Summary

1. The reaction between acetamide and alkyl bromides, showing its general applicability to the synthesis of substituted acetamides and the corresponding amines, has been investigated.

2. A possible mechanism for the reaction, accounting for the production of ammonium bromide, has been suggested.

HOUSTON, TEXAS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF SASKATCHEWAN]

STUDIES IN URETHANS
I. MONO- AND DICARBETHOXY-GUANIDINES: DICARBETHOXY-ETHYL-ISO-UREA

BY S. BASTERFIELD AND L. EVELYN PAYNTER

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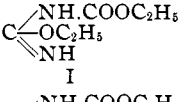
During a study of the pharmacological properties of some iso-urea derivatives, it was found by one of us[1] that carbethoxy-ethyl-iso-urea had well-marked physiological action, the chief effects being a mild central depression, a rapid and considerable fall of body temperature, and an increased muscle tonus. The muscular hypertonus suggested an action similar to that of guanidine which is known to stimulate the myo-neural receptors.[2]

It was decided for the purpose of a comparative study to prepare the mono- and dicarbethoxy-guanidines (guanidine mono- and di-formic esters) and examine their pharmacological properties. At the same time it was thought desirable to prepare the dicarbethoxy-ethyl-iso-urea, to determine the effect of introducing a second carbethoxy group into the iso-urea molecule. The compounds may be regarded as urethans, and the study of them is therefore included in a series of studies being carried on in this Laboratory on the chemistry and pharmacology of some mono- and diurethans. Formulas I and II show the structures of the iso-urea derivatives and III and IV the structures of the carbethoxy-guanidines.



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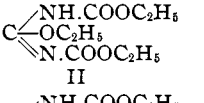

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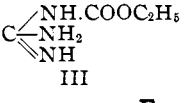

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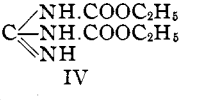

IV

Experimental Part

Dicarbethoxy-guanidine was first prepared by Nencki[3] by the action of ethyl chlorocarbonate on an alcohol solution of guanidine. The mono-

[1] Basterfield, *J. Pharmacol.*, **20**, 451 (1923).

[2] Camis, *J. Physiol.*, **39**, 73 (1909).

[3] Nencki, *Ber.*, **7**, 1588 (1874).

carbethoxy-guanidine was obtained by the action of alcoholic ammonia upon the di compound, the equation for the reaction as given by Nencki being $2HN:C(NHCOOC_2H_5)_2 + 2\ NH_3 = 2\ NH_2.COOC_2H_5 + C_8N_6H_{18}O_4$. It will be noted that a urethan group is split off the dicarbethoxy compound, and also that Nencki uses a double formula for the mono-compound. The production of urethan in this reaction suggested, in part, a study of the decomposition of di-urethans by ammonia and amines, the result of which is reported in another paper.

An alcoholic solution of guanidine (3 molecular proportions) prepared according to Morrel and Bellars[4] was treated with ethylchlorocarbonate (2 molecular proportions) the mixture being cooled and shaken. Fine, white needles were precipitated, which after being recrystallized from alcohol melted at 165° (Nencki gives 162°).

Anal. Calcd. for $C_7H_{13}N_3O_4$: N, 20.68. Found: 20.44.

The yield was 30% calculated on the basis that only one-third of the total guanidine is available for conversion into the ester. Nencki does not state the yield he obtained.

An investigation of the filtrate from the reaction mixture showed that in addition to guanidine hydrochloride, considerable carbonyl-diurethan was present. This must have been formed by hydrolysis of dicarbethoxy-guanidine, and would account for the poor yield of the latter. There is always some water in the alcoholic solution of guanidine, and the hydrogen chloride produced in the reaction would catalyze the hydrolysis. That guanidine itself is not first hydrolyzed to urea is proved by the fact that urea does not react with ethyl chlorocarbonate to give carbonyl-diurethan, but allophanic ester, and neither urea nor allophanic ester was found in the reaction mixture.

Attempts were made to obtain a reaction between ethyl chlorocarbonate and guanidine in the presence of a strong base, contained in a second liquid phase, so that all the guanidine might be available for conversion into the dicarbethoxy compound. The limited solubility of guanidine in solvents other than water and alcohol has so far prevented any successful scheme being devised.

A better method for the preparation of dicarbethoxy-guanidine is by the action of cold alcoholic ammonia on dicarbethoxy-ethyl-iso-urea.[5] A yield of 60% was readily obtained.

Monocarbethoxy-guanidine, $NH_2.C(:NH).NHCOOC_2H_5$.—This was prepared according to the method of Nencki[3] by heating the dicarbethoxy compound with alcoholic ammonia in a pressure bottle at 100° for five hours. The liquid was evaporated and the residue separated by crystallization from alcohol into carbethoxy-guanidine and urethan. The former compound after being dried in the air melted at 99°. After being dried over sulfuric acid in a vacuum it melted at 120°. The melting point changed again to 99° after the crystals had been exposed to the air for a time. The substance of lower melting point is undoubtedly a hydrate. Nencki gives 98° and 114° as the melting points of the two compounds. The yield was 80%.

Anal. Calcd. for $(C_4N_3H_9O_2)_2.H_2O$: N, 29.98. Found: 29.92.

