[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE RICE INSTITUTE]

Imidazole Derivatives of Barbituric Acid

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Following the discovery of Fisher and Mehring in 1903 that 5,5-diethyl-barbituric acid was an excellent hypnotic, chemical and medicinal interest in the barbituric acid derivatives has become very great.

The known derivatives of barbituric acid are, in general, the aliphatic and aromatic substituted compounds. The heterocyclic derivatives of barbituric acid have not received the chemical attention that they deserve. The purpose of this investigation was to prepare several heterocyclic derivatives of barbituric acid. Among the possibilities in this field, imidazole derivatives were considered to be of outstanding interest. This was suggested by the known physiological importance of simple imidazole compounds such as histidine, histamine, pilocarpine, etc.

The method of preparation was to condense 4(or 5)-chloromethylimidazole with monoalkylated malonic esters and subsequently to condense these compounds with urea. In this manner 5-*n*-butyl-5-[4(or 5)-imidazolemethyl]-barbituric acid and 5-isoamyl-5-[4(or 5)-imidazolemethyl]-barbituric acid were prepared. The 4(or 5)-chloromethylimidazole was prepared by the method of Pyman[1] with some modifications suggested by Koessler and Hanke.[2]

Experimental Part

Acetone Dicarboxylic Acid.—This material was prepared according to the directions given in "Organic Syntheses" (Vol. V, p. 5) except that the excess sulfuric acid was not removed as this was one of the reagents in the following synthesis.

Diisonitrosoacetone.—The crude material obtained above was converted into diisonitrosoacetone by means of the reaction described by Pechmann.[3]

Diaminoacetone Chlorostannite.—This material was prepared by the reduction of diisonitrosoacetone according to the method described by Kalischer.[4]

Diaminoacetone Hydrochloride.—The diaminoacetone chlorostannite was decomposed by means of hydrogen sulfide in the manner described by Koessler and Hanke.[2] Frequently in this treatment a colloidal suspension of the tin sulfide is obtained; if this occurs, dilution with distilled water will cause the sol to coagulate.

2-Thiol-4(or 5)-aminomethylimidazole Hydrochloride.—The diaminoacetone hydrochloride was condensed with sodium thiocyanate in the manner described by Pyman.[1]

4(or 5)-Hydroxymethylimidazole Picrate.—Following the method of Pyman this compound was prepared by the oxidation of 2-thiol-4-aminomethylimidazole hydrochloride and subsequent treatment of the material with picric acid. In this connection it was noted that a sodium-free picrate could be conveniently obtained by omitting the neutralization with dry sodium carbonate as recommended by Koessler and Hanke. This is made possible by the relative insolubility of the picrate in water.

(1) Pyman, *J. Chem. Soc.*, **99**, 668 (1911).
(2) Koessler and Hanke, THIS JOURNAL, **40**, 1717 (1918).
(3) Pechmann, *Ber.*, **19**, 2465 (1886).
(4) Kalischer, *ibid.*, **28**, 1519 (1895).

4(or 5)-Hydroxymethylimidazole Hydrochloride.—The above picrate was decomposed by hydrochloric acid and the picric acid extracted with benzene.

4(or 5)-Chloromethylimidazole Hydrochloride.—This material was prepared by the action of phosphorus pentachloride on the above alcohol according to the directions of Pyman.

Condensation of 4(or 5)-Chloromethylimidazole with Ethyl *n*-Butylmalonic Ester.—The apparatus was dried by a stream of dry air heated to 150°. After cooling to room temperature 200 cc. of a special grade of absolute alcohol was distilled into the reaction flask and 4.6 g. of clean sodium dissolved in it. The *n*-butylmalonic ester was added, and the excess alcohol removed by distillation; 15 g. of the chloromethylimidazole hydrochloride dissolved in alcohol was then added over a period of several hours. The solution was then refluxed for two hours and the alcohol distilled off *in vacuo*. The material was transferred to a separatory funnel and treated with 150 cc. of approximately 5% hydrochloric acid and extracted with ether several times. The aqueous solution was then made alkaline with sodium carbonate and extracted with ether. The ether solution was dried over anhydrous sodium sulfate, and the ether removed *in vacuo;* a glassy solid was obtained which weighed 16.3 g. (55.9%). Better yields can be obtained by carrying the reaction out at lower temperatures and for shorter times.

5-*n*-Butyl-5[4(or 5)-imidazolemethyl]-barbituric Acid.—Ninety cc. absolute alcohol was placed in a Pyrex tube closed at one end and 3.8 g. of sodium was dissolved in it; 4.86 g. of urea and 16 g. of the substituted malonic ester were then added, and the tube sealed off and heated for twenty-two hours with steam. It is essential that the substituted malonic ester be thoroughly dried over phosphorus pentoxide before use. At the end of this period the tube was opened and the contents were evaporated to near dryness and then dissolved in 80 cc. of water. The solution was extracted twice with ether to recover the unchanged malonic ester, and then very carefully treated with dilute acetic acid. At first considerable tar separated which was immediately removed; a fine crystalline material gradually separated from the filtrate on standing overnight. This material was treated with norite and recrystallized from dilute alcohol, giving snowwhite crystals of indefinite melting point. The material decomposed around 290°, and no true melting point was obtained.

Anal. Calcd. for $C_{12}H_{16}O_3N_4$: N, 21.21. Found: N, 21.72.

4(or 5)-Imidazolemethyl-isoamylmalonic Ester.—The reaction was carried out in a similar fashion to that for the preparation of the corresponding butyl compound. It differed, however, in the following details. The chloride in 120 cc. of alcohol was added over a period of two hours and the temperature during the addition was 95°. The materials were refluxed for one-half hour after the addition. The mixture was worked up as was the *n*-butylmethylimidazole malonic ester, the yield being 52.3%.

5-Isoamyl-5-[4(or 5)-imidazolemethyl]-barbituric Acid.—The condensation with urea was essentially the same as that described for the preparation of the *n*-butyl derivative. The tube was heated for ten hours, and the product obtained in the manner outlined above. Like the lower homolog, the material showed no tendency to melt but decomposed with considerable charring.

Anal. Calcd. for $C_{13}H_{18}O_3N_4$: N, 20.15. Found: N, 20.32.

An attempt to prepare the corresponding allyl compound met with little success.

Summary

The synthesis of substituted barbituric acid derivatives in which one of the groups in the 5-position is a methylimidazole residue is described.

HOUSTON, TEXAS RECEIVED AUGUST 22, 1933
PUBLISHED MARCH 7, 1933