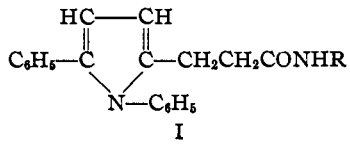
[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Propionamides and N-(Hydroxyalkyl)-substituted Propionamides which Contain the 2-(1,5-Diphenyl)-pyrryl or the 2-(1-Methyl-5-phenyl)-pyrryl Nucleus[1]

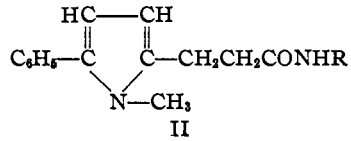
BY F. F. BLICKE, J. A. FAUST, R. J. WARZYNSKI AND J. E. GEARIEN

This paper deals with the preparation of two series of propionamides of the general types I and II.



I

R = H, $CH(CH_3)(CH_2OH)$, $CH(CH_2OH)_2$, $C(CH_3)(CH_2OH)_2$, $CH(C_2H_5)(CH_2OH)$



II

R = H, $CH(CH_3)(CH_2OH)$, $C(CH_3)(CH_2OH)_2$, $CH(C_2H_5)(CH_2OH)$

The unsubstituted amides (I and II, R = H) were obtained by conversion of the required propionic acid into the acid chloride, and interaction of the latter with ammonia.

In order to obtain the N-substituted amides, the methyl or ethyl ester of the propionic acid was heated with hydrazine hydrate to form the hydrazide, and the latter treated with nitrous acid to produce the acid azide which reacted with the necessary amino alcohol to yield the desired product.[2]

Originally it was planned to prepare compounds which did not contain a substituent in the 1 position of the pyrrole nucleus. However, when an intermediate such as β-[2-(5-phenyl)-pyrryl]-propionhydrazide was brought into contact with nitrous acid, a black tar was formed, and little or no azide could be isolated.[3] This difficulty in the preparation of the azide was entirely overcome by replacement of the 1 hydrogen by methyl or phenyl.

The hydrazides which we prepared, like certain other representatives,[4] are converted into the acetone condensation products merely by recrystallization from acetone.

The amides were prepared in order that they might be examined for oxytocic activity. The substituents attached to the amide nitrogen are identical with, or similar to, the N-hydroxyalkyl group in ergonovine but the cyclic structure is much simpler than that found in the alkaloid. In our products we have used a phenylpyrrole instead of an indole nucleus which is a characteristic part of the ergonovine molecule. It should be stated that no data seem to be available relative to the extent to which a phenylpyrrole is equivalent, pharmacologically, to indole. Pharmacological examination proved that the amides were inactive as oxytocics.

Experimental Part

β-[2-(1,5-Diphenyl)-pyrryl]-propionamide.—A suspension of 11.6 g. of β-[2-(1,5-diphenyl)-pyrryl]-propionic acid in 75 cc. of dry chloroform was stirred and maintained at 0–5° while 8.6 g. of phosphorus pentachloride was added in one portion. The red solution was stirred for two hours at room temperature, and the solvent then removed under reduced pressure at a temperature below 30°. The brown, crystalline residue, the acid chloride, was pulverized under 150 cc. of cold, concd. ammonia water. The cream-colored amide was filtered, washed with water and dried. The colored impurity was removed when the product was washed with a small amount of warm benzene. After recrystallization from dilute alcohol 9.5 g. (82%) of the acid amide was obtained; m. p. 158–159°.

Anal. Calcd. for $C_{19}H_{18}ON_2$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.76; H, 6.35; N, 9.46.

β-[2-(1,5-Diphenyl)-pyrryl]-propionhydrazide.—A mixture of 22.3 g. of ethyl β-[2-(1,5-diphenyl)-pyrryl]-propionate[5] and 16.5 g. of 85% aqueous hydrazine hydrate was refluxed for one hour, 10 cc. of absolute alcohol added, and then refluxed for three hours longer. When the solution was cooled, the crystalline hydrazide precipitated. It was washed with dilute alcohol; yield 20.7 g. (97%); m. p. 151–153°.

Anal. Calcd. for $C_{19}H_{19}ON_3$: C, 74.73; H, 6.27. Found: C, 75.14; H, 6.39.

The acetone condensation product, $C_{16}H_{12}NCH_2CH_2CONHNC(CH_3)_2$, was obtained when a small portion of the hydrazide was refluxed with acetone for ten minutes.[6] The product separated from the cold mixture; m. p. 143–144° after recrystallization from acetone.

