[CONTRIBUTION FROM THE DEPARTMENT OF CHEMICAL RESEARCH, PARKE, DAVIS AND COMPANY, No. 46]

DIRECT SUBSTITUTION ON THE NITROGEN OF 5,5-DIALKYLBARBITURIC ACIDS

BY ARTHUR W. DOX AND EDWARD G. JONES

RECEIVED OCTOBER 8, 1928 PUBLISHED JANUARY 8, 1929

On account of the high dissociation constant of barbituric acid as compared with that of the 5,5-dialkylbarbituric acids, Wood and Anderson[1] concluded that the unsubstituted barbituric acid exists in solution in the tautomeric enol form representing a migration of hydrogen from the methylene to an adjacent carbonyl. As a further proof of this structure they synthesized the sodium salt of barbituric acid from ureidomalonamide and sodium hydroxide, the reaction, according to their view, consisting in hydrolysis of the amide with formation of a sodium salt, migration of a hydrogen from the methylene to carboxyl and ring closure with loss of water.

If, however, the sodium salt of barbituric acid is actually the enolic form, as postulated by Wood and Anderson, it is rather surprising that alkyl derivatives prepared therefrom are not known to occur in this form. Treatment of sodium barbiturate with alkyl halides yields apparently only derivatives in which alkyl has replaced the methylene hydrogen. Thus, 5-allyl- and 5,5-diallylbarbituric acids may be prepared from barbituric acid and allyl bromide in the presence of sodium acetate.[2] Since barbituric acid is a stronger acid than acetic, it may be assumed that sodium barbiturate is first formed in this reaction. A somewhat more direct reaction is described by Volwiler,[3] where *n*-butylallylbarbituric acid is prepared from allyl bromide and the sodium salt of *n*-butylbarbituric acid. The less reactive alkyl halides, *e. g.*, ethyl bromide, however, give a poor yield of alkylbarbituric acids, and the preparation of such derivatives by direct alkylation has not been developed commercially. All derivatives thus far prepared in this way are identical with the corresponding derivatives prepared by condensation of alkylmalonic esters with urea; that is, the tautomeric alkyl derivatives of barbituric acid are not known.

Further substitution to yield tri- and tetra-alkylbarbituric acids has not hitherto been performed by direct alkylation. Fischer and Dilthey[4] prepared N-methyl- and N-phenyldiethylbarbituric acids by condensation of ethyl diethylmalonate with methylurea and phenylurea, respectively, and tetra-ethylbarbituric acid from diethylmalonyl chloride and

[1] Wood and Anderson, *J. Chem. Soc.*, **95**, 979 (1909).

[2] Preiswerk and Grether, U. S. Patent 1,042,265 (1912).

[3] Volwiler, U. S. Patent 1,636,201 (1927).

[4] Fischer and Dilthey, *Ann.*, **335**, 334 (1904).

sym.-diethylurea. The series of 1,5,5-trialkylbarbituric acids was recently extended by Dox and Hjort[5] and that of 1-aryl-5,5-dialkylbarbituric acids by Hjort and Dox.[6] All of these derivatives were obtained by condensation of the ethyl dialkylmalonate with the appropriate alkyl- or arylurea.

In view of the ease with which the 5,5-dialkylbarbituric acids react with *p*-nitrobenzyl chloride in the presence of alkali, as shown by Lyons and Dox,[7] to give further substitution on one or both of the imide hydrogens, it seemed probable that other reactive halides might yield analogous products. Here the possibility of tautomeric forms again arises, since the imide groupings are adjacent to carbonyls and the alkali salts of 5,5-dialkylbarbituric acids are believed by some to exist in the enolic form. The question of tautomerism was definitely disposed of in the case of 1-benzyl-5,5-diethylbarbituric acid. This derivative was prepared by both methods, *viz.*, direct benzylation of sodium veronal and condensation of ethyl diethylmalonate with benzylurea. Both products were identical.

