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

STUDIES IN URETHANS. III. THE PREPARATION OF VARIOUS SUBSTITUTED URETHANS

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As part of a study of the chemistry and pharmacology of urethans, a number of substituted urethans have been prepared in this Laboratory, and it seemed desirable to record those that have not previously been described in the literature, and to describe improved or modified methods of preparation for some that have been reported already.

These compounds have been prepared (1) by treating a solution of an amine in ether or benzene with the required amount of alkyl chlorocarbonate in the presence of an aqueous solution of sodium or potassium hydroxide, or (2) by heating together an amino compound and an alkyl chlorocarbonate with or without a solvent, or (3) by heating together a urethan with an acid chloride with or without a solvent.

Preliminary observations on the pharmacological properties of some of these compounds are included in this paper but detailed studies will be reported elsewhere.

Experimental Part

Acetylphenylurethan, $CH_3CO.N(C_6H_5).COOC_2H_5$.—This has been prepared by Sanders[1] and Nijk,[2] both of whom acetylated phenylurethan with a mixture of acetyl chloride and acetic anhydride. The second named worker also obtained it by the action of ethyl chlorocarbonate on the sodium salt of acetanilide.

In the present study an attempt was made to acetylate phenylurethan in ether solution by the action of acetyl chloride in the presence of aqueous alkali, but without success. The acetylation as carried out by Sanders and Nijk gave the most satisfactory results. The urethan was obtained as a colorless oil boiling at 142° at 10 mm. pressure; yield, 85–90%.

Anal. Calcd. for $C_{11}H_{13}NO_3$: N, 6.77. Found: 6.91.

The oil was quite viscous when first obtained, but after standing some months in a sealed tube it became considerably more mobile.

For a comparative pharmacological study two isomers of this urethan were prepared, namely, phenylacetylurethan and *p*-acetylphenylurethan.

Phenylacetylurethan, $C_6H_5CH_2.CO.NHCOOC_2H_5$.—This was obtained by heating equimolecular proportions of urethan and phenylacetyl chloride together under a reflux condenser at 60–70° until hydrogen chloride ceased to be evolved. This took several days, as the mixture became solid and had to be broken up frequently. Better results were obtained

[1] Sanders, THIS JOURNAL, **22,** 378 (1900).

[2] Nijk, *Rec. trav. chim.*, **39,** 699 (1920).

by heating the urethan and acid chloride in boiling benzene; the reaction was complete in 16 to 24 hours. The product was recrystallized from hot alcohol or ligroin (b. p., 60–90°) and formed soft, white needles; m. p., 113°; yield, 70%.

Anal. Calcd. for $C_{11}H_{13}NO_3$: N, 6.77. Found: 6.61, 6.76.

p-Acetylphenylurethan, $CH_3CO.C_6H_4.NHCOOC_2H_5$ (p-carbethoxy-amino-acetophenone) is reported by Nijk[2] to be produced when p-amino-acetophenone and potassium hydroxide are dissolved in hot alcohol, treated with ethyl chlorocarbonate dissolved in ether, and the mixture refluxed for an hour. Several attempts to obtain the urethan by this method failed. Most of the product obtained was alkali carbonate, a result that might be expected under the conditions described, since the p-amino-acetophenone is not very reactive, and would not be likely to react appreciably with the chlorocarbonate with strong alkali present in the same phase.

The p-amino-acetophenone was dissolved in ether and a concentrated aqueous solution of sodium or potassium hydroxide added as a second phase. The calculated amount of ethyl chlorocarbonate was added in small quantities during vigorous shaking to ensure thorough mixing of the two phases. The ether layer was dried over sodium sulfate and evaporated. The solid obtained was recrystallized from alcohol and melted at 158°, as reported by Nijk; yield, 48%.

A better yield was obtained by the direct action of ethyl chlorocarbonate on p-amino-acetophenone without any solvent present. There was no action when the two were mixed in the cold, but on being warmed they reacted vigorously. The reaction was complete in a few minutes and the excess of ester was driven off in a current of air. The yield was practically quantitative.

Anal. Calcd. for $C_{11}H_{13}NO_3$: N, 6.77. Found; 6.80.

