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THE SYNTHESIS OF POTENTIAL ANTIMALARIALS. THE PREPARATION OF METHYLATED AMIDES OF TAURINE AND THEIR PANTOYL DERIVATIVES[1]

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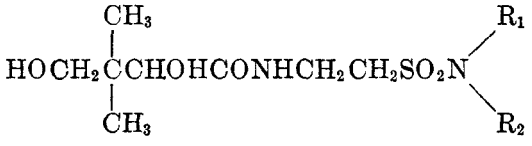
During an investigation of compounds related to pantoyltaurine as potential antimalarials, a number of derivatives of pantoyltaurylamide (I) were prepared (1). In each instance these compounds were characterized by a free acidic hydrogen on the sulfonamide nitrogen. In order to investigate the effect of this hydrogen on the antimalarial properties of the drugs, it was thought best to substitute for it the methyl group and to compare the activity of compounds possessing one, two, and no acidic hydrogens. For this purpose, the methylamide and the dimethylamide derivatives of taurine were prepared and condensed with pantolactone to give crude preparations of pantoyltaurine methylamide (II) and dimethylamide (III). The antimalarial activities of these latter compounds are comparable to that of pantoyltaurylamide (SN 3279) and are reported elsewhere.[3, 4]



I, $R_1 = R_2 = H$; II, $R_1 = H$, $R_2 = CH_3$; III, $R_1 = R_2 = CH_3$

In the preparation of the monomethyl amide, an interesting reaction was observed which lead to the elimination of two steps in the synthesis. In the reaction of methylamine with β-phthalimidoethanesulfonyl chloride, the methylamine not only replaced the chlorine of the acid chloride, but also removed the phthalyl group with the formation of N-methylphthalimide. Thus the usual hydrolysis with hydrazine hydrate and hydrochloric acid (2) was elimi-

[1] This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the California Institute of Technology.

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[3] The Survey number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activity will be tabulated in a monograph entitled "Antimalarial Drugs, 1941–1945", F. Y. Wiselogle, editor, in press.

[4] While this paper was in press, the authors learned by private communication that some of the compounds described had also been prepared by R. Winterbottom, J. W. Clapp, W. H. Miller, J. P. English, and R. O. Roblin, Jr.; *J. Am. Chem. Soc.*, in press. Footnote added to proof Feb. 25, 1947.

nated, and the desired taurine methylamide was obtained directly from the reaction mixture. This reaction is illustrated below:

$$C_6H_4(CO)_2{=}NCH_2CH_2SO_2Cl + 2\,CH_3NH_2 \rightarrow$$

$$C_6H_4(CO)_2{=}NCH_3 + NH_2CH_2CH_2SO_2NHCH_3$$

An instance in which methylamine unexpectedly acted in an analogous manner has been reported by Ristenpart (3), who, in an attempt to prepare β-phthalimidoethylmethylamine from β-phthalimidoethylbromide and methylamine, obtained N-methylphthalimide in 85% yield. The possibility of the use of methylamine as a general reagent for this type of reaction is being investigated further.

EXPERIMENTAL[5]

β-Phthalimido-N-dimethylethanesulfonamide. Fifty-four grams of β-phthalimidoethanesulfonyl chloride was dissolved in 600 ml. of warm benzene and dry dimethylamine was passed into the hot solution until the precipitation of dimethylamine hydrochloride was complete. The benzene solution was decanted and evaporated to dryness, and the residue was dried over sulfuric acid. The resulting oil solidified when treated with water and a little hydrochloric acid. The solid thus formed was filtered and dried to give 43 g. of product of m.p. 153–156°. A sample crystallized from water as long colorless needles, m.p. 154–156°.

Anal. Calc'd for $C_{12}H_{14}N_2O_4S$: C, 51.0; H, 5.0; N, 9.9.
Found: C, 51.0; H, 4.8; N, 9.6.

Taurine dimethylamide hydrochloride. Forty grams of the above prepared phthalyl compound was dissolved in 300 ml. of absolute ethanol and treated with 9 g. of hydrazine hydrate (2). By working up the reaction mixture in the usual manner (1, 4), there was obtained 20 g. of crystalline hydrochloride of m.p. 141–143°. A sample crystallized from isopropyl alcohol for analysis melted at 144–146°.

