with Darco G-60, and finally recrystallized from water to yield 15.6 g. of product, m.p. 228–229°.

Anal. Calcd. for $C_9H_7N_3O_2$: C, 57.14; H, 3.73. Found: C, 57.01; H, 3.57.

5-(2-Pyridinemethyl)hydantoin. To a solution of 5 g. of 5-(2-pyridinemethylidine)hydantoin in 150 ml. of 95% alcohol was added 2 g. of palladium on charcoal, and the mixture was treated with hydrogen gas under about 3 atm. with continuous shaking for about 12 hr. The catalyst was recovered, and the filtrate was reduced to a small volume *in vacuo*. Upon cooling, crystals separated which were finally recrystallized from methanol-water to yield 3.9 g. of product, m.p. 171–172°.

Anal. Calcd. for $C_9H_9N_3O_2$: N, 22.00. Found: N, 21.91.

DL-*2-Pyridinealanine.* A mixture of 3.5 g. of 5-(2-pyridinemethyl)hydantoin, 10 g. of barium hydroxide, and 15 ml. of water was placed in a stainless steel beaker fitted with a reflux condenser, and heated over a steam cone until the evolution of ammonia ceased. The reaction mixture was filtered, the filter was washed several times with boiling water, and the combined filtrates were then cooled and treated with carbon dioxide. After filtration, the filtrate was finally adjusted to *p*H 4.5 with concentrated sulfuric acid to remove the remaining barium present, and the resulting solution was treated with Darco G-60, filtered, and the filtrate was reduced to a small volume *in vacuo*. Upon chilling, a precipitate formed which was recrystallized from alcohol-water to yield 1.3 g. of material, m.p. 209–210°. This product was chromatographically identical with material prepared by a previously reported procedure.[15]

AUSTIN, TEX.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF BUFFALO]

The Synthesis of Phthaloyltauryl Peptides[1]

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A number of phthaloyl peptide esters have been prepared by treatment of β-phthalimidoethanesulfonyl chloride with amino acid esters or dipeptide esters. These esters were converted to carboxylic acids by alkaline hydrolysis.

Although the occurrence of taurine in the body and its formation from cysteine has been recognized for some time, recent investigation had indicated that taurine may also be formed by unknown, pyridoxal independent, routes.[4] High concentrations of taurine have been reported in the supernatant fluid of Ehrlich Ascites tumors.[5] In an attempt to isolate a naturally occurring tumor inhibitor from Ehrlich Ascites tumor fluid, taurine was isolated.[6] Although taurine was void of inhibitory properties in mouse tumors and mammalian cell cultures, it was suggested that taurine may be a degradation product of the original inhibitor.[6]

In order to investigate a possible biological significance of the taurine moiety, some taurine derivatives were prepared. The present paper reports the synthesis of phthaloyltauryl peptides which may be considered as analogs of the corresponding carboxamido peptides. These are the first of a number of model compounds synthesized as potential antineoplastic agents. Preliminary results indicate some tumor inhibitory activity in Krebs 2 carcinoma for I and IV.[7,8]

The phthaloyltauryl peptides were prepared by treatment of amino acid esters or dipeptide esters with β-phthalimidoethanesulfonyl chloride (I) in the presence of triethylamine. The resulting products were then saponified with 1*N* sodium hydroxide at room temperature but attempted removal of the phthaloyl group by treatment with hydrazine and then hydrochloric acid under the conditions employed by Sheehan and Frank did not give tauryl peptides.[9] It was shown by the use of paper partition chromatography that the products of the reaction were taurine, phthalhydrazide and the constituent amino acids.

In order to substantiate the structures of the compounds prepared infrared spectra were obtained and neutralization equivalents determined when applicable. Absorptions typical of the phthaloyl group were found in all spectra and neutralization equivalents indicated that the acids were monocarboxylic.