Alkylation on the nitrogen apparently does not occur until both methylene hydrogens have been substituted. For example, we treated the sodium salt of *iso*propylbarbituric acid with the molecular equivalent of benzyl chloride and obtained an *iso*propylbenzylbarbituric acid identical with that prepared by Dox and Yoder[8] from ethyl *iso*propylbenzylmalonate and urea. Both products melted at 229°.

The method used in preparing N-substituted derivatives of 5,5-dialkylbarbituric acids consisted simply in dissolving the dialkylbarbituric acid in one equivalent of normal sodium hydroxide and refluxing for several hours with one equivalent of the alkyl halide. The halides used in this work were benzyl chloride and allyl bromide. The product in most cases separated as an oil which became crystalline on standing overnight. Occasionally a by-product insoluble in alkali was obtained which had the properties of a dialkylacetylurea. This is known to result from certain dialkylbarbituric acids when treated with alkali, the reaction consisting in hydrolysis of the pyrimidine ring and loss of carbon dioxide The trisubstituted barbituric acids invariably melted lower than the parent dialkylbarbituric acid. They were purified by recrystallization from dilute alcohol or by acidifying the solution in dilute alkali.

In the following table eight such derivatives are described.

The purification of the trialkylbarbituric acid thus formed involves a fractional crystallization. Even though molecular proportions of the

[5] Dox and Hjort, *J. Pharmacol.*, **31**, 455 (1927).

[6] Hjort and Dox, unpublished data.

[7] Lyons and Dox, THIS JOURNAL, **51**, 288 (1929).

[8] Dox and Yoder, *ibid.*, **44**, 1144 (1922).

TABLE I

BARBITURIC ACID DERIVATIVES

N-Benzyl deriv. of	M. p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found
Diethylbarbituric acid	127	10.22	10.19, 10.24
Ethyl *iso*-amylbarbituric acid	90	8.88	8.96, 8.97
Ethylphenylbarbituric acid	113	8.69	8.48, 8.66
Diallylbarbituric acid	116	9.39	9.29, ...
Allyl *sec.*-butylbarbituric acid	90–91	8.92	9.13, 9.14
N-Allyl deriv. of			
Diethylbarbituric acid	75	12.50	12.66, 12.61
Diallylbarbituric acid	68–69	11.29	11.40, 11.38
Dipropylbarbituric acid	73	11.11	10.90, 10.71

reactants are used, some tetra-alkyl derivative is simultaneously formed and a corresponding amount of the original substance remains unreacted. The former is readily removed by means of its insolubility in dilute alkali, but for the separation of tri- and dialkylbarbituric acids several crystallizations are necessary. In only one case was the tetra-alkyl derivative isolated and identified, *viz.*, diallyldipropylbarbituric acid, which melted at 62–63°; N found, 9.50, calcd., 9.59.

Summary

The sodium salts of 5,5-dialkylbarbituric acids react with such halides as benzyl chloride and allyl bromide to give further substitution on the nitrogen. A trialkyl- or even a tetra-alkylbarbituric acid can thus be obtained. This further substitution results in a marked lowering of the melting point.

DETROIT, MICHIGAN

NEW BOOKS

The Physics of Crystals. By ABRAM F. JOFFE, Ph.D., D.Sc., D.Eng., LL.D., Director, Roentgen Institute; Director, Physical Technical Institute, Leningrad, Russia. Edited by Leonard B. Loeb, Associate Professor of Physics in the University of California. McGraw-Hill Book Company, Inc., 370 Seventh Avenue, New York City, 1928. xi + 198 pp. 61 figs. 15 × 23.5 cm. Price $3.00.

When the reviewer first read the publisher's announcement of this book he was at once prejudiced against it. The story in that announcement of the way in which the author's results had first been treated looked too much like the efforts of a newspaper sob-reporter. After having studied the book (it deserves study, not merely reading), the reviewer's prejudice has been entirely overcome and he has even pasted the publisher's announcement on the flyleaf as a permanent record of some of the difficulties which the author overcame.

The first two chapters give a highly compressed account of the electrical theory of crystal lattices. After these two introductory chapters the