Dicarbethoxy-ethyl-iso-urea, (ethoxy-carbonyl-diurethan), $C_2H_5OOC.N:C(OC_2H_5).NHCOOC_2H_5$, was prepared by the method of Dains from the silver salt of carbonyl-diurethan and ethyl iodide. Carbonyl-diurethan was obtained by the action of phosgene on urethan in a benzene-pyridine solution as described by the same investigator.[5]

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[4] Morrel and Bellars, *J. Chem. Soc.*, **91**, 1011 (1907).

[5] Dains, THIS JOURNAL, **21**, 186 (1899).

The reaction mixture separates into a red oil and a benzene-pyridine layer which contains generally rather more than half of the total product. The red oil may be extracted repeatedly with hot benzene or better simply treated with cold water. The carbonyl-diurethan, which is not very soluble in cold water, is precipitated to a great extent, while pyridine hydrochloride remains in solution. Invariably we found that when the oil was treated with water and the whole cooled in a freezing mixture as suggested by Dains, a mixture of the two compounds separated. Yields as high as 85% were obtained in our later preparations.

In the preparation of the silver salt of carbonyl-diurethan according to the method of Folin[6] it was found that the addition of 1 or 2% of potassium nitrate to the solution of carbonyl-diurethan in alkali accelerated the coagulation of the gelatinous silver compound, so that the precipitate could be rapidly filtered, washed and dried.

The conversion of the silver salt to the ethoxy compound was accomplished most effectively by refluxing a suspension of the salt in dry benzene with ethyl iodide on a water-bath for 28 hours. The solid was removed by filtration and the benzene distilled. The ethoxy compound was obtained as an oil of sweetish odor. It was purified as described by Dains;[5] yield, 83%. The yield was not increased by longer heating, but seemed rather to be diminished. Refluxing in dry ether or standing at room temperature in dry ether for lengthy periods failed to give such good results as were obtained by heating in benzene. The age of the silver salt seemed to be of some importance. Better yields were always obtained with the freshly prepared salt.

Attempts to purify the ethoxy compound by distillation in a vacuum were unsuccessful. At a pressure of 8 mm. most of the oil distilled between 140° and 150°, but no steady boiling point was observed. The distillate was colorless but had a rather unpleasant odor suggesting decomposition. Analysis for nitrogen gave 11.38 and 11.29% as compared with the calculated value 12.07%.

Pharmacological Properties

Preliminary experiments on rabbits were made with the compounds described above.

Monocarbethoxy-guanidine (0.6 g. in aqueous solution) was given by slow intravenous injection to a rabbit weighing 2.8 kg. A mild central depression was produced with a distinct muscular hypertonus. Respiration was rapid and shallow. The rectal temperature fell nearly 3° in one hour. The total effect resembled very closely that of monocarbethoxy-ethyl-iso-urea referred to in the introduction to this paper.

Dicarbethoxy-guanidine was found to be relatively inert though given in doses as large as 0.8 g. to a rabbit weighing only 1.3 kg. There was a fall of temperature of nearly a degree in one and a quarter hours, but this may have little significance in the rabbit.

Dicarbethoxy-ethyl-iso-urea given in doses of 0.35 g. per kilogram by subcutaneous injection was observed to have a powerful physiological action. Drowsiness and incoördination were apparent within five minutes after administration. In 20 minutes, there was deep depression with *complete muscular relaxation.* All reflexes were sluggish. In two hours there were signs of recovery, though after a lapse of five hours, there were still considerable drowsiness and incoördination.

[6] Folin, *Am. Chem. J.*, **19**, 350 (1897).

The rectal temperature fell rapidly during the first two hours, in one animal as much as 4.2° without the production of shivering or rigor.

All animals treated were fully recovered in 24 hours and showed no harmful after-effects.

In comparison with monocarbethoxy-ethyl-iso-urea the dicarbethoxy derivative shows more rapid and intense central depressant action and greater effect on body temperature. There is, however, a complete disappearance of muscular hypertonus with this compound.

Studies in oxygen consumption on animals treated with the iso-urea derivatives indicate that the fall of temperature must be due mainly to increased heat loss. This effect is similar to the antipyresis induced by acetanilide and allied compounds of the aromatic series.

Summary

A study of the methods of preparation of mono- and dicarbethoxy-guanidines, and of dicarbethoxy-ethyl-iso-urea, has been made and some modifications of existing methods have been introduced.

Preliminary observations on the pharmacological properties of these compounds are recorded.

SASKATOON, CANADA

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

PIPERIDINE DERIVATIVES. II. 1-ALKYL-3-CARBETHOXY-4-PIPERIDYL BENZOATES

BY S. M. MCELVAIN

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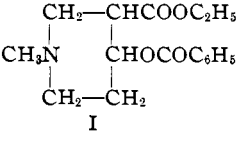
In an earlier paper[1] the preparation of a piperidine derivative (I) with essentially the same structure as the piperidine portion of the cocaine molecule was described. It was compared as to physiological action with the compound (II) which has the same characteristic groups but an open-chain structure.



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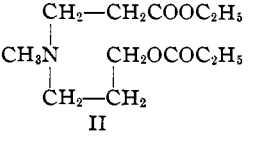

II

Inasmuch as the piperidine derivative possessed considerable physiological activity and the open-chain compound showed practically none, it appeared that a more detailed study of substances of Type I might bring to light some relationship between chemical constitution and physiological action.

[1] McElvain, THIS JOURNAL, **46**, 1721 (1924).