I was first prepared by Miller *et al.*, by a rather circuitous route.[10] Phthalic anhydride was treated with ethanolamine, phosphorus pentachloride and then thiourea. Oxidation of the resulting inter-

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mediate with chlorine gave I. In the present work it was found that I could be more conveniently prepared by treatment of taurine with phthalic anhydride and then phosphorus pentachloride. It was not necessary to isolate the already characterized intermediate, phthalimidoethanesulfonic acid.[10]

EXPERIMENTAL

β-Phthalimidoethanesulfonyl chloride (I). A mixture of 25 g. (200 mmoles) of taurine and 30 g. (200 mmoles) of phthalic anhydride was fused and retained in the molten state for 2 hr. The mixture was then cooled and 21 g. (100 mmoles) phosphorus pentachloride added. This mixture was heated for 30 min. at approximately 120°. After cooling the brown solid was washed with 200 ml. of ice water and collected by filtration. Treatment with charcoal and recrystallization from a mixture of benzene and ligroin (b.p. 35–60°) yielded 22.8 g. (42%) of product, m.p. 158–161°. A second recrystallization gave a compound of m.p. 160–161°, (lit.[10] m.p. 157–158°).

Anal. Calcd. for $C_{10}H_8ClNO_4S$:[11] C, 43.88; H, 2.94; N, 5.12. Found: C, 43.99; H, 3.07; N, 5.38.

General method for the preparation of amino acid esters. Approximately 5.0 g. of the amino acid was dissolved or suspended in 200 ml. of absolute ethanol. To this solution or suspension was added anhydrous hydrogen chloride at a rate such that the temperature of the reaction mixture did not go above 40°. After 2 hr. the addition of hydrogen chloride was discontinued and the mixture allowed to stand at room temperature for at least 4 hr. The solvent and the hydrogen chloride were then removed. The yields of amino acid ester hydrochlorides were nearly quantitative.

Phthaloyltaurylglycine, ethyl ester[12] (II). Two grams (7.3 mmoles) of I in 50 ml. of dichloromethane was added slowly to a mixture of 1.0 g. (7.3 mmoles) of ethyl glycinate hydrochloride and 2.0 ml. (14.6 mmoles) of triethylamine in 50 ml. of dichloromethane. The mixture was then allowed to stand overnight at room temperature under anhydrous conditions. The mixture was refluxed for 3.5 hr. The solvent was evaporated, the resulting solid triturated with water and cooled near 0° before collection of the solid by filtration. The crude yield was 1.8 g. (72%), m.p. 115–120°. The sample for analysis was obtained after several recrystallizations from methanol, white needles, m.p. 121–122°.

Anal. Calcd. for $C_{14}H_{16}N_2O_6S$: C, 49.40; H, 4.74; N, 8.23. Found: C, 49.17; H, 4.50; N, 8.20.

Phthaloyltauryl-DL-alanine, ethyl ester[12] (III). With the method for II, 1.0 g. (7.3 mmoles) of the methyl ester of DL-alanine hydrochloride in 25 ml. of dichloromethane, 2.0 ml. (14.6 mmoles) of triethylamine, and 2.0 g. (7.3 mmoles) of I in 50 ml. of dichloromethane gave 2.4 g. (97%) of III, m.p. 138–141°. Several recrystallizations from 95% ethanol gave the sample for analysis, white needles, m.p. 143–144°.

Anal. Calcd. for $C_{14}H_{16}N_2O_6S$: C, 49.40; H, 4.74; N, 8.23. Found: C, 49.01; H, 4.65; N, 8.10.

Phthaloyltauryl-DL-alanyl-DL-methionine, ethyl ester (IV). Esterification of DL-alanyl-DL-methionine with ethanol and anhydrous hydrogen chloride gave an oil which was dried over phosphorus pentoxide under reduced pressure. The resulting material was a hygroscopic solid. Assuming that the yield of the ethyl ester of DL-alanyl-DL-methionine, hydrochloride was 6.5 g. (100%), 6.2 ml. (46 mmoles) of triethylamine in 200 ml. of dichloromethane was added. To this mixture 6.2 g. (23 mmoles) of I in 200 ml. of dichloromethane was added over a period of 1 hr. with continuous stirring. The temperature of the reaction mixture was maintained near room temperature by the slow rate of addition. After stirring for an additional 2 hr. and then standing overnight the solvent was removed by evaporation and the resulting oil triturated with cold water. After standing in the cold for several hours the material solidified. Filtration gave 10.2 g. (92%) of a white solid, m.p. 80–85°. Several recrystallizations from a mixture of ethyl acetate and cyclohexane gave the sample for analysis, m.p. 94–96°.

Anal. Calcd. for $C_{20}H_{27}N_3O_7S_2$: C, 49.47; H, 5.61; N, 8.65. Found: C, 49.18; H, 5.66; N, 8.20.

