Anal. Calcd. for C_4H_9NS: C, 46.56; H, 8.79; N, 13.58; S, 31.07. Found: C, 46.82; H, 8.63; N, 13.64; S, 30.88.

Thiamorpholine hydrochloride prepared in isopropyl alcohol formed white needles which melted at 174–175°.

Anal. Calcd. for $C_4H_{10}ClNS$: C, 34.40; H, 7.22. Found: C, 34.18; H, 7.11.

Thiamorpholine picrate crystallized from ethanol as long yellow needles, m.p. 204–205°.

Anal. Calcd. for $C_{10}H_{12}N_4O_7S$: C, 36.14; H, 3.64. Found: C, 36.30; H, 3.56.

Thiamorpholine picrolonate formed dark yellow needles from ethanol, m.p. 246°.

Anal. Calcd. for $C_{14}H_{17}N_5O_5S$: C, 45.77; H, 4.67. Found: C, 46.05; H, 4.81.

Davies[2] gives the following constants for thiamorpholine and its derivatives: b.p. of base, 166–167° at 743 mm.; hydrochloride, m.p. 160–165°; picrate, m.p. 198°; picrolonate, m.p. 242°. Langlet[1] gives 165° as the boiling point of the base and 163° as the melting point of the hydrochloride. In every case these values are lower than those now reported.

Method B.—When 13.1 g. (0.1 mole) of 3,5-diketo-1,4-thiazane was reduced with 9.5 g. (0.25 mole) of lithium aluminum hydride in the same manner as described under method A, 4.4 g. (43%) of product, b.p. 173–177°, was obtained. This material, in contrast to that obtained earlier, had an unpleasant "mercaptan" odor. It was dissolved in 20 ml. of water and shaken with ether. The aqueous phase was separated and treated with 20 ml. of 25% sodium hydroxide solution. The oil which separated was extracted with ether, and the extract was dried over potassium carbonate. Distillation gave 2.2 g. (21%) of thiamorpholine, b.p. 174–175° at 758 mm.

4-Methylthiamorpholine.—A mixture of 3.8 g. of thiamorpholine, 3 cc. of 40% formalin and 1.9 g. of 98% formic acid was heated on a steam-bath for 1.5 hours after the initial vigorous reaction had subsided. About 4 ml. of concentrated hydrochloric acid was added, and the solution was evaporated to dryness. Treatment of the white solid with 10 ml. of 25% sodium hydroxide produced an oil which was distilled to give 3.1 g. (72%) of product, b.p. 164–165° at 751 mm., $n^{25}D$ 1.5068.

4-Methylthiamorpholine hydrochloride crystallized from isopropyl alcohol as stout colorless needles, m.p. 248–249°.

Anal. Calcd. for $C_5H_{12}ClNS$: C, 39.08; H, 7.87. Found: C, 39.32; H, 7.64.

Clarke prepared 4-methylthiamorpholine by the action of mustard gas on methylamine.[11] He reported that the base boiled at 163–164° at 757 mm., and the hydrochloride melted at 239°.

4,4-Dimethylthiamorpholinium Iodide.—When a solution of 2 g. of 4-methylthiamorpholine in 10 ml. of absolute ethanol was treated with 4 ml. of methyl iodide, a white crystalline precipitate formed which weighed 4.4 g. and melted at 297°, unchanged by recrystallization from ethanol.

Anal. Calcd. for $C_6H_{14}INS$: C, 27.81; H, 5.45. Found: C, 28.10; H, 5.18.

The same quaternary salt was obtained when an alcoholic solution of thiamorpholine and methyl iodide was allowed to stand 12 hours.

4-Ethylthiamorpholine Hydroiodide.—When a solution of 0.5 g. of thiamorpholine and 5 ml. of ethyl iodide in 10 ml. of ethanol stood for several days at room temperature no solid formed. The solution was concentrated on steam to a volume of 5 ml., and when cooled gave white needles, m.p. 140–141°.

Anal. Calcd. for $C_6H_{14}INS$: C, 27.81; H, 5.45. Found: C, 27.99; H, 5.45.

The identity of this compound was established by conversion to the *picrate*, m.p. 189–190°, reported[11] to melt at 185–186°.

Anal. Calcd. for $C_{12}H_{16}N_4O_7S$: N, 15.57. Found: N, 16.00.

4,4'-Carbonyldithiamorpholine.—A solution of 10.3 g. (0.1 mole) of thiamorpholine in 20 ml. of dry toluene was added with stirring to a solution of 5 g. (0.05 mole) of phosgene and 20 g. (0.25 mole) of pyridine in 250 ml. of anhydrous ether. The mixture was then stirred for 30 minutes and shaken three times with water. Evaporation of the ether solution and crystallization of the residue from isopropyl alcohol gave 5.5 g. (47%) of product. Upon recrystallization from aqueous methanol it formed white crystals, m.p. 143–144°.