Benzylurethan, $C_6H_5CH_2.NH.COOC_2H_5$ (ethylbenzylcarbamate).—Benzylamine in ether solution was treated with ethyl chlorocarbonate (one molecular proportion) added in small quantities, and the whole shaken with aqueous alkali after every addition. The ether solution was separated and dried, and the ether distilled. The urethan was left as a colorless oil of slight aromatic odor. It distilled with slight decomposition at 230°. The substance remained liquid for about two weeks and then suddenly solidified to a mass of white needles. After recrystallization from ether at 5° the substance melted at 44°; yield, 80–90%.

Anal. Calcd. for $C_{10}H_{13}NO_2$: N, 7.82. Found: 7.88, 7.72.

p-Bromophenylurethan, $BrC_6H_4.NH.COOC_2H_5$.—This was prepared from p-bromo-aniline by the method described above. The reaction was slow. The substance was recrystallized from ligroin (b. p., 60–90°), and melted at 85°; it formed long, thin needles; yield, almost 100%.

Anal. Calcd. for $C_9H_{10}NBrO_2$: N, 5.7. Found: 5.5.

***p*-Iodophenylurethan,** $IC_6H_4.NHCOOC_2H_5$.—This was prepared in similar manner from *p*-iodo-aniline. The reaction was more vigorous than with the bromo-aniline, but much slower than with unsubstituted aniline. The product crystallized in small needles from ligroin; m. p., 116°; yield, 90%.

Anal. Calcd. for $C_9H_{10}NIO_2$: N, 4.8. Found; 4.6.

Malonyldiphenyldiurethan, $CH_2(CO.N(C_6H_5).COOC_2H_5)_2$.—This compound was prepared by heating together malonyl chloride and phenylurethan (two molecular proportions) at 50–60° for about a week. Hydrogen chloride was slowly evolved and a brown viscid liquid was produced which slowly deposited crystals after cooling. The mass was worked up with cold alcohol and the solid obtained filtered off and recrystallized from hot alcohol. An alternative method of separation was to add ether to the viscid product until no further precipitation occurred. The precipitate was a brown, amorphous solid which was rejected. The ether solution was evaporated, leaving a residue of oil and crystals. The latter were separated by filtration, and the adhering oil was washed away with cold alcohol. The pure product consisted of white needles; m. p., 123–124°. The yield was very small.

Anal. Calcd. for $C_{21}H_{22}N_2O_6$: N, 7.03. Found: 6.75.

Malonyl-dibenzyl-diurethan, $CH_2(CON(CH_2C_6H_5).COOC_2H_5)_2$.—This was prepared in the manner described above from benzylurethan. The reaction was much more vigorous than with phenylurethan. The reddish, viscid liquid that was formed, solidified slowly to an orange mass. After recrystallization from dilute alcohol, the compound appeared as white needles melting at 75°; yield, 36%.

Anal. Calcd. for $C_{23}H_{26}N_2O_6$: N, 6.57. Found: 6.68.

1,3-Diphenyl-2-iminobarbituric Acid,

$$C_6H_5N.\underline{C(:NH).N(C_6H_5).CO.CH_2.CO.}—$$

Although this is not a urethan, it is described here because it was prepared in connection with the study of malonyl diurethanes. Diphenylguanidine was dissolved in ether and treated with malonyl chloride (1 molecular proportion) in the presence of aqueous potassium hydroxide. The reaction was quite vigorous and the mixture was cooled in water from time to time. The product was obtained as a brownish solid from the ether. It was recrystallized from a mixture of alcohol and ligroin; m. p., 148°; yield, 76%.

Anal. Calcd. for $C_{16}H_{13}N_3O_2$: N, 15.05. Found: 14.93.

Diphenyl-ethylene-diurethan, $(CH_2NH(C_6H_5).COOC_2H_5)_2$.—This compound was prepared from diphenylethylenediamine by the two-phase

method. The yield was practically quantitative. Recrystallized from alcohol or benzene, it formed needles; m. p., 88°.

Anal. Calcd. for $C_{20}H_{26}N_2O_4$: N, 7.87. Found: 7.85, 7.92.

Carbo-*n*-butoxy-ethyl-iso-urea, $HN:C(OC_2H_5).NH.COOC_4H_9$ (*o*-ethylallophanic butyl ester).—This was prepared from ethyl-iso-urea hydrochloride, potassium hydroxide and chlorocarbonic *n*-butyl ester by the two-phase method. The reaction mixture was cooled in ice. The product was recrystallized from ligroin (b. p., 65–90°), and melted at 77°. The yield was quantitative.

