stream of air. The syrup was diluted with an equal volume of absolute alcohol, and two volumes of ether were added. Methylamine hydrochloride crystallized from the solution and was removed by centrifugation. The decanted solution was diluted to several times its volume with ether and was then refrigerated. An oily layer formed and crystals separated in the alcohol-ether layer; the mixture was decanted from the oil. The crystals were then separated from the liquid by centrifugation, and after they had been dried *in vacuo*, melted at 76–85°. A second crop of crystals was obtained in the same manner when the alcohol-ether solution was diluted with more ether and refrigerated; m. p. 73–82°. The combined crystalline material was recrystallized from absolute alcohol-ether; m. p. 109–111°.

Anal.—Calcd. for $C_{13}H_{20}O_2NCl$: C, 60.57; H, 7.82; N, 5.43; Cl, 13.75. Found: C, 60.62; H, 7.66; N, 5.69; Cl, 13.74.

Ethyl Ester of N-Methyl-α-(α′-naphthylmethyl)-β-alanine Hydrochloride (Vb).—Diethyl α-naphthylmethylmalonate (16) was hydrolyzed to the corresponding acid. The latter substance was then subjected to the above series of reactions. The product, recrystallized from alcohol-ether, melted at 168–170°.

Anal.—Calcd. for $C_{17}H_{22}O_2NCl$: C, 66.33; H, 7.20; N, 4.55. Found: C, 66.11; H, 7.34; N, 4.79.

[4] Schöpf and Steuer (13) reported that the distillate slowly solidified and melted at 76°.

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