Anal. Calcd. for $C_9H_{16}N_2OS_2$: C, 46.52; H, 6.94; N, 12.06. Found: C, 46.71; H, 6.89; N, 11.89.

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5-Ethyl-5-(β-phenylpropyl)-barbituric Acid from β-Chlorocumene

BY GLENN S. SKINNER AND DONALD L. KNAUSS

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We have prepared 5-ethyl-5-(β-phenylpropyl)-barbituric acid from β-chlorocumene through the intermediate diethyl ethyl-β-phenylpropylmalonate. The β-chlorocumene required was prepared by the action of dry chlorine on hot cumene in sunlight. It was shown to have the assigned structure by oxidation to benzoic acid and conversion through the Grignard reaction to β-phenylbutyramide.

β-Chlorocumene is relatively inert[1] in its reaction toward alkali or silver acetate. Under ordinary conditions of refluxing in benzene we found it to be inert also toward sodioethylmalonic ester, but reaction occurred after distilling enough benzene to permit a temperature of 140°.

Orally administered to rats this barbiturate produced no hypnosis, but convulsions and death at 400 mg./kg. Since it is ineffective, no resolution of the compound was attempted.

Experimental

β-Chlorocumene.—Cumene in lots of 350 cc. at gentle reflux in sunlight was subjected to the action of a rapid stream of dry chlorine until the temperature of the boiling liquid reached 190–195°. Fractional distillation of the combined product from several runs gave 656 g. of unchanged cumene, b.p. 45–50° (14 mm.); 80 g. of a mixture, b.p. 50–90° (14 mm.); 1259 g. of β-chlorocumene, b.p. 90–95° (14 mm.); 694 g. of products of undetermined constitution, b.p. 95–160° (14–3 mm.) and 62 g. of viscous residue. There was no evidence of decomposition during the distillation. β-Chlorocumene is reported[2] to boil at 95–100° (21 mm.) while α-chlorocumene is decomposed with the loss of hydrogen chloride when boiled under diminished pressure.

Characterization of β-Chlorocumene.—Oxidation with hot alkaline permanganate under reflux gave benzoic acid, showing that in our preparation the chlorine is located in the side chain. The Grignard reagent prepared from the chloro compound was treated with solid carbon dioxide and the resulting acid was converted through the acid chloride to β-phenylbutyramide, m.p. 104–105°, showing that the chlorine is in the beta position. Kohler and Reimer[3] give m.p. 105° for this amide which they prepared by an independent method.

Diethyl Ethyl-(β-phenylpropyl)-malonate.—Diethyl ethylmalonate (376 g., 2 moles) was added to a stirred and cooled suspension of 23 g. of powdered sodium in 600 cc. of dry benzene. When the reaction was complete 154.5 g. (1 mole) of the above β-chlorocumene was added at once with stirring. No precipitation of sodium chloride occurred, and very little at 90–95° in 15 hours. Benzene was then distilled through a column until the temperature of the

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residual liquid was favorable to reaction (140°) where it was maintained for seven hours. In working up the mixture in the usual way, 30 cc. (0.36 mole) of hydrochloric acid was required for neutralization, indicating that 36% of the sodioethylmalonate still had not reacted; yield 125.5 g. (41%), b.p. 140–145° (1 mm.).

Anal. Calcd. for $C_{18}H_{26}O_4$: C, 70.5; H, 8.6. Found: C, 70.2; H, 8.3.

5-Ethyl-5-(β-phenylpropyl)-barbituric Acid.—The above ester (26.0 g., 0.084 mole) and 9.2 g. (0.152 mole) of urea were refluxed six hours in a solution of sodium ethoxide prepared from 5.2 g. (0.228 mole) of sodium and 100 cc. of absolute alcohol. The yield of crude acid was 18.0 g. (79%). The pure acid (13.5 g.) was obtained by crystallization from 50 cc. of toluene; m.p. 155–156°.

Anal. Calcd. for $C_{15}H_{18}O_3N_2$: N, 10.2. Found: N, 9.9.

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Lactam of N-(β-Aminoethyl)-chelidamic Acid—A Pyridopiperazine Ring[1]

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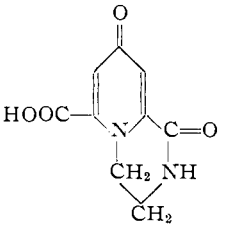
Chelidamic acid is a tridentate molecule which has proved to be an excellent metal-inactivating agent for vegetable oil systems.[2] Because chelidamic acid is easily prepared from chelidonic acid and ammonia,[3] it was thought that chelidonic acid and ethylenediamine might give 1,1′-ethylene-bis-[2,6-dicarboxy-4-pyridone]. This compound would be sexadentate and would be expected to have unusual metal-chelating properties.

