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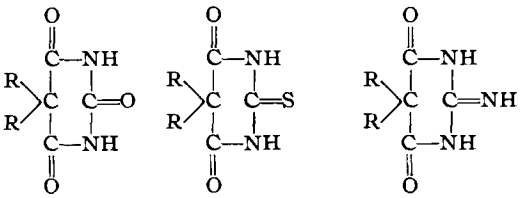
The Synthesis of Several Dialkylmalonylguanidines with a Preliminary Note on Their Pharmacology*

By Orville H. Miller† and Louis Fischer‡

In searching for new therapeutically valuable hypnotics of the barbiturate series, much attention has been devoted to replacing the two hydrogen atoms in the 5,5 position of barbituric acid with a wide variety of alkyl, aryl and other radicals. Recently a series of dialkyl thiobarbiturates (2 thio-5,5 dialkylbarbituric acids) have likewise been prepared. Of these several were found to be hypnotics and better adapted to certain uses than the barbiturates.

A few members of a third series in which the urea oxygen is replaced by an imino group (2 imino-5,5 dialkylbarbituric acids) have also been prepared, chiefly for the purpose of converting to the corresponding barbiturate. The chemical relationship of the three series may be best expressed structurally:



Barbiturate | Thiobarbiturate | Iminobarbiturate (Substituted Malonyl Guanidine)

Aside from an early experiment by Fischer and von Mering (1) there has been little interest indicated in the pharmacology of this iminobarbiturate series. Apparently basing their results on a single administration, Fischer and von Mering found dipropylmalonylguanidine to be devoid of any

* Presented to the Scientific Section of the A. PH. A., Richmond meeting, 1940.

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Suggestion of problem and supervision of preliminary pharmacology by Dr. J. M. Dille, Associate Professor of Pharmacology, University of Washington.

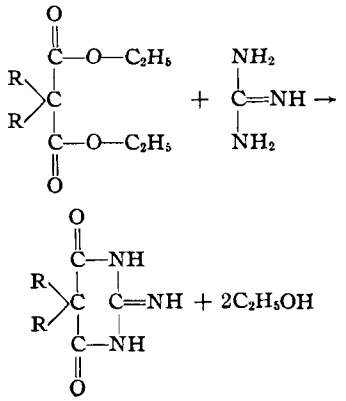
hypnotic or other pronounced pharmacological activity.

Since the soporific action of the thiobarbiturates indicates that the oxygen of the urea group is not an indispensable factor in the barbiturate type of hypnotic, the authors have prepared a series of dialkyl substituted malonylguanidines, namely, diethylmalonylguanidine, ethylisopropylmalonylguanidine, ethyl - *n* - butylmalonylguanidine, ethylisoamylmalonylguanidine and ethylphenylmalonylguanidine and made a preliminary pharmacological study to determine whether or not these derivatives possess any hypnotic properties. Of these diethylmalonylguanidine has been previously prepared by several investigators (2, 3, 4, 5, 6, 7, 8, 9). In addition, monoethylmalonylguanidine (3); dimethylmalonylguanidine (6); dipropylmalonylguanidine (2, 6, 7, 8); ethylpropylmalonylguanidine (5); benzylmalonylguanidine (10); allylmalonylguanidine, diallylmalonylguanidine and allylbenzylmalonylguanidine (11); monomethylmalonylguanidine (isosuccinylguanidine) (12) and unsubstituted malonylguanidine (13, 14) were previously reported.

EXPERIMENTAL

Method of Preparation.—The procedure was similar to that used by Fischer and Dilthey (2). Fifteen Gm. of guanidine hydrochloride (12 Gm. was used in the preparation of ethylisoamylmalonylguanidine and ethylphenylmalonylguanidine) and 25 Gm. of the proper disubstituted malonic ester were heated in a pressure flask, at 80–90° C., in the presence of sodium alcoholate (9 Gm. sodium plus 150 cc. absolute alcohol), for a period of sixty hours. The mixture was dissolved in water, then neutralized with acetic acid, the precipitated dialkylmalonylguanidine filtered off and washed free of chlorides.

Essentially the condensation proceeds as follows:



The compounds were purified by dissolving in warm dilute nitric acid and reprecipitated by adding dilute ammonia until faintly alkaline, avoiding an excess. The precipitate was washed first with water to remove the ammonium nitrate, then with alcohol to remove traces of barbiturates and finally dried at 105° C. On precipitation no crystalline structure was discernible but on cooling a hot alcoholic or aqueous solution, long, slender, colorless, friable needles were obtained.

The purity and percentage yields of each derivative are presented in table form.