Phthaloyltaurylglycylglycine, ethyl ester[12] (V). With the method for II, 3.2 g. (12 mmoles) of I in 50 ml. dichloromethane, 2.0 g. (10 mmoles) of the ethyl ester of glycylglycine hydrochloride dissolved in 25 ml. of dichloromethane and 3.2 ml. (23 mmoles) of triethylamine, gave 3.6 g. (76%) of a yellow solid, m.p. 94–100°. Several recrystallizations from tetrahydrofuran gave the sample for analysis, m.p. 102–103°.

Anal. Calcd. for $C_{16}H_{19}N_3O_7S$: C, 48.38; H, 4.82; N, 10.60. Found: C, 48.61; H, 4.83; N, 10.40.

Phthaloyltauryl-DL-glutamic acid, diethyl ester (VI). With the method used for II, 2.0 g. (7.3 mmoles) of I in 25 ml. of dichloromethane, 1.7 g. (7.3 mmoles) of the diethyl ester of DL-glutamic acid hydrochloride and 2.0 ml. (14.6 mmoles) of triethylamine in 50 ml. of dichloromethane gave 3.1 g. (96%) of VI, m.p. 60–65°. Several recrystallizations from approximately 70% ethanol gave the sample for analysis, m.p. 75–77°.

Anal. Calcd. for $C_{19}H_{24}N_2O_8S$: C, 51.80; H, 5.49; N, 6.36. Found: C, 51.99; H, 5.45; N, 5.95.

Phthaloyltaurylglycyl-DL-methionine, ethyl ester (VII). With the method for II, 2.0 g. (7.3 mmoles) of I in 50 ml. of dichloromethane, a suspension of 1.9 g. (7.3 mmoles) of ethyl glycyl-DL-methionate, hydrochloride in 25 ml. of dichloromethane and 2.0 ml. (14.6 mmoles) of triethylamine gave 3.1 g. (90%) of VII, m.p. 112–115°. Recrystallization from 95% ethanol yielded white needles, m.p. 123–124°.

Anal. Calcd. for $C_{19}H_{25}N_3O_7S_2$: C, 48.39: H, 5.34; N, 8.91. Found: C, 48.83; H, 5.30; N, 8.05.

General method for the saponification of esters. The ester was added to a solution of sodium hydroxide and stirred until dissolved. The solution was allowed to stand overnight at room temperature, neutralized with 10% hydrochloric acid and evaporated to dryness at reduced pressure.

Phthaloyltaurylglycine (VIII). One gram (2.9 mmoles) of II was added to 20 ml. of 1.0*N* sodium hydroxide and the mixture treated as described in the general method. The residue was dissolved in a little water and treated with 2 g. of Dowex 50-X8 in the hydrogen form. Shortly after the addition of the resin the product started to precipitate. The solution was warmed until the product dissolved and then filtered. After cooling the filtrate to 0° the product was collected by filtration. The yield of white solid was 0.8 g. (88%), decomposition above 300°. The product was recrystallized from water.

Anal. Calcd. for $C_{12}H_{12}N_2O_6S$: N, 8.97. Found: N, 8.74.

Phthaloyltauryl-DL-alanine. One gram (2.9 mmoles) of III was added to 20 ml. of 1.0*N* sodium hydroxide and the mixture treated as described in the general method. The product was isolated in the same manner as VIII. After recrystallization from water the yield of white crystals was 0.8 g. (85%), decomposition above 300°.

Anal. Calcd. for $C_{13}H_{14}N_2O_6S$: N, 8.58. Found: N, 9.08.

Phthaloyltauryl-DL-alanyl-DL-methionine. Four grams (8.2 mmoles) of IV was added to 100 ml. of 1.0*N* sodium hydroxide and the mixture treated as described in the general method. The residue was treated with 20 ml. of 10% hydrochloric acid and cooled to 0°. After standing in the cold for several days and with occasional shaking a white solid precipitated. Filtration gave 2.0 g. (54%) of product, gradual decomposition above 300°. The product was recrystallized from an ethanol-water mixture.

Anal. Calcd. for $C_{18}H_{23}N_3O_7S_2$: N, 9.18. Found: N, 8.82.

(11) Microanalyses by Galbraith Laboratories, Knoxville, Tenn.

(12) After the present paper was submitted M. Frankel and P. Moses, *Tetrahedron* 9, 289 (1960) reported this compound.

