Summary

1. The volatility of ten substituted 2-chloroethylamines has been measured between 0 and 60° by an air saturation method.

2. From the measured volatilities vapor pressures have been calculated. Logarithmic equations have been developed for both the vapor pressure and the volatility as a function of the temperature.

3. The mean molar latent heat of evaporation over the temperature range 0 to 60° has been computed from the vapor pressure equation for each compound.

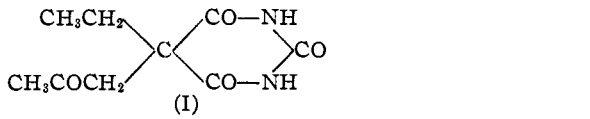
CHICAGO 37, ILLINOIS RECEIVED DECEMBER 5, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

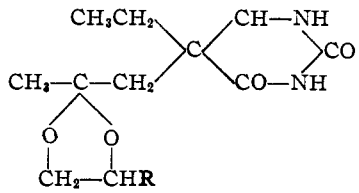
Cyclic Acetals Related to Ethylacetonylbarbituric Acid

BY CHARLES D. HURD AND MARGARET L. MCAULEY

This investigation deals with the synthesis and reactions of certain new derivatives of ethylacetonylbarbituric acid (I). This acid was synthesized from sodium ethylbarbiturate and chloroacetone, instead of the previously used[1] bromoacetone. To use chloroacetone, it was found that sodium iodide was an effective catalyst.[2] Yields of 75% of I were obtained with this catalyst as contrasted with 10–32% yields without it. Butylacetonylbarbituric acid was similarly prepared and with the same high yield. In view of this, it is of interest to note that no significant reaction product could be obtained when solutions of sodium ethylbarbiturate, 2-chloromethyl-2-methyldioxolane (made from chloroacetone and ethylene glycol), and sodium iodide were mixed and treated similarly. Ethyl *sodio*-butylmalonate also failed to give a reaction product with 2-chloromethyl-2-methyldioxolane at refluxing temperature in alcohol solution.



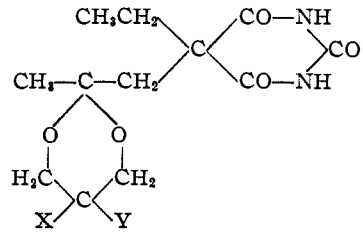
(I)



II, R = H
III, R = CH_3

Dioxolanes of the structure II or III were synthesized by reaction of ethylacetonylbarbituric acid with ethylene glycol or propylene glycol in the presence of *p*-toluenesulfonic acid. The water formed in the reaction was removed as formed by slowly distilling benzene or toluene from the reaction mixture. The compounds formed were high melting, crystalline solids.

1,3-Dioxanes represented by formula IV, V were synthesized similarly from I by reaction with trimethylene glycol or tris-(hydroxymethyl)-nitromethane. These compounds all melt above 200°. Conditions were not found for satisfactory interaction of (I) and 2-nitro-2-methyl-1,3-propanediol.



IV (X = Y = H)
V (X = NO_2, Y = CH_2OH)
VI (X = NH_2, Y = CH_2OH)
VII (X = NHAc, Y = CH_2OH)

The nitro group in 5-ethyl-5-(1-methyl-4-nitro-4 - hydroxymethyl - 2,6 - dioxacyclohexyl)-methylbarbituric acid (V) was readily reduced at 100° to an amino group under a hydrogen pressure of 1600 lb./sq. in., using Raney nickel catalyst The amine (VI) is moderately soluble in water. In accordance with its dipolar ion character, it is insoluble in non-polar solvents. Conditions were not found for the acetylation of this amine by acetic anhydride, but acetylation to VII was achieved readily by the use of ketene.

We are indebted to Edgar B. Carter, Lucy Johnson and G. M. Everett of Abbott Laboratories for pharmacological tests made on the above compounds. These compounds were tested: II, III, IV, butylacetonylbarbituric acid (VIII), and acetonylbarbituric acid (IX). The compounds were non-toxic toward mice by intravenous injection in doses of 50 to 200 mg./kg., but such doses produced no hypnotic effect. To test anticonvulsant activity, mice were given 400 mg./kg. orally and after various periods of time were tested with 100 mg./kg. of metrazol with results shown in Table I.

It is seen that all except IX show some anticonvulsant action. Compound III was tested further with oral doses of 500 mg./kg. After periods of 10, 30, 60, 120 minutes, 100 mg./kg. of metrazol was given. All mice showed jerks and approximately half showed convulsions after all

(1) (a) Kirsanov and Ivashchenko, *J. Gen. Chem.* (*U. S. S. R.*), **8**, 1576 (1938); (b) Dox and Houston, THIS JOURNAL, **46**, 252 (1924).