Anal. Calcd. for $C_{22}H_{23}ON_3$: C, 76.49; H, 6.71. Found: C, 76.40; H, 6.86.

A mixture of the acetone condensation product and the hydrazide melted at 127–136°.

A substance which they stated was the hydrazide, and which melted at 142°, was described by Holdsworth and Lions.[7] Since their crude hydrazide was brought into contact with acetone in order to purify it, they must have iso-

(1) We wish to express our indebtedness to Parke, Davis and Company, Eli Lilly and Company and the Board of Governors of the Horace H. Rackham School of Graduate Studies for their joint support of this project.

(2) This series of reactions was used successfully by Stoll and Hofmann to prepare N-substituted amides of isolysergic acid (*Z. physiol. Chem.*, **250**, 7 (1937); **251**, 155 (1938); U. S. Patents 2,265,207 and 2,265,217).

(3) Robinson and Todd (*J. Chem. Soc.*, 1743 (1939)) had a similar experience. However, Fischer and co-workers have been able to obtain azides from hydrazides in which the 1 hydrogen of the pyrrole ring had not been replaced (*Z. physiol. Chem.*, **132**, 72 (1924); **257**, 61 (1939); **262**, 37 (1939); *Ann.*, **481**, 159 (1930); **512**, 195 (1934); **531**, 245 (1937); **540**, 30 (1939).

(4) Curtius and Ulmer, *J. prakt. Chem.*, **125**, 58, 69, 114, 116 (1930); Darapsky and Stauber, *ibid.*, **146**, 215 (1936); Fischer and Elhardt, *Z. physiol. Chem.*, **257**, 61 (1939)

(5) Blicke, Warzynski, Faust and Gearien, THIS JOURNAL, **66**, 1675 (1944).

(6) The reaction took place very rapidly.

(7) Holdsworth and Lions, *J. Proc. Roy. Soc. N. S. Wales*, **70**, 431 (1937).

lated the acetone condensation product instead of the hydrazide itself.

β-[2-(1,5-Diphenyl)-pyrryl]-propionazide.—A solution, prepared from 18.6 g. of the hydrazide, 360 cc. of acetic acid and 50 cc. of water, was placed in a liter 3-necked flask fitted with a stirrer and a thermometer, cooled to 0° with an ice–salt mixture, and maintained at that temperature. The solution was stirred and 4.2 g. of solid sodium nitrite was added slowly during the course of one-half hour. The azide began to precipitate after about one-half of the nitrite had been added. The mixture was stirred for fifteen minutes after complete addition of the nitrite, and then poured into three liters of cold water which was stirred during the addition. After some time the crystalline azide formed a layer on the surface of the liquid. Since the material filtered extremely slowly, it was found advisable to remove most of the liquid below the crystals, with the aid of a siphon, before filtration. The product was washed thoroughly with water. The crude, yellow azide (19 g.) was stirred with 250 cc. of ether, the mixture filtered, and the ether removed from the filtrate at room temperature under reduced pressure; yield 17.8 g. (92%).

2-(1-Hydroxy)-propylamide of β-[2-(1,5-Diphenyl)-pyrryl]-propionic Acid.—The azide, before it was used in this experiment, was dissolved in ether, and the solution was shaken with 2% sodium bicarbonate solution until the aqueous layer remained alkaline to litmus. The ether solution was shaken with water, dried with magnesium sulfate and the solvent removed at ordinary temperature under reduced pressure. For some reason we were unable to convert the azide into a crystalline amide unless the azide had been treated in the manner described.

A solution, prepared from 9.48 g. of the azide and 150 cc. of acetone, was cooled to 0°. A mixture of 4.5 g. of 2-aminopropanol (described below) and 25 cc. of water was cooled to 0° and then added to the solution of the azide. After three hours at 0° the mixture was allowed to remain at room temperature for twelve hours. The acetone was removed at room temperature under reduced pressure, and the semi-solid residue was washed with hot water to remove unchanged aminopropanol. The product solidified to a hard brown mass which was recrystallized twice from toluene. The pale yellow needles weighed 8 g. (76%); m. p. 142–143°.

Anal. Calcd. for $C_{22}H_{24}O_2N_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 75.98; H, 6.90; N, 7.94.

2-Aminopropanol.—2-Nitropropanol was prepared from 75.1 g. of pure nitroethane, 0.3 g. of calcium hydroxide, 80 g. of 40% aqueous formaldehyde and 75 cc. of alcohol according to the general procedure of Vanderbilt and Hass.[8] When the product was distilled, 48 g. (46%) of the propanol (b. p. 100–105° (13 ml.)) and 14.3 g. of 2-nitro-2-methyl-1,3-propanediol were[9] obtained; the latter remained as a crystalline residue in the distillation flask after distillation of the propanol. A fraction of the propanol which boiled at 85–86° (6 mm.)[10] was used for the next experiment.