Anal. Calcd. for $C_8H_{16}N_2O_3$: N, 14.91. Found: 14.74.

The compound is readily soluble in alcohol, ether, benzene and vegetable oils. It was prepared for the purpose of comparing its pharmacological action with that of the carbethoxy-ethyl-iso-urea, already studied by one of us.[3]

Pharmacological Part

A preliminary examination of the physiological action of acetylphenylurethan and its two isomers has been made. Acetylphenylurethane was administered to guinea pigs and rabbits by subcutaneous injection in olive oil solution. Two cc. of a 10% solution produced in a guinea pig of 570 g. weight a mild central depression, which was decidedly increased by the injection of 1 cc. more, half an hour after the first injection. There was marked respiratory depression and some salivation. A dose of 0.35 g. given to a guinea pig of about the same weight as the first produced incoördination and drowsiness in about seven minutes. Respiration became dyspnoeic and the pulse rapid and arrhythmic. In 30 minutes the animal was deeply narcotized, but reflexes were still present. There was some involuntary muscular movement. Recovery was complete by next morning.

In a rabbit weighing 1700 g. a dose of 1.2 g. produced only mild central depression, but the rectal temperature fell from 38° to 35.1° in a little over two hours.

No very definite physiological action was elicited by either phenylacetylurethan or *p*-acetylphenylurethan. Their solubilities in oil are much less than that of acetylphenylurethan.

Carbo-*n*-butoxy-ethyl-iso-urea given by subcutaneous injection in olive oil produced only slight physiological effect. After a dose of 0.4 g. per kilogram a rabbit showed only a small fall of temperature in one hour. An additional dose of 0.5 g. had little or no effect. The total fall of temperature observed was 1°, and there was a scarcely perceptible central depression. This result is in striking contrast to the effect of the corresponding carbethoxy compound. Since the physical properties of the

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

two compounds are very similar it would seem that the *n*-butyl radical on oxygen is deficient in some way in its relation to the lipoids of the nervous system.

Summary

The preparation of various substituted urethans and of 1,3-diphenyl-2-iminobarbituric acid is described.

A preliminary study of the physiological action of acetylphenylurethan is reported.

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

THE CONDENSATION OF MESITYL OXIDE WITH ALIPHATIC KETONES

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Introduction

The simplest of the unsaturated cyclic ketones that can be prepared by the condensation of an aliphatic ketone is 1,3,3-trimethyl-cyclohexenone-5, or the well-known isophorone. Recently methylethyl ketone[2] and diethyl ketone[3] have been subjected to the action of condensing agents and the corresponding homologs of isophorone have been isolated. In the case of methylethyl ketone it was shown that four isomeric homologs of isophorone are theoretically possible, and two of them were isolated, 1,2,3,6-tetramethyl-3-ethyl-cyclohexenone-5 and 1,3-diethyl-3,4-dimethyl-cyclohexenone-5, which have been designated, respectively, as γ- and δ-homo-isophorones, each with the empirical formula $C_{12}H_{20}O$. The structure of these compounds was proved by the same method originally used by Knoevenagel.[4] In the case of diethyl ketone the only homolog of isophorone theoretically possible, 1,3,3-triethyl-2,4,6-trimethyl-cyclohexenone-5, having the empirical formula $C_{15}H_{26}O$, was prepared.

Thus by condensing the saturated aliphatic ketones, unsaturated cyclic ketones are formed, bearing the type formula $C_nH_{2n-4}O$. As the homologous series is ascended, it is apparent that for a carbon increment of one in the initial ketone, the carbon increment in the final product is three; thus, acetone (C_3H_6O) $\longrightarrow$ $C_9H_{14}O$; methylethyl ketone (C_4H_8O) $\longrightarrow$ $C_{12}H_{20}O$; diethyl ketone ($C_5H_{10}O$) $\longrightarrow$ $C_{15}H_{26}O$.

Other members of this cyclic series should exist, containing an interme-

[1] From a thesis submitted by M. Scott Carpenter to the Graduate Faculty of the University of Colorado in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] Ekeley and Howe, THIS JOURNAL, **45**, 1917 (1923).

[3] Ekeley and Carpenter, *ibid.*, **46**, 446 (1924).

[4] Knoevenagel, *Ann.*, **289**, 10 (1895); **299**, 160 (1897).