Campbell and his co-workers have prepared γ-pyridones simply by the addition of an aqueous solution of the γ-pyrone to an aqueous solution of the amine.[4] Previously, Armit and Nolan had prepared this type of compound in alcohol solution.[5] Freeman, Ringk and Spoerri also used alcoholic solutions for the preparation of N-aralkyl derivatives of 4-pyridone and chelidamic acid.[6] Prior to this, N-substituted chelidamic acids were prepared by the method of Haitinger and Lieben.[7]

It was found that the addition of ethylenediamine to a hot ethanol solution of chelidonic acid gave an insoluble salt. This compound appears to be the salt of equimolar amounts of chelidonic acid and ethylenediamine. When an aqueous solution is treated with hydrochloric acid, an insoluble precipitate settles out which analysis indicates to be compound I. This lactam is bidentate and shows only slight metal-inactivating properties compared with chelidamic acid.[8]



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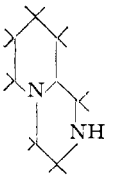

II

This lactam I or the basic ring system II to which it belongs has not been reported. Based on the aromatic system, compound I might be named as a pyridopiperazine derivative, but a simpler name would be the lactam of N-(β-aminoethyl)-chelidamic acid. Using the azabicycloalkane system, compound II is named 1,4-diazabicyclo(4.4.0)decane.

Experimental

Ethylenediamine Chelidonic Acid Salt.—Seven grams of ethylenediamine (95%) was added dropwise to a refluxing ethanol solution containing 7.0 g. of chelidonic acid. Upon addition of the first drop of ethylenediamine, a precipitate settled out, and this insoluble compound continued to form as more and more ethylenediamine was put in. The solution was refluxed for 2 hours after the addition of the ethylenediamine. It was then cooled, and the insoluble product was filtered off. Recrystallization from water produced large colorless needles. These needles were filtered off and then dried over phosphorus pentoxide in a vacuum desiccator. The yield was approximately 4.0 g., m.p. 239–240° (dec.). The salt was neutral to *p*H indicator paper, and was hygroscopic. Additional quantities of the salt were obtained by concentrating the filtrates. Analysis showed the compound to have the composition of equimolar amounts of chelidonic acid and ethylenediamine.

Anal. Calcd. for $C_9H_{12}O_6N_2$: C, 44.3; H, 4.92; N, 11.5. Found: C, 44.2; H, 4.92; N, 11.7.

Lactam of N-(β-Aminoethyl)-chelidamic Acid.—When a saturated aqueous solution of the ethylenediamine salt of chelidonic acid was treated with dilute hydrochloric acid, an insoluble precipitate settled out. This precipitate was filtered and washed with ice-water. It was dried over phosphorus pentoxide in a vacuum desiccator. This compound did not melt below 300°. It was acid to *p*H paper and had a neutral equivalent of 208 (theory 208). The ultraviolet absorption spectrum of a 0.00012 *M* solution of this compound in 0.01 *N* sodium hydroxide showed a peak at 232 mμ with ε 19000 and a shallow peak at 272 mμ with ε 7700. These data were found to be consistent with the spectra of closely related substances.[3,9,10]

The infrared spectrum was determined using powdered potassium bromide and sample in a pressed disk[11] with a Perkin–Elmer, Model 21, Infrared Spectrograph and is given in Fig. 1. It is to be observed that there is a single sharp band at 3.09 μ which is evidence of the presence of a substituted amide.[12] No doublet was observed in this region which might indicate the primary amine group. Peaks were observed at 5.84 and 5.90 μ which could indicate the presence of the carbonyl and amide groups, respectively. A peak at 6.12 μ might be attributed to the presence of a zwitterion.[13] Before complete confirmation could be obtained through infrared investigations, it would be necessary to compare spectra of a number of known and new compounds of similar structure.

Anal. Calcd. for $C_9H_8O_4N_2$: C, 51.9; H, 3.85; N, 13.5. Found: C, 51.1; H, 3.93; N, 13.4.

The *p*-bromophenacyl derivative crystallized with 2 molecules of water and melted at 172–174° with charring.

(1) From one of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Service, U. S. Department of Agriculture. Article not copyrighted. This paper is based on some work submitted by A. W. Schwab in partial fulfillment of the requirements for the Ph.D. Degree at Bradley University, Peoria, Illinois.

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