(2) Hurd and Perletz, *ibid.*, **68**, 38 (1946).

TABLE I

ANTICONVULSANT ACTIVITY

Conv. = convulsions. Conv. F = convulsions with some fatalities

Compound	15 min.	30 min.	60 min.
II	Conv. F	Jerks, conv.	Jerks
III	Conv.	Jerks	Jerks, conv.
IV	Conv. F	Jerks	Jerks
VIII	Conv.	Jerks	Jerks, conv.
IX	Conv. F	Jerks, conv. F	Jerks, conv. F

time intervals. The protection against the minimum convulsant dose (75 mg./kg. of metrazol) was also unsatisfactory. All test animals had jerks and three out of six had convulsions.

Experimental

Ethylacetonylbarbituric Acid.—For this synthesis, ethylbarbituric acid of m. p. 193–194° was prepared in accordance with the method of Fischer and Dilthey[3] except for the modification of not separating the sodium ethylbarbiturate. Instead, water was added to dissolve it, then the free acid was precipitated by adding concentrated hydrochloric acid and chilling. The yield was 83%, in contrast to the reported yield of 45%.

A solution of 72.2 g. of ethylbarbituric acid, 40 ml. of alcohol and 900 ml. of 0.5 *N* sodium hydroxide was adjusted to neutrality to litmus. It was stirred vigorously while a mixture of 91 ml. of chloroacetone, 10 g. of sodium iodide and 300 ml. of alcohol was added rapidly. After a half hour of refluxing, the solvents were removed at 40 mm. pressure, thereby causing separation of a solid which was collected, washed with a little water, and dried; yield, 81.6 g., or 74.6%. The m. p. was 237–238°, agreeing with 238–239° listed in the literature.[1]

When 2.5 g. of sodium iodide was used instead of 10 g. the yield was about the same, but when longer or shorter reaction times were taken, the yield dropped. The yield was about 50% with either ten minutes or one hour of refluxing, and the yield dropped to 39% with two hours of refluxing.

If no sodium iodide was present, the yield changed progressively from 10 to 32% with a refluxing change from thirty minutes to two hours. The yield was no better using the method of Dox and Houston.[1b]

Butylacetonylbarbituric Acid.—Substitution of butylbarbituric acid for ethylbarbituric acid in the above preferred procedure (use of sodium iodide and thirty minutes of refluxing) gave rise to a 75% yield of butylacetonylbarbituric acid. Kirsanov and Ivashchenko[1] used bromoacetone (no sodium iodide) and reported yields of 50–70%.

Ethyl Acetonylmalonate.—This compound has been made previously from bromoacetone.[4] The present synthesis uses chloroacetone.

To a suspension of 15 g. of finely divided sodium in 500 ml. of dry ether was added 33 ml. of absolute alcohol. After twelve hours, when hydrogen was no longer evolved, 99 ml. of ethyl malonate was added, followed by slow addition of a solution of 52 ml. of chloroacetone in 90 ml. of dry ether. Three hours later the mixture was filtered and the filtrate distilled, thereby recovering 59 g. of ethyl malonate and obtaining 32.5 g. of ethyl acetonylmalonate, b. p. 110–111° (2 to 4 mm.). This is a 61% yield, based on unrecovered malonic ester.

Black tarry materials resulted from the interaction of ethyl acetonylmalonate with ethyl iodide in the presence either of anhydrous potassium carbonate, or dimethylaniline, or sodium ethoxide solutions at refluxing temperatures. About half of the ethyl acetonylmalonate was recovered. Likewise, no ethyl butylacetonylmalonate was obtained starting with ethyl butylmalonate, chloroacetone, and refluxing sodium ethoxide solution.

Reaction of Ethylacetonylbarbituric Acid (I) with Glycols.—This general procedure was followed. Five to fifteen grams of (I) was taken for each run. For each mole of (I) there was added 1.3 moles of the glycol and 0.1 g. of *p*-toluenesulfonic acid. Then 120–250 ml. of benzene or toluene was added. The apparatus was set for distillation with an automatic separator for the hydrocarbon and water in the distillate, the hydrocarbon layer being continuously returned to the flask. Reaction proceeded for about fifty hours. The products were then separated and purified by crystallization. Usually a little of the (I) was recovered. Yields were in the range of 61–69%, based on unrecovered (I). 2-Nitro-2-methyl-1,3-propanediol was the only glycol tested which failed to react, and 83% of I was recovered.