Phthaloyltaurylglycylglycine. Four grams (7.8 mmoles) of V was added to 100 ml. of 1.0*N* sodium hydroxide and the mixture was treated as described in the general method. The residue was treated with 20 ml. of 10% hydrochloric acid and the mixture cooled to 0°. The precipitate which resulted was collected by filtration. The yield was 2.5 g. (86%), m.p. 274–275°. No change in melting point was observed after recrystallization from an ethanol-water mixture.

Anal. Calcd. for $C_{14}H_{15}N_3O_7S$: N, 11.37. Found: N, 11.01.

Phthaloyltauryl-L-glutamic acid. Two grams (4.5 mmoles) of VI was added to 100 ml. of 1.0*N* sodium hydroxide and the mixture treated as described in the general method. The residue was treated with 20 ml. of 10% hydrochloric acid and cooled to 0°. An oil separated which solidified on shaking. Filtration gave 1.1 g. (64%) of product, gradual decomposition above 300°. The product was recrystallized from water.

Anal. Calcd. for $C_{15}H_{16}N_2O_8S$: N, 7.29. Found: N, 7.72.

Phthaloyltaurylglycyl-DL-methionine. Five grams (11 mmoles) of VII was added to 100 ml. of 1.0*N* sodium hydroxide and the mixture treated as described in the general method. The residue was treated with 20 ml. of 10% hydrochloric acid and cooled to 0°. The white precipitate which formed was collected by filtration, yield 3.2 g. (65%), gradual decomposition above 300°. The product was recrystallized from an ethanol-water mixture.

Anal. Calcd. for $C_{17}H_{21}N_3O_7S_2$: N, 9.47. Found: N, 9.01.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, LEPETIT S.P.A.]

Bicyclic Homologs of Piperazine. Synthesis of 8-Methyl-3,8-diazabicyclooctanes. I

GIORGIO CIGNARELLA AND GIANGIACOMO NATHANSOHN

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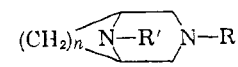
The synthesis of bicyclic homologs of piperazine belonging to the class of 8-methyl-3,8-diazabicyclo[3.2.1]octanes (VIII) is reported. The compounds are prepared by reduction with lithium aluminum hydride of the corresponding 3-substituted 8-carbobenzyloxy-3,8-diazabicyclo[3.2.1]octane-2,4-diones (VII) obtained from the still unknown pyrrolidine-2,5-dicarboxylic acid (III) through the *N*-carbobenzyloxy derivative IV. This was converted with acetic anhydride into the anhydride (V), which by reaction with ammonia or primary amines and subsequent cyclization with acetic anhydride gave the desired VIII.

In the last years several piperazine derivatives were found to possess interesting therapeutical properties. This is the case, for instance, of 1-diethylcarbamyl-4-methylpiperazine dihydrogen citrate (diethylcarbamazine) as antifungal agent,[1] *N*-methyl-*N'*-(4-chlorobenhydryl)piperazine dihydrochloride (chlorcyclizine) as antihistaminic agent,[2] piperazine citrate as an antihelmintic,[3] *N*-methyl-*N*-ethyl-*N'*-2-chlorobenzhydrylpiperazinium chloride as antiacetylcholinic agent,[4] and 1-(2'-cyclohexyl-2')hydroxy-2'-phenylethyl-4,4-dimethylpiperazinium methyl sulfate (hexocyclium methylsulfate) as gastric secretion inhibitor.[5]

In many instances an improvement in the activity of already known products was observed by introducing a piperazine ring in place of secondary aliphatic amino groups. *N*-(γ-[4-Hydroxyethyl-1-piperazinyl]-propyl)-3-chlorophenothiazine (chlorperphenazine) has recently been found to possess a more rapid effect than chlorpromazine.[6]

These results prompted us to consider a particular structure having the piperazine ring embodied in a condensed biheterocyclic system of general formula.



R, R' = H, alkyl etc.

Only two derivatives of this type are known in the literature, *i.e.* 9-methyl-3,9-diazabicyclo[3.3.1]nonane (n = 3, R = H, R' = CH_3) and 3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonane (n = 3, R = $CH_2C_6H_5$, R' = CH_3).[7] A closely related bicyclic system was described by Grogan and Rice[8] who prepared 3-azabicyclo[3.2.1]octanes in the course of an extensive work on 3-azabicycloalkanes[9]: However, the 3,8-diazabicyclo[3.2.1]octane (n = 2) ring is still undescribed. This structure seemed to us of particular interest when R' = CH_3, because of the structural analogy with the tropane

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