[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF DELAWARE]

Conditions Affecting the Formation of Malonates and Barbiturates. Halogenalkyl Derivatives

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In a previous paper[1] it was reported that better yields of a 5-β-hydroxyethyl-5-alkyl barbiturate are obtained by refluxing the reaction mixture for relatively short periods of time followed by the distillation of the alcohol. It has now been shown to be unnecessary to heat the reaction mixture according to the generally followed procedure of Fischer and von Mering. In fact, the observance of the more vigorous treatment causes a decrease in the yield. According to the procedure herein described yields of more than 90% are obtainable.

Experience also has been gained in the preparation of the necessary malonates. Using benzene as the medium it was found that ethylene bromide did not react with sodiophenylmalonic ester at temperatures below approximately 60°. This may explain why a previous attempt to carry out this condensation in ether was unsuccessful. While the reaction above this temperature is comparatively slow, it is possible to obtain yields of the corresponding lactone in excess of 50%.

In using an inert solvent as a medium it has been found possible to increase the yield of the *n*-butyl β-bromoethyl derivative from approximatively 52% (based on sodium) to 80% simply by using one equivalent of sodium to two of the other reactants. The finely divided sodium not only dissolves much more readily but the reaction with the halide takes place more rapidly. Trimethylene bromide has been reported to condense with sodioisoamylmalonic ester to give a 44% yield of the γ-bromopropyl derivative.[2] The yield may be increased to 68% by using the sodium, ester and bromide in the ratio 1:3:4. No solvent was used in this experiment and this yield could doubtless be further improved by a more extensive study. Here the reaction is more rapid and a very considerable amount of high boiling material is formed, hence the greater importance of having the bromide in excess of the other reagents. With ethylene bromide the amount of high boiling material is small and is only slightly increased by using the other reactants in excess of the sodium. The omission of a solvent and the use of a sodium:ester:bromide ratio as high as 1:6:2 instead of a 1:2:2 ratio in benzene shows no appreciable change in the yield of β-bromoethyl ester or high boiling residue based on sodium but a slight increase based upon the ester consumed in the process. Potassium is not as satisfactory as sodium since the potassium derivative shows a greater tendency to precipitate and the yields are lower. The reaction of both halides with ethyl phenylmalonate gives a sharp increase in the amount of high boiling material.

Before a recently described improvement[3] of the method for the preparation of phenylmalonic ester was published, we had made some study of the conditions during the preparation of a quantity of it for our work. It had been reported that ethyl carbonate[4] could be condensed with ethyl phenylacetate to give phenylmalonic ester in yields not greater than 20%. Accordingly the effect of potassium was studied with the result that 10% potassium–sodium alloy, 50% potassium–sodium alloy and potassium showed maximum yields of 45, 49 and 41%, respectively. The condensation of ethyl oxalate with ethyl phenylacetate by potassium is too vigorous to be controlled properly. With 10 and 50% alloys in benzene the yields of phenylmalonic ester were 77 and 71%, respectively, using a ratio of 1:2:1 for the metal, oxalate and phenylacetate. Under the same conditions using sodium the yield was 66%. Using ether as the medium and a 10% potassium–sodium alloy the comparative yield based on metal was 80 or 87% based on ethyl phenylacetate.

The tendency of ethyl phenylacetate to react with itself rather than ethyl carbonate is diminished by potassium judging from the amount of ethyl phenylacetate recovered and the weight of the high boiling residue. An increase of the carbonate/acetate ratio increases the yield of phenylmalonic ester and decreases the loss of ethyl phenylacetate. Increasing the acetate/metal ratio decreases the yield of phenylmalonic ester and increases the loss of ethyl phenylacetate.

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[1] Rosenberg, Kneeland and Skinner, THIS JOURNAL, **56**, 1339 (1934).

[2] Dox and Yoder, *ibid.*, **45**, 1757 (1923).

[3] "Organic Syntheses," **16**, 33 (1936).

[4] Nelson and Cretcher, THIS JOURNAL, **50**, 2759 (1928).

Markedly better results are obtained by the use of the metal, oxalate and phenylacetate in 1:2:1 ratio rather than the customary equivalent ratio.

5-β-Halogenethyl-5-alkyl barbiturates are formed in excellent yields by the action of the fuming halogen acids on the corresponding hydroxy compounds. The reaction proceeds smoothly for the bromides and iodides while the chlorides are formed with difficulty.

The γ-bromopropyl alkyl malonates are not converted to the lactones by distillation under similar conditions while, for example, β-bromoethyl phenylmalonate could not be distilled without decomposition to the lactone. This indicates a greater tendency for the formation of a five than a six-atom ring. Being an intramolecular temperature reaction this sharp difference is interesting especially as being in line with the older classical theory of ring formation. However, the experience that barbiturate formation takes place at ordinary temperatures encouraged the attempt to condense the halogen ester directly. The reaction mixture from γ-bromopropyl isoamylmalonic ester was successfully converted to γ-bromopropyl isoamylbarbiturate.

From the results of tests made through the courtesy of Dr. E. H. Volwiler of the Abbott Laboratories, β-iodoethyl and γ-bromopropyl isoamylbarbiturates appear to be the best tolerated and produce the most uniform depression. The latter employed intravenously in rabbits produced ataxia lasting one-half hour (300 mg./kg.) and Stage II anesthesia for one-half hour (500 mg./kg.).

