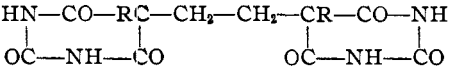
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS AND COMPANY. PAPER NO. 469]

Ethylene-N,N'-bisbarbital, a Dimolecular Barbital with Hypnotic Properties

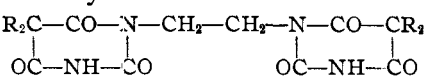
BY ARTHUR W. DOX

Structures previously synthesized containing two dialkylbarbituric acid groupings in the molecule are represented by the type



where the two heterocycles are joined at the 5-C through an ethylene chain. Derivatives of this type, with R = ethyl, propyl and benzyl, were prepared in 1911[1] by condensation of ethyl 1,4-dialkylbutane-1,1,4,4-tetracarboxylate with urea. The substances are described as having no melting point up to 300°, and no mention is made of their physiological properties. From the fact that no synthetic hypnotics are known with melting points above 200°, it may be assumed that these products were physiologically inert.

Another type of dimolecular barbital is possible, in which the two barbituric acid groupings are joined at the 1-N through an ethylene chain. This type is represented by the formula



and should result from condensation of ethyl diethylmalonate with ethylenediurea. More strictly considered, this type might also be regarded as a trialkylbarbituric acid derivative[2] in which the N-alkyl of each of two molecules is linked together.

Experimental

Ethylenediurea was prepared in 1861 by Volhard[3] from ethylenediamine hydrochloride and silver cyanate, but has not appeared in subsequent literature. The product used in this work was obtained in 70% yield from the diamine hydrochloride and potassium cyanate instead of the more costly silver cyanate, and readily purified by crystallization from hot water.

Ethylene-N,N'-bisbarbital.—Condensation of ethylenediurea with two moles of ethyl diethylmalonate was effected by heating the mixture with a 10% alcoholic solution of sodium ethoxide for seven hours at 100–106°, according to the usual procedure for barbituric acid synthesis. The sodium salt of the product, which separated out on cooling, was filtered and washed with alcohol. It dissolved readily in water and gave a crystalline separation of the free acid when the solution was acidified with hydrochloric acid. By recrystallization from alcohol the acid was obtained in slender needles, melting at 189°. A mixed melting point with barbital (m. p. 191°) showed a depression of about 30°. The yield was 75%.

(1) German Patent 233,968 (1911).
(2) Dox and Hjort, *J. Pharm. Exp. Therapeutics*, **31**, 455 (1927).
(3) Volhard, *Ann.*, **119**, 349 (1861).

Anal. Calcd. for $C_{18}H_{26}O_6N_4$: C, 54.82; H, 6.60; N, 14.21. Found: C, 54.06; H, 6.50; N, 14.22.

Ethylene-N,N'-bis(5-hexyl-5-ethylbarbituric acid).—The same procedure was followed, using ethyl hexylethylmalonate[4] in place of ethyl diethylmalonate. The sodium salt of the product was soluble in alcohol and did not separate on cooling the reaction mixture, as did the lower homolog. The alcohol was removed by evaporation, the pasty residue taken up in water and the free acid precipitated by addition of hydrochloric acid. The free acid was a colorless transparent gum which solidified to a vitreous mass and softened again on warming. It was readily soluble in most organic solvents, including petroleum ether, but has not thus far been induced to crystallize. Since the molecule contains two asymmetric C-atoms, the failure of the product to crystallize may be attributed to the presence of two pairs of optical isomers.

Anal. Calcd. for $C_{26}H_{42}O_6N_4$: C, 61.66; H, 8.30; N, 11.07. Found: C, 60.40; H, 8.43; N, 11.19.

Ethylenebis(carbethoxyurea), $C_2H_5O_2CNHCONHCH_2CH_2NHCONHCO_2C_2H_5$.—Reaction between ethylenediurea and ethyl phenylethylmalonate. This reaction was expected to yield the analogous ethylene-N,N'-bisphenobarbital. Although the condensation was repeatedly performed at various reaction temperatures, the main product was in each instance an alkali-insoluble substance with none of the properties of a barbital. Recrystallization from a large volume of alcohol, in which the substance is difficultly soluble, gave colorless needles melting at 219° with evolution of gas. The yield was 50–58%.

Anal. Calcd. for $C_{10}H_{18}O_6N_4$: C, 41.38; H, 6.21; N, 19.31. Found: C, 41.38; H, 6.31; N, 19.09.

The empirical formula does not correspond to that of any possible barbital, but coincides with that of ethylenebis(carbethoxyurea). The latter, being an allophanic ester, should react with ammonia to form the corresponding biuret, and thus establish its identity.

