ance of melting and of the clearance of the last particle of solid. A hand lens was used in observing both of these points as the sample was slowly heated in an oil-bath under constant agitation. Close agreement was obtained in checked temperature determinations, usually 0.1 and never more than 0.5°. The results of the three experiments are recorded in Charts I and II (Anschütz thermometers were used).

Several significant points were found in the behavior of the various acids studied. Mixtures of diethylcarbinylethylbarbituric acid and propylmethylcarbinylethylbarbituric acids containing 60–70% of diethylcarbinylethylbarbituric acid showed almost constant melting ranges irrespective of the composition of the sample. A second example of this phenomenon occurs in mixtures of diethylcarbinylallylbarbituric acid and propylmethylcarbinylallylbarbituric acid containing 65–80% of diethylcarbinylallylbarbituric acid. Evidence of a eutectic point was found in mixtures of isoamylethylbarbituric acid and active amylethylbarbituric acid containing about 45% of isoamylethylbarbituric acid.

It was found possible to estimate, from melting point data, the composition of various "unknown" mixtures with an accuracy of 2 to 3%, the samples having been prepared by another investigator. It is thus possible to establish whether or not the alcohols used in the preparation of the barbituric acids were pure or whether in the case of secondary alcohols isomerization had occurred.

The authors wish to express their appreciation to Mr. W. J. Doran, who weighed samples of the barbituric acids for this investigation.

Summary

Temperature–composition phase curves have been established for (a) diethylcarbinylethyl and propylmethylcarbinylethyl barbituric acids; (b) diethylcarbinylallyl and propylmethylcarbinylallyl barbituric acids; and (c) isoamylethyl and active amylethyl barbituric acids.

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[CONTRIBUTION FROM LILLY RESEARCH LABORATORIES]

Barbituric Acids Containing a Secondary Amyl Group[1]

BY H. A. SHONLE

The preparation of certain barbituric acids containing the diethylcarbinyl and the propylmethylcarbinyl groups was described in a previous article from this Laboratory, wherein the following melting points were reported: (a) diethylcarbinylethylbarbituric acid, 127–129°; (b) propylmethylcarbinylallylbarbituric acid, 86–88°; (c) diethylcarbinylallylbarbituric acid as wax-like; and (d), diethylcarbinylbarbituric acid, 165–168°.[2]

Tabern and Volwiler[3] discuss the ease with which the diethylcarbinyl group isomerizes to the propylmethylcarbinyl group and give two procedures which overcome, at least in part, this tendency to isomerize, and describe the first three of the above barbituric acids as melting at 158.5–159.5°, 98–100° and 129–130°, respectively.

When the earlier work of this Laboratory was repeated, it was reported[1] that a certain and rather definite proportion of the propylmethylcarbinyl isomer was present in the barbituric acids obtained when urea was condensed with the ester resulting from the reaction of pure 3-bromopentane and the sodio-malonic ester. Through the use of mixed melting point curves, it is possible to estimate the degree of isomerization present in the barbituric acid.[4]

Although it was not possible to demonstrate the proportion of the isomers present in the ester, it is believed that they were present in approximately the same proportion as observed in the barbituric acid, and that the diethylcarbinylmalonic esters do not undergo further isomerization when condensed with urea.

The experimental data reported below give the method of preparation and the melting points of the isomer-free barbituric acid.

Experimental

Diethylcarbinylbarbituric Acid.—Diethylcarbinylmalonic ester, b. p. 85–86° (12 mm.), n^{20} 1.4293–4, was prepared

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(1) Presented in part before the Division of Medicinal Chemistry at the Chicago Meeting of the American Chemical Society, September, 1933.

(2) Shonle, Keltch and Swanson, THIS JOURNAL, **52**, 244 (1930).

(3) Tabern and Volwiler, *ibid.*, **56**, 1139 (1934).

(4) Shonle and Kleiderer, *ibid.*, **56**, 2489 (1934).

from pure 3-bromopentane, n^{20} 1.4444,[5] and sodio-malonic ester in the usual manner. Diethylcarbinylbarbituric acid, obtained by condensing this ester with urea, melted at 196–197.5° after recrystallizing from dilute alcohol.[6]

Anal. Calcd. for $C_9H_{14}O_3N_2$: N, 14.14. Found: (Micro Dumas) N, 14.29, 14.32.