Table I.—Yields and Nitrogen Determinations

Substituted Malonylguanidine	Yield Per Cent	Per Cent of Nitrogen by Micro Dumas Method Calculated	Found
Diethyl	60	22.95	23.14
Ethylisopropyl	49	21.31	21.48
Ethyl-*n*-butyl	69	19.90	19.70
Ethylisoamyl	58	18.66	18.58
Ethylphenyl	64	18.18	18.01

General Properties.—The compounds were white in color, non-crystalline in structure and did not melt on heating to 300° C. They were soluble in dilute mineral acids, alkalis, alkali carbonates, very slightly soluble in hot water and hot alcohol and practically insoluble in acetone, chloroform, ether and benzene.

On attempting to prepare hydrochlorides and nitrates according to the method of Fischer and Dilthey (2) the corresponding barbiturates were obtained instead. The conversion to barbiturates took place much more readily in hot hydrochloric acid than with hot dilute nitric acid. The reaction consists of the hydrolytic replacement of the imido group by oxygen, with the formation of ammonia.

Preliminary Pharmacology.—The compounds were prepared for injection by dissolving in a slight excess of alkali, neutralizing until the first appearance of a precipitate and filtering. Intravenous injection into rabbits indicated that ethylisopropylmalonylguanidine, ethyl-*n*-butylmalonylguanidine and ethylisoamylmalonylguanidine produced death apparently by respiratory depression in relatively small doses. Diethylmalonylguanidine and ethylphenylmalonylguanidine were found to be less toxic. While the compounds depress the respiration in doses approaching the lethal dose, there is little evidence of general depression or abolition of reflexes. The evidence obtained in this study is insufficient to form any definite conclusions as to the hypnotic properties of the dialkylmalonylguanidines. Further investigation, using other animals, is now in progress.

SUMMARY

Five dialkylmalonylguanidines, diethylmalonylguanidine, ethylisopropylmalonylguanidine, ethyl - *n* - butylmalonylguanidine, ethylisoamylmalonylguanidine and ethylphenylmalonylguanidine, were pre-

pared by the condensation of the proper dialkylmalonic ester and guanidine hydrochloride, in the presence of sodium alcoholate.

In a preliminary investigation of their pharmacological properties, the compounds were found to produce death by respiratory failure. Sufficient evidence has not yet been obtained to definitely classify the dialkylmalonylguanidines as hypnotics.

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Condensation of Amino Acids with Terpenes

I. Aminoacetic Acid and Limonene Nitrosochloride*

By C. F. Krewson

This paper is presented as an introduction to a research project in which it is planned to prepare a variety of condensation products of amino acids and terpenes and to study their biological properties. These remarks will be confined to the condensation of aminoacetic acid and limonene nitrosochloride.

The behavior of nitrosochlorides of terpenes toward a variety of bases has been studied and three different types of reactions observed.

I. $C_{10}H_{16}\begin{cases}NO\\Cl\end{cases} + KOH \xrightarrow{-HCl}$

Terpene nitrosochloride (or heat)

$C_{10}H_{15}NO \rightarrow C_{10}H_{14}NOH$

Nitroso-terpene Isonitroso-terpene (oxime), (1)

II. $C_{10}H_{16}\begin{cases}NO\\Cl\end{cases} + 2HNHR' \text{ (or } HNR') \rightarrow$

Terpene nitrosochloride Primary or secondary base

$C_{10}H_{16}\begin{cases}NOH\\NHR'\end{cases} + HNH.HCl.R'$

Nitrolamine Hydrochloride of base

III. $C_{10}H_{16}\begin{cases}NO\\Cl\end{cases} \xrightarrow{-NOCl} C_{10}H_{16}$

Terpene nitrosochloride Regenerated terpene, (2)

Reactions of type II have long been used to characterize terpenes since nitrolamines of this type are well-defined crystalline compounds.

Several preliminary experiments with aminoacetic acid (2 moles) and limonene nitrosochloride (1 mole) indicated that these compounds do not combine quantitatively according to reaction II but that the former seems to behave like an inorganic base removing hydrogen chloride, a fact verified by the isolation of carvoxime and the recovery of much of the aminoacetic acid as a hydrochloride.

The reaction products obtained from several experiments where equimolecular quantities of reactants were used showed the presence of the compound desired, a new compound, limonene nitrolaminoacetic acid hydrochloride, [Glycine, *N*-(2-oxo-1-$\Delta^{8(9)}$-*p*-menthenyl)-, oxime hydrochloride], and the volatile oil obtained by steam distillation of the reaction products was found to contain, not only carvoxime, but also a relatively large amount of carvone apparently a result of the hydrolysis of carvoxime to carvone and hydroxylamine.

EXPERIMENTAL

In order to effect condensation 60 Gm. of aminoacetic acid and 158 Gm. of limonene nitrosochloride,

* Presented before the Division of Medicinal Chemistry at the ninety-ninth meeting of the American Chemical Society, Cincinnati, Ohio, April 11, 1940, as a contribution from the laboratory of Edward Kremers, University of Wisconsin, and the Department of Chemistry, University of Kentucky.