In order to reduce the nitro compound, 14.2 g. of the latter, 100 cc. of 95% alcohol and Raney nickel catalyst were shaken and subjected to an initial hydrogen pressure of 2.5 atmospheres. The calculated amount of hydrogen was absorbed after four hours. After removal of the catalyst and solvent the amino alcohol boiled at 80–86° (20 mm.), and at 165–170° (740 mm.)[11]; yield 6.6 g. (65%).

2-(1,3-Dihydroxy)-propylamide of β-[2-(1,5-Diphenyl)-pyrryl]-propionic Acid.—To 9.48 g. of the azide, dissolved in 175 cc. of acetone and cooled to 0°, there was added 5.25 g. of 2-amino-1,3-propanediol (described below) which had been dissolved in 25 cc. of water and cooled to 0°. After the mixture had been kept at 0° for three hours, and at room temperature for twelve hours, it was filtered, the acetone removed from the filtrate, and the yellow residue washed several times with 50-cc. portions of hot water in order to remove the hydrazoic acid salt of the amino alcohol; yield 9 g. (82.5%). After recrystallization from xylene the pale yellow needles weighed 6.5 g. (59%); m. p. 151–152°.

Anal. Calcd. for $C_{22}H_{24}O_3N_2$: C, 72.50; H 6.64; N, 7.69. Found: C, 72.70; H, 6.75; N, 7.60.

2-Amino-1,3-propanediol.—To 30.5 g. of nitromethane, which had been dissolved in 470 cc. of absolute methyl alcohol and poured into a liter, 3-necked flask fitted with a condenser, there were added 51.0 g. of paraformaldehyde and 0.3 g. of potassium carbonate. The mixture was heated on a steam-bath until the formaldehyde had disappeared, and then for ten minutes longer. The solution of the triol, $NO_2C(CH_2OH)_3$, was cooled to 0°, the flask fitted with a stirrer and dropping funnel, and a solution of sodium methylate, which had been prepared from 14 g. of sodium and 245 cc. of absolute methyl alcohol, added dropwise during the course of one-half hour while the mixture was stirred and kept at 0°. The mixture was stirred for one-half hour longer at 0° and then maintained at that temperature for two hours. The precipitated sodium derivative of the diol, $NO_2CNa(CH_2OH)_2 \cdot 2CH_3OH$, was filtered and washed with cold methyl alcohol; yield 84 g. (81%).

A solution, prepared from 24.8 g. of salicylic acid and 400 cc. of ether, was refluxed and 41.4 g. of the sodium derivative added during the course of one-half hour. After the mixture had been refluxed for one and one-half hours, the precipitated sodium salicylate was removed and the solvent distilled under reduced pressure. The residue was cooled and the crystalline product pressed free from oil. The yield of 2-nitro-1,3-propanediol[12] was 12 g. (55%); m. p. 54–56°.[13]

When 4.8 g. of the nitro diol was reduced in the presence of oxalic acid[13] with the aid of a palladium-barium sulfate catalyst[14] under an initial hydrogen pressure of two and one-half atmospheres, the calculated amount of hydrogen was absorbed after five hours; the 2-amino-1,3-propanediol oxalate weighed 4.6 g. (85%); m. p. 197° (dec.).[15]

The free, oily amino diol was obtained from the salt by the addition of barium hydroxide.[13]

2-(1,3-Dihydroxy-2-methyl)-propylamide of β-[2-(1,5-Diphenyl)-pyrryl]-propionic Acid.—This amide was prepared in the same manner as the preceding one from 7.9 g. of the azide, dissolved in 150 cc. of acetone, and 5.3 g. of 2-amino-2-methyl-1,3-propanediol,[16] dissolved in 20 cc. of water. The crude, semi-solid amide was recrystallized twice from benzene; the colorless needles weighed 3.5 g. (37%); m. p. 132–133°.

Anal. Calcd. for $C_{23}H_{26}O_3N_2$: C, 72.99; H, 6.93; N, 7.40. Found: C, 72.87; H, 6.86; N, 7.32.