Ethylenebisbiuret, $H_2NOCNHCONHCH_2CH_2NHCONHCONH_2$.—The product just described was heated several hours with 25% ammonia in a sealed tube at 100°. The crystals did not dissolve perceptibly but gradually assumed a more granular appearance. The product, which was practically insoluble in water or alcohol, was washed and dried. It melted at 245° with evolution of gas.

Anal. Calcd. for $C_6H_{12}O_4N_6$: C, 31.03; H, 5.17; N, 36.21. Found: C, 30.65; H, 5.31; N, 35.12.

Further proof of the identity of the $C_{10}H_{18}O_6N_4$ compound was obtained by preparing ethylenebis(carbethoxyurea) by a method generally applicable to the preparation of allophanic esters.[5] Ethylenediurea and alcoholic sodium ethoxide were heated six hours at 95–100° with an excess of ethyl carbonate. The reaction mixture was evaporated to dryness, the residue washed with water and recrystallized from a large volume of alcohol. The yield was 77.4% of needle-shaped crystals which melted at 219° with evolution of gas, and gave no melting point depression when mixed with the $C_{10}H_{18}O_6N_4$ product.

The so-called "biuret reaction" for proteins and their high molecular products of hydrolysis was applied to both the allophanic ester and the biuret derivative. With sodium hydroxide and a trace of copper sulfate, the former gave a deep blue and the latter a deep pink color, although both substances are nearly insoluble.

The formation of an allophanic ester in the condensation of a substituted malonic ester with a urea was quite beyond the writer's experience in the preparation of numerous

(4) Dox, THIS JOURNAL, **46**, 1709 (1924).

(5) German Patent 427,417 (1926).

barbituric acid derivatives. No such reaction is mentioned in the literature. Empirically it represents an exchange of carbethoxyl for hydrogen between the two reacting substances. A second product of the reaction should then be ethyl phenylethylacetate. This was isolated by ether extraction of the mother liquor and identified as the free acid (α-phenylbutyric) after hydrolysis. The acid melted at 42°, boiled at 270–275° and showed molecular weight by titration 163; theoretical 164.

A control experiment in which ethylenediurea and sodium ethoxide were heated in the absence of ethyl phenylethylmalonate yielded no trace of the ethyl ethylenediallophanate. Two moles of ethylenediurea might conceivably split off two ammonia to form a fourteen-membered cyclic biuret which might then undergo alcoholysis into the ethylenebis(carbethoxyurea) and ethylenediamine. The possibility of such a reaction having occurred seems to be excluded by the failure to obtain any trace of the allophanate when the ethyl phenylethylmalonate was omitted.[6]

Physiological Action

Tests by intraperitoneal injection of the sodium salt of ethylenebisbarbital in white mice showed hypnotic potency equal to about three-fourths that of barbital. The homologous hexyl derivative administered in the same way was much feebler in its action. A 2-mg. dose caused very noticeable drowsiness in a 20-g. mouse but no anesthesia. An increase to two and four times this dosage gave precisely the same effect as the smaller dose. Evidently the limiting factor here is the rate of absorption which in turn is limited by the insolubility of the free acid.

Summary

Ethylene-N,N′-bisbarbital, the double structure consisting of two barbital molecules joined at the nitrogen through an ethylene chain, retains the hypnotic properties of the components. This is in contrast to a previously known structure where the connecting chain was attached to carbon instead of nitrogen.

The homologous ethylene-N,N′-bis(5-hexyl-5-ethylbarbituric acid) is much feebler in physiological action than its hexylethylbarbituric acid components.

Attempts to prepare the analogous ethylene-N,N′-bisphenobarbital by the same procedure resulted in the formation of ethylenebis(carbethoxyurea)—an allophanic ester derivative identified by analysis and by conversion into ethylenebisbiuret—and ethyl phenylethylacetate. The reaction appears to be an exchange of carbethoxyl for hydrogen instead of the usual barbituric acid condensation.

DETROIT, MICHIGAN

RECEIVED OCTOBER 13, 1932
PUBLISHED MARCH 7, 1933

(6) An excellent paper by Cope and McElvain [THIS JOURNAL, **54**, 4319 (1932)] which appeared shortly after the writer's manuscript had been submitted for publication, furnishes a simple explanation for the above reaction in which an allophanic ester is obtained instead of the expected barbituric acid. As shown by Cope and McElvain, ethyl ethylphenylmalonate forms an addition product with sodium ethoxide, and this on warming decomposes into the sodium enolate of ethyl ethylphenylacetate and *ethyl carbonate*. The latter would then react with the urea derivative in the presence of sodium ethoxide to form the corresponding allophanic ester, just as in the above synthesis performed according to the German patent.