5-Ethyl-5-(1-methyl-2,5-dioxacyclopentyl)-methylbarbituric acid (II), 5-ethyl-5-(1,3-dimethyl-2,5-dioxacyclopentyl)-methylbarbituric acid (III), and 5-ethyl-5-(1-methyl-2,6-dioxacyclohexyl)-methylbarbituric acid (IV) were made, respectively, using ethylene glycol, propylene glycol, and trimethylene glycol. These compounds were purified by crystallization from benzene, then from water. Analytical data and properties are listed in Table II. Analyses were by the micro Dumas method, by T. S. Ma.

TABLE II

Compound	M. p., °C.	Formula	Nitrogen, % Calcd.	Found
II	216–217	$C_{11}H_{16}N_2O_5$	10.94	10.37
III	202–204	$C_{12}H_{18}N_2O_5$	10.37	10.27
IV	264–265	$C_{12}H_{18}N_2O_5$	10.37	10.24
V	239–240, dec.	$C_{13}H_{19}N_3O_8$	12.17	12.23
VI	236–237, dec.	$C_{13}H_{21}N_3O_6$	13.33	12.78
VII	231–232, dec.	$C_{15}H_{23}N_3O_7$	11.80	11.25

That compounds II and I form a eutectic, m. p. 191–192°, may be demonstrated simply by crystallization of a mixture of equal amounts of the pure ingredients from water.

Tris-(hydroxymethyl)-nitromethane was the glycol used in the synthesis of 5-ethyl-5-(1-methyl-4-nitro-4-hydroxymethyl-2,6-dioxacyclohexyl)-methylbarbituric acid (V). The crude reaction product was washed thoroughly with water and then crystallized from water. A mixture of I (m. p. 237–238°) and V melts at 213–216°. Since I melts without decomposition whereas V blackens and evolves gas on fusion, it is easy to distinguish one from the other in spite of the close melting points. The solubility in water is another difference, since 0.2 g. of I or V require 5.5 and 14.6 cc., respectively, of boiling water for solution.

5-Ethyl-5-(1-methyl-4-amino-4-hydroxymethyl-2,6-dioxacyclohexyl)-methylbarbituric Acid (VI), by Reduction of V.—Two catalytic reductions of V (3.5, 6.4 g.) in purified dioxane (20 ml.) at 1600 lb./sq. in. of hydrogen pressure with Raney nickel catalyst (0.2, 1.0 g.) at 100–125° gave rise to 55–58% of amine (VI). Thirty minutes was required for the calculated drop in pressure. The product was crystallized from dioxane or from equal parts of dioxane and ethyl acetate. To dissolve 0.2 g. of VI in boiling water, 14.6 ml. is required, thus showing the same solubility as V.

Reaction with Ketene.—A stream of ketene was bubbled at the rate of 0.47 mole per hour for five minutes into a warm solution of 1.4 g. of VI in 100 ml. of water. On cooling, 0.64 g. of 5-ethyl-5-(1-methyl-4-acetamido-4-hydroxymethyl-2,6-dioxacyclohexyl)-methylbarbituric acid (VII) separated. From the filtrate, 0.56 g. of VI was recovered. The amide was crystallized from water. This material depressed the m. p. of I and VI. It dissolved readily in dilute sodium hydroxide. Hydrolysis by boiling dilute hydrochloric acid (ten minutes) gives rise to I, m. p. and mixed m. p. 239–240°.

(3) Fischer and Dilthey, *Ann.*, **355**, 334 (1908).

(4) Gault and Salomon, *Compt. rend.*, **174**, 754 (1922); *Ann. chim.*, **2**, 133 (1924).

No evidence for the acetylation of VI was obtainable, using acetic anhydride in pyridine or in glacial acetic acid. Also V was unacetylated by treatment with acetic anhydride and sodium acetate at 100°.

Summary

Ethylacetonylbarbituric acid may be made in good yields from sodium ethylbarbiturate and chloroacetone in the presence of a little sodium iodide. Several cyclic acetals were prepared by reaction of ethylacetonylbarbituric acid with glycols, including a nitro glycol. The nitro acetal was hydrogenated to an amino acetal, and the latter was acetylated with ketene to an acetamido acetal. Pharmacological toxicity data and anticonvulsant tests are included.