2-(1-Hydroxy)-butylamide of β-[2-(1,5-Diphenyl)-pyrryl]-propionic Acid.—A solution, prepared from 4.4 g. of the azide and 100 cc. of ether, was cooled to 0°; 1.4 g. of 2-amino-1-butanol,[16] dissolved in 10 cc. of ether and cooled to 0°, was added. After three hours at that temperature an oil had separated. After eight hours at room temperature the ether was removed, the oily residue washed with hot water, the material dissolved in alcohol, the solution treated with Norite, and the alcohol removed under reduced pressure. The amide was recrystallized three times from xylene; yield 25 g. (49%); m. p. 121–122°.

Anal. Calcd. for $C_{23}H_{26}O_3N_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 76.33; H, 7.10; N, 7.56.

β-[2-(1-Methyl-5-phenyl)-pyrryl]-propionamide.—(a) Prepared in the same manner as the 1-phenyl analog,

(8) Vanderbilt and Hass, *Ind. Eng. Chem.*, **32**, 34 (1940). We substituted alcohol for water in the general procedure.

(9) Henry, *Chem. Zentr.*, **68**, I, 741 (1897).

(10) The reported boiling point is 99° (10 mm.) (ref. 8).

(11) Karrer (*Helv. Chim. Acta*, **4**, 98 (1921)) found 173–176° (760 mm.).

(12) So far our procedure is a modification of that described by den Otter (*Rec. trav. chim.*, **57**, 13 (1938)); see also Gorski and Makarow, *Ber.*, **67**, 996 (1934).

(13) Schmidt and Wilkendorf (*ibid.*, **52**, 398 (1919)) found 56–58°.

(14) Houben, "Die Methoden der organischen Chemie," **2**, 270 (1922).

(15) Ref. 13, m. p. 202° (dec.).

(16) Purchased from Commercial Solvents Corporation.

there was obtained 9.5 g. (83%) of the amide from 11.45 g. of the required propionic acid,[5] 10.6 g. of phosphorus pentachloride, 75 cc. of chloroform and 150 cc. of ammonia water; m. p. 160–161° after recrystallization from benzene.

Anal. Calcd. for $C_{14}H_{16}ON_2$: C, 73.66; H, 7.07; N, 12.27. Found: C, 73.63; H, 7.08; N, 12.18.

(b) To 0.41 g. of the acid azide (described below), dissolved in 50 cc. of ether, there was added 25 cc. of concd. ammonia water. The mixture was stirred and allowed to remain at room temperature for ten hours in a beaker in order that part of the ether might evaporate slowly. The solid material was filtered, and washed with water; yield 0.37 g. (99%); m. p. 157–159°.

β-[2-(1-Methyl-5-phenyl)-pyrryl]-propionhydrazide.—A mixture of 23.3 g. of methyl β-[2-(1-methyl-5-phenyl)-pyrryl]-propionate,[5] 100 cc. of methyl alcohol and 22.6 g. of 85% aqueous hydrazine hydrate were refluxed for five hours, the mixture cooled, the colorless, crystalline precipitate filtered and washed with methyl alcohol; yield 19.7 g. (84%); m. p. 150–151°. The melting point was not changed after recrystallization from alcohol.

Anal. Calcd. for $C_{14}H_{17}ON_3$: C, 69.11; H, 7.04. Found: C, 68.95; H, 7.07.

The hydrazide is converted into the acetone condensation product, merely upon recrystallization from acetone; m. p. 133–134°. However, in order to obtain a pure sample for analysis, 1.2 g. of the hydrazide and 20 cc. of reagent acetone were refluxed for one hour, 10 cc. of alcohol added, and the mixture concentrated to a volume of 10 cc. The solution was cooled whereupon 1.2 g. (86%) of the product precipitated in the form of colorless needles; m. p. 133–134°.

Anal. Calcd. for $C_{17}H_{21}ON_3$: C, 72.05; H, 7.47. Found: C, 71.91; H, 7.52.

β-[2-(1-Methyl-5-phenyl)-pyrryl]-propionazide.—A solution of 24.3 g. of the hydrazide in 400 cc. of acetic acid and 100 cc. of water was placed in a 1000-cc., 3-necked flask, fitted with a stirrer and a thermometer, and cooled with an ice–salt mixture to about −5°. The solution was stirred and maintained at this temperature while 7.6 g. of solid sodium nitrite was added during a fifteen-minute period. The mixture was then stirred for fifteen minutes longer. During this time the azide began to separate in crystalline form. The material was poured into a four-liter beaker and enough water (about 3000 cc.) was added to completely precipitate the azide. The yellow product was filtered, washed with water and dried. The azide was mixed with 300 cc. of ether, filtered from insoluble material (3.8 g.), the filtrate shaken several times with 2% bicarbonate solution, then with water, dried with fused sodium sulfate, and the ether removed from the solution in a stream of air; yield 21.6 g. (85%).