On working up the mother liquor, an amount of propylmethylcarbinyl barbituric acid melting at 165.5–166.5° was obtained. This represented 20% of the total barbituric acid formed.

Diethylcarbinylethylbarbituric Acid.—Diethylcarbinylethylmalonic ester prepared from pure 3-bromopentane, n^{20} 1.4444, and sodio-ethylmalonic ester, boiled at 125–128° at 10 mm., n^{25} 1.4350. It was condensed with urea in the usual manner, and the resulting diethylcarbinylethylbarbituric acid after several recrystallizations from dilute alcohol melted at 145°. This is the melting point of a mixture of 60–70% diethylcarbinylethylbarbituric acid and 40–30% propylmethylcarbinylethylbarbituric acid.[4] It is difficult to raise the melting point to 160° by repeated crystallization.

Diethylcarbinylethylmalonic ester was also prepared from sodioethylmalonic ester and diethylcarbinyl-*p*-toluene sulfonate.[3] After fractionating and condensing the ester with urea, diethylcarbinylethylbarbituric acid was obtained which could more readily be brought to a constant melting point of 161–161.5° by recrystallizing from dilute alcohol.[7]

Anal. Calcd. for $C_{11}H_{18}O_3N_2$: N, 12.38. Found: (Micro Dumas) N, 12.48, 12.31.

We found that diethylcarbinyl-*p*-toluene sulfonate melted at 43–45° when prepared from pure diethylcarbinol, but that when technical alcohol was used, the melting point is lower. Tabern and Volwiler[3] used in their preparations a 3-bromopentane giving n^{20} 1.4440 and a diethylcarbinyl-*p*-toluene sulfonate melting at 32–35°.

Diethylcarbinylallylbarbituric Acid.—This was prepared from allyl bromide and a dilute alcoholic solution of the sodium salt of diethylcarbinylbarbituric acid, m. p. 196–197°. After several recrystallizations from dilute alcohol, the diethylcarbinylallylbarbituric acid had a constant melting point of 131–132°.

Anal. Calcd. for $C_{12}H_{18}O_3N_2$: N, 11.76. Found: (Micro Dumas) N, 11.81, 11.80.

When mixed with 60 to 80% of its isomer it is a wax-like solid which crystallizes with difficulty, if at all.

Propylmethylcarbinylallylbarbituric Acid.—This was prepared similarly from propylmethylcarbinylbarbituric acid, m. p. 164–166°, and after repeated recrystallization from dilute alcohol had a constant melting point of 99–100°.

Anal. Calcd. for $C_{12}H_{18}O_3N_2$: N, 11.76. Found: (Micro Dumas) N, 11.71, 11.81.

These barbituric acids were evaluated, pharmacologically, by injecting 2% solutions of the sodium salts intraperitoneally into white rats with the results shown in Table I.

TABLE I

Barbituric acid	M. A. D. mg./kg.	M. L. D. mg./kg.
Propylmethylcarbinylethyl	45	110
Diethylcarbinylethyl	60	100
Propylmethylcarbinylallyl	40	100
Diethylcarbinylallyl	45	110

Several hundred animals were used in obtaining these results.

The author wishes to express his thanks to Dr. E. C. Kleiderer and Mr. J. H. Waldo for their help in the preparation of certain of the compounds and to Mr. W. J. Doran for the micro analysis, and to Messrs. E. E. Swanson and W. H. Fry for the pharmacological tests.

Summary

The preparation and melting points of diethylcarbinyl, diethylcarbinylethyl, diethylcarbinylallyl and propylmethylcarbinylallyl barbituric acids are described and certain of their pharmacological effects given.

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[5] Sherrill, Otto and Pickett, THIS JOURNAL, **51**, 3023 (1929), give n^{20} 1.4443 for pure 3-bromopentane.

[6] German Patent 293,163 gives 198° as the melting point.

[7] German Patent 293,163 gives 162° as the melting point.