EVANSTON, ILLINOIS RECEIVED DECEMBER 8, 1947

NOTES

Amide Vinylogs

BY ROBERT H. BAKER AND ARTHUR H. SCHLESINGER[1]

In a survey of the behavior of ethoxymethylenediketones and esters as alkylating agents toward amines, amides, the Grignard reagent and in Friedel–Crafts and other type reactions some new compounds have been encountered and are described below.[2]

Ethoxymethyleneacetoacetic ester reacts readily with aminoacetic ester and with progressive difficulty with *p*-aminobenzoic ester and urethan to produce open chain amide vinylogs which are cleaved by hydrogen (PtO_2, 2 atm., 25°) as are derivatives of typical amines.[3] Thiourea reacts to form the mercaptopyrimidine similar to the cyclization product of the urea derivatives.[3]

Experimental[4]

Ethyl α-(N-Carbethoxyaminomethylene)-acetoacetate.—Equimolar quantities of ethyl ethoxymethyleneacetoacetate and ethyl carbamate were heated at 143–165° for 1.7 hours and then cooled at 0° for three hours to induce crystallization. Three crystallizations from cyclohexane, employing activated alumina as decolorizing agent, produced yellow needles, m. p. 40.5–41.0°; 13% yield.

Anal. Calcd. for $C_{10}H_{15}NO_5$: C, 52.3; H, 6.55; N, 6.11. Found: C, 52.4; H, 6.90; N, 6.10.

Ethyl α-(*p*-Carbethoxyanilinomethylene)-acetoacetate.—This was produced similar to the above from ethyl *p*-aminobenzoate at 110–135° for one hour. It was decolorized in hot ethanol solution by alumina. Five crystallizations from ethanol, then from cyclohexane and finally ethanol gave colorless crystals, m. p. 105°, 70% yield.

Anal. Calcd. for $C_{16}H_{19}NO_5$: C, 63.0; H, 6.26; N, 4.60. Found: C, 63.2; H, 6.50; N, 4.50.

Ethyl α-(N-Carbethoxymethylaminomethylene)-acetoacetate.—Slow addition of freshly distilled glycine ethyl ester to an equivalent of the ethoxymethylene compound at 0° produced a vigorous reaction, and the contents of the reaction flask were solid within thirty minutes. Two crystallizations from 70% ethanol gave matted colorless needles, m. p. 71.0–71.5°; 66% yield.

Anal. Calcd. for $C_{11}H_{17}NO_5$: C, 54.4; H, 7.00; N, 5.76. Found: C, 55.2; H, 7.15; N, 5.58.

Ethyl 2-Mercapto-4-methylpyrimidine-5-carboxylate.—Thiourea and an equivalent of the ester vinylog were heated at 150° for thirty minutes. The mixture frothed vigorously and a hard, red solid was obtained which was purified by digestion on the steam-bath with ethanol. The liquors upon chilling gave a red powder which was treated three more times in a similar manner. The red product, 52% yield, failed to melt but sintered at 160° and decomposed. Sublimation *in vacuo* failed to improve its appearance. It is soluble in 10% sodium hydroxide solution and decolorizes iodine.

Anal. Calcd. for $C_6H_{10}N_2O_2S$: N, 14.10. Found: N, 13.94.

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EVANSTON, ILLINOIS RECEIVED SEPTEMBER 12, 1947

(1) Allied Chemical and Dye Corporation Fellow, 1946–1947.

(2) Except toward amines the results were largely of a negative nature and cannot be published here, *cf.* A. H. S., Ph.D. Thesis, 1947.

(3) Baker and Schlesinger, THIS JOURNAL, **68**, 2009 (1946).

(4) Microanalyses by Patricia Craig and Nelda Mold.

Some Quaternary Ammonium Salts of Substituted Thiazoles

BY CARL T. BAHNER, DONALD PICKENS[1] AND DOROTHY BETTIS BALES[2]

The biological results obtained by Shear and associates[3] at the National Cancer Institute using quaternary salts derived from pyridine and its homologs and benzologs have led us to prepare similar quaternary salts containing the thiazole ring. Particular interest attaches to this series in view of the fact that thiamin chloride is a quaternary salt containing this ring. The substituted thiazoles which we have used are 4-methyl-2-β-hydroxyethylthiazole, 2,4-dimethylthiazole, 2-ethyl-4-methylthiazole, 4-methylthiazole, benzothiazole, and 2-methylbenzothiazole. These have been caused to react with phenacyl and substituted phenacyl bromides and with phenylethyl and cyclohexylethyl halides. Most of these bases reacted with the phenacyl bromides readily upon

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(3) Shear, *et al.*, in "Approaches to Cancer Chemotherapy," American Association for the Advancement of Science, F. R. Moulton, Editor, Washington, D. C., 1947, p. 236 ff.; Hartwell and Kornberg, THIS JOURNAL, **68**, 1131 (1946).