2-(1-Hydroxy)-propylamide of β-[2-(1-Methyl-5-phenyl)-pyrryl]-propionic Acid.—To 12.7 g. of the azide, dissolved in 350 cc. of absolute ether and cooled to 0°, there was added 7.5 g. of 2-aminopropanol, dissolved in 100 cc. of the same solvent. The latter solution was not cooled because of the relative insolubility of the amino alcohol. The mixture became turbid immediately, and after one-half hour lemon-yellow crystals began to precipitate. After three hours at 0°, and twelve hours at room temperature, the precipitated material was heated with 75 cc. of water in order to dissolve the hydrazoic acid salt of the amino alcohol, the liquid decanted, and the process repeated. The amide (10.2 g.) was recrystallized twice from benzene; yield 8 g. (56%); m. p. 133–135°.

Anal. Calcd. for $C_{17}H_{22}O_2N_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.13; H, 7.72; N, 9.90.

2-(1,3-Dihydroxy-2-methyl)-propylamide of β-[2-(1-Methyl-5-phenyl)-pyrryl]-propionic Acid.—From 19.6 g. of the azide, dissolved in 200 cc. of acetone, and 16.2 g. of 2-amino-2-methyl-1,3-propanediol, dissolved in 40 cc. of water, there was obtained 19 g. (78%) of crude amide. The latter was recrystallized from 115 cc. of benzene, and then four times from 75 cc. of 30% alcohol. The colorless amide then weighed 9.3 g.; m. p. 125–127°.

Anal. Calcd. for $C_{18}H_{24}O_3N_2$: C, 68.33; H, 7.64; N, 8.86. Found: C, 68.19; H, 7.67; N, 8.83.

2-(1-Hydroxy)-butylamide of β-[2-(1-Methyl-5-phenyl)-pyrryl]-propionic Acid.—After 20.3 g. of the azide, dissolved in 500 cc. of absolute ether, and 14.2 g. of 2-aminobutanol, dissolved in 50 cc. of ether, had been treated in the described manner, the ether layer was decanted from the yellow, crystalline amide. The latter was triturated four times with 100-cc. portions of hot water, dried, boiled with 175 cc. of benzene for ten minutes, and filtered. The product (17.9 g.) was then recrystallized twice from 75 cc. of 66% alcohol, and four times from 95% alcohol. The colorless amide weighed 13.6 g.; m. p. 133–134°.

Anal. Calcd. for $C_{18}H_{24}O_2N_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 71.81; H, 8.08; N, 9.32.

Summary

The preparation of the amides and a variety of N-(hydroxyalkyl) substituted amides of β-[2-(1,5-diphenyl)-pyrryl]- and β-[2-(1-methyl-5-phenyl)-pyrryl]-propionic acid has been described.

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[CONTRIBUTION FROM THE LEDERLE LABORATORIES, INC.]

A New Synthesis of 2-Aminopyrimidine

BY ROBERT W. PRICE AND ANTHONY MOOS[1]

A few months after the announcement of sulfadiazine,[2] investigations in this Laboratory yielded a new method of synthesizing 2-aminopyrimidine, the N^1-moiety[3] of the sulfadiazine molecule.

β-Ethoxyacroleindiethylacetal,[4] prepared in two steps from acrolein dibromide, condensed readily with a guanidine salt in acid solution under varying conditions to yield the desired pyrimidine salt.

It is rather surprising in view of the ease of preparation and interesting properties of β-ethoxyacroleinacetal, that this substance has not been utilized more in chemical syntheses.

Experimental

α-Bromo-β-ethoxypropionaldehydediethylacetal was prepared from acrolein dibromide according to the method described by Fischer[5]; yield 54%, b. p. 104–107.5° (13 mm.), (recorded b. p. 103–104° (14 mm.)).

β-Ethoxyacroleindiethylacetal was obtained from the above acetal by treatment with alcoholic potassium hy-

(1) Present address: R. H. Macy & Co., Inc., Drug Dept., New York City, N. Y.

(2) R. O. Roblin, *et al.*, THIS JOURNAL, **62**, 2002 (1940).

(3) E. H. Northey, *Chem. Rev.*, **27**, 91 (1940).

(4) L. Claisen, *Ber.*, **36**, 3670 (1903).

(5) E. Fischer and G. Giebe, *ibid.*, **30**, 3056 (1897).