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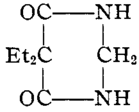
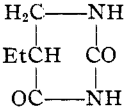
Homodesoxyveronal and Some of its Homologs

BY ARTHUR W. DOX

By electrolytic reduction of veronal (barbital) Tafel and Thompson[1] obtained a diethyldiketohexahydropyrimidine (I) which they designated desoxyveronal. Hydrolysis of this product, whereby diethylmalonic acid was obtained, showed that the reduction had occurred in the urea carbonyl. When, however, the corresponding monoethylbarbituric acid was electrolyzed in the same manner, the reduction occurred in one or both of the malonyl carbonyls, depending on temperature and current density, yielding ethylhydrouracil (II) or ethyltrimethyleneurea (III).


I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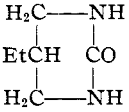
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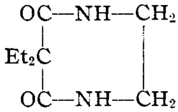
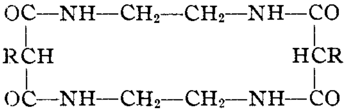
Desoxyveronal (I) may be regarded as a cyclic amide of a dibasic acid, the ring closure being effected by substitution of methylene. It should be possible to prepare the substance by direct condensation of diethylmalonyl chloride with methylenediamine. From the high melting point (292°) of desoxyveronal, however, together with the fact that no further study was made, the inference seems warranted that the unrecorded pharmacological tests failed to reveal hypnotic action.[2]

The homologous seven-membered structure, which may be designated homodesoxyveronal (IV), was considered of sufficient interest in this connection to make desirable its preparation and examination. Such a structure should result by condensation of the chloride or ester of diethylmalonic acid with ethylenediamine. Since the esters of malonic acids are more readily available than the chlorides, they were used in the present experiments. The condensations were effected by heating molecular proportions of ester and amine for six to eight hours at 100–110° with absolute alcohol in which two equivalents of sodium had been dissolved. In place of the free base the hydrochloride was also used successfully, with two additional equivalents of sodium ethoxide to liberate the base. Both


IV


V

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[1] Tafel and Thompson, *Ber.*, **40**, 4489 (1907).

[2] Desoxyveronal was also prepared by Einhorn [*Ann.*, **359**, 176 (1908)] by sodium reduction of veronal, but he likewise omits mention of its pharmacological properties.

procedures gave the same condensation products and in practically the same yields. In all, six esters were used, three of dialkyl- and three of monoalkyl-malonic acids. Analyses of the products gave values in satisfactory agreement with those calculated for the seven-membered ring structures.

TABLE I

HOMODESOXYBARBITURIC ACIDS

			Found, %			Calcd., %		
Dialkyl	Formula	M. p., °C.	C	H	N	C	H	N
Diethyl	$C_9H_{16}N_2O_2$	306	58.22	8.71	15.31	58.69	8.70	15.22
Dibutyl	$C_{13}H_{24}N_2O_2$	290	64.42	10.30	11.51	65.00	10.00	11.67
Hexylethyl	$C_{13}H_{24}N_2O_2$	188	65.16	10.21	11.47	65.00	10.00	11.67
Monoalkyl		(decompn.)						
Ethyl	$C_7H_{12}N_2O_2$	350–355	53.25	7.74	17.47	53.85	7.69	17.95
Propyl	$C_8H_{14}N_2O_2$	242–245	55.22	8.45	16.53	56.47	8.24	16.47
Sec-butyl	$C_9H_{16}N_2O_2$	335–340	57.48	8.75	14.78	58.69	8.70	15.22

Dialkyl-homodesoxybarbituric Acids.—A striking difference was at once apparent between the dialkyl and the monoalkyl derivatives. The former are well-defined crystalline products, but obtained in rather poor yield. They have high, but sharp melting points; on cooling, the melt rapidly solidifies in crystals which show the same melting point as before. Recrystallization is readily effected by cooling or diluting the alcoholic solution. The diethyl derivative has a slightly bitter taste, the two homologs are tasteless. In contrast to desoxyveronal they are insoluble in alkali.

Monoalkyl-homodesoxybarbituric Acids.—These were obtained in much better yields but were invariably amorphous and could not be crystallized from any of the solvents tried. They dissolve in hot glacial acetic acid, but separate as an amorphous slime when the solution is chilled or allowed to evaporate spontaneously. They show a strong tendency to swell to a semi-gelatinous mass in water and for that reason are difficult to filter and purify. Dry powders free from ash were eventually obtained by successive treatments with alcohol and ether. The melting points are high but not sharp and decomposition occurs with darkening in color and evolution of gas. The amorphous character of these products suggests a polymeric structure such as might be represented by Formula V.

The difference in behavior of the esters of dialkyl- and monoalkyl-malonic acids in the condensation with ethylenediamine is not surprising in view of a somewhat similar difference in their reaction with hydrazine.[3] The product there consisted of a single pyrazole ring or the double pyrazo-pyrazole ring, depending on the absence or presence of an unsubstituted hydrogen in the malonyl grouping. Differences also in reactivity toward ammonia to form amides have long been known.[4]

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(3) Dox, THIS JOURNAL, **54**, 3674 (1932).

(4) Fischer and Dilthey, *Ber.*, **35**, 884 (1902).

Homodesoxybarbituric Acid.—A reaction between ethyl malonate and ethylenediamine is mentioned in the older literature. Freund[5] obtained an "ethylenemalonamide" by direct condensation without solvent or catalyst. The same substance was again obtained by Ruhemann and Sedzwick[6] as a by-product in the reaction between ethyl dicarboxyglutaconate and ethylenediamine. Aside from the statement that the substance is readily soluble in water, precipitated by alcohol, and melts with decomposition at 280°, nothing is said of its properties.

The writer prepared this ethylenemalonamide (homodesoxybarbituric acid) by the Freund reaction and obtained an amorphous polymeric substance which melted at 280° with decomposition. Its aqueous solution was distinctly colloidal. For example, the warm solution is water clear; on cooling it becomes opaque, but clears up again on warming. In the direct condensation, without solvent or catalyst, between a malonic ester and ethylenediamine, the effect of alkyl substitution in the former is rather striking. Ethyl malonate and the amine react at once with a very considerable rise in temperature, and in a few moments the mixture sets to an opaque gel containing the amorphous condensation product. Ethyl ethylmalonate and the amine form a homogeneous solution but no reaction occurs even after twenty-four hours of standing. When the solution is heated in the steam-bath a white precipitate gradually forms and the mass eventually becomes gelatinous. Ethyl diethylmalonate, on the other hand, does not react with ethylenediamine even after several hours of heating.

As might be expected from the properties of homodesoxyveronal and its higher homologs, these derivatives were found to be pharmacologically inert. Administered orally to rabbits in doses equivalent to the hypnotic dose of barbital no effect whatever was observed.

Summary

Homodesoxyveronal, the seven-membered heterocycle homologous to desoxyveronal, has been synthesized by condensation of ethyl diethylmalonate and ethylenediamine. Its dibutyl and hexylethyl homologs have also been obtained by the same procedure.

Esters of monoalkylmalonic acids also condense with ethylenediamine, yielding products with empirical formulas corresponding to the seven-membered homodesoxybarbituric acids. These products, however, are amorphous and colloidal in character and probably have a polymeric structure.

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(5) Freund, *Ber.*, **17**, 137 (1884).

(6) Ruhemann and Sedzwick, *ibid.*, **28**, 824 (1895).