Anal. Calc'd for $C_4H_{13}ClN_2O_2S$: C, 25.5; H, 6.9.
Found: C, 25.9; H, 7.0.

Taurine dimethylamide. To 9.5 g. of the above prepared hydrochloride dissolved in a small amount of water was added the theoretical amount of sodium bicarbonate. The water was evaporated *in vacuo*, and the residue was dried thoroughly and extracted with a small amount of absolute ethanol. On evaporation of the solvent, there was obtained 6.9 g. of light green oil which did not solidify above 0°. For purification, it was distilled at 110–115°/50–60μ.

Anal. Calc'd for $C_4H_{12}N_2O_2S$: C, 31.6; H, 8.0.
Found: C, 31.6; H, 8.0.

(+)-Pantoyltaurine dimethylamide (II) (SN 7468).[3] A mixture of 5.4 g. of taurine dimethylamide and 4.8 g. of *l*-pantolactone was heated for two hours at 100°. The resulting liquid was cooled, washed thoroughly with ether, and dried under high vacuum to give 10 g. of a viscous oil which could not be induced to crystallize and could not be obtained pure enough to give reproducible analyses; $[\alpha]_D^{25}$ +19.2° (0.1206 g. in 5.00 ml. of water).

Taurine methylamide hydrochloride. Twenty-seven grams of β-phthalimidoethanesulfonyl chloride was dissolved in 250 ml. of hot benzene, and a rapid stream of dry methylamine was passed into the hot solution. After fifteen minutes, the cloudy solution was placed on the steam-bath, and the methylamine addition continued for one-half hour. The benzene solution was decanted from the gummy precipitate which had formed and the pre-

[5] All melting points have been corrected for exposed stem. The microanalyses reported have been carried out by Dr. Gertrude Oppenheimer and Mr. G. A. Swinehart.

cipitate was dried thoroughly to remove excess methylamine, dissolved in a little water, and treated with sodium bicarbonate. The basic solution was filtered and evaporated to dryness *in vacuo*. The residue was dissolved in hot ethanol, acidified with concentrated hydrochloric acid, and allowed to cool. The crystals which precipitated on cooling were filtered and dried to give 6.2 g. of product m.p. 166–169°, pure enough for the next reaction. On recrystallization from ethanol, it was obtained as colorless platelets, m.p. 169–170°.

Anal. Calc'd for $C_3H_{11}ClN_2O_2S$: C, 20.6; H, 6.4; N, 16.3.
Found: C, 21.0; H, 6.4; N, 16.3.

Taurine methylamide. The taurine methylamide hydrochloride obtained above was dissolved in a small amount of water, and the theoretical amount of sodium bicarbonate was added. The solution, after filtration, was evaporated to dryness, and the dried residue extracted with absolute ethanol. After evaporation of the solvent and thorough drying of the residue, an oily solid was obtained. This was purified by dissolving it in isopropyl alcohol, filtering the solution, and precipitating the product as a colorless crystalline solid, m.p. 69–70°, with petroleum ether (30–60°). A portion of the product was recrystallized from a mixture of isopropyl alcohol and isopropyl ether giving clusters of colorless needles, m.p. 71–72°.

Anal. Calc'd for $C_3H_{10}N_2O_2S$: C, 26.1; H, 7.3; N, 20.3.
Found: C, 26.0; H, 7.0; N, 20.3.

(+)-Pantoyltaurine methylamide (II) (SN 7469). The condensation with pantolactone was carried out as described above with 6.2 g. of the methylamide and 6.0 g. of *l*-pantolactone. The product was a viscous oil which could not be induced to crystallize and could not be obtained sufficiently pure to give reproducible analyses; $[\alpha]_D^{23}$ +17.0° (0.0294 g. in 2.00 g. water).

SUMMARY

The preparation is described of taurine methylamide and dimethylamide and their pantoyl derivatives.

The metathesis of β-phthalimido-N-methylethanesulfonamide by methylamine is discussed.

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