Experimental Part

Halogenalkyl Malonates.—For the introduction of the β-bromoethyl group it is preferable to use the reagents in the following molal ratios: finely divided Na, 1.0; $RCH(CO_2C_2H_5)_2$, 2.0; $C_2H_4Br_2$, 2.0. The stirrer is run and the mixture is cooled during the addition of the alkylmalonic ester. If two mols of the ester is employed the complete solution of the sodium is fairly rapid. When the reaction slackens it is allowed to go to completion at room temperature. The ethylene bromide is added at once with stirring and cooling. The temperature of the bath is allowed to rise slowly to 70–75° where it is maintained for eight to ten hours. It is of no advantage to heat for longer periods to the disappearance of the last trace of alkali as the reaction is then substantially complete. The precipitation of sodium bromide begins near room temperature. However, if R is phenyl it is necessary to heat for seventy to seventy-five hours to secure substantial completion of the reaction, which does not begin until the temperature is near 60°. The phenyl bromoethyl compound could not be distilled without decomposition to the lactone which was obtained in only 52% yield.

Trimethylene bromide reacts more rapidly and the reaction flask must be surrounded with iced water at first. The mixture is then allowed to stand in a bath of water at room temperature for an hour and heated for about five hours at 70–75°. If R is phenyl the reaction begins near 45°. The phenyl derivative showed slight evidence of decomposition during distillation under diminished pressure with the bath at 220°, which is also indicated by the analysis. An attempt to convert the isoamyl derivative to the lactone by distilling it slowly at 196° (24 mm.) was unsuccessful.

n-Butyl γ-bromopropylmalonic ester: calcd. for $C_{14}H_{25}O_4Br$, Br 23.76%; found, Br 23.88%, b. p. 138 (2 mm.), n^{20}_D 1.4602; n^{25}_D 1.4580; d^{20}_4 1.188, d^{25}_4 1.182.

Phenyl γ-bromopropylmalonic ester: calcd. for $C_{16}H_{21}O_4Br$, Br 22.38%; found, Br 21.03%; b. p. 172° (1 mm.); n^{20}_D 1.5167, n^{25}_D 1.5143; d^{20}_4 1.274, d^{25}_4 1.269.

Ethyl Phenylmalonate.—From the results of ten runs in which both ether and benzene were used as solvents and the mass relationships were varied widely, the following procedure was selected as giving the best yield. Sodium (0.275 at.) and potassium (0.275 at.) are converted to a powdered alloy in the usual way except that overheating is avoided and the xylene is not removed. The alloy is covered with 250 cc. of dry benzene, cooled in finely crushed ice and at the incipient crystallization of the benzene a mixture of 0.50 mol. of ethyl phenylacetate and 2.00 mole of ethyl carbonate is added rapidly with mechanical stirring and readiness for additional cooling if necessary. The metal reacts completely within an hour. After standing for twenty-four hours and decomposing with a freezing mixture of ice and hydrochloric acid, there is obtained 1.20 mol. of ethyl carbonate, 0.116 mol of ethyl phenylacetate, 0.267 mol of ethyl phenylmalonate and 14 g. of residue. The malonate yield is thus 49% based on metal, 53% on ethyl phenylacetate used and 69% on ethyl phenylacetate consumed in the process. Similarly a 10% alloy gives a yield of 42% (metal) and a residue of 20 g. With 10% alloy, carbonate and phenylacetate in a 1:2:2 ratio the yield drops to 31% (metal) and the weight of the residue rises to 71 g. If the ratio is 1:4:2 the yield is 45% (metal) and the residue weighs 43.5 g. Pure potassium, carbonate and phenylacetate in a 1:2:1 ratio gives a yield of 41% (metal) and a residue of 20 g.

Similarly from an alloy of 0.055 at. potassium, 0.495 at. sodium, 250 cc. of dry ether, 1.00 mol of ethyl oxalate and 0.50 mol of ethyl phenylacetate there is obtained 0.418 mol of ethyl oxalate, 0.001 mol of ethyl phenylacetate, 0.437 mol of ethyl phenylmalonate and a residue of 10 g., corresponding to a yield of 80% (metal) and 87% (ethyl phenylacetate). With sodium alone under these conditions the yield dropped to 64 and 72%, respectively. Benzene, 50% alloy, and especially a lower oxalate–phenylacetate ratio decrease the yield.

Lactones.—The following new lactones are made by the distillation of the β-bromoethyl alkyl malonates under reduced pressure such that the material will not distil until the decomposition is complete. α-Carbethoxy-α-*n*-butyl-γ-butyric Lactone. Calcd. for $C_{11}H_{18}O_4$: C, 61.64; H, 8.47. Found: C, 61.1; H, 8.4; n^{20}_D 1.4487, n^{25}_D 1.4467;

d^{20}_4 1.063, d^{25}_4 1.059; b. p. 119 (3 mm.). α-Carbethoxy-α-phenyl-γ-butyric Lactone. Calcd. for $C_{13}H_{14}O_4$: C, 66.64; H, 6.03. Found: C, 66.6; H, 6.5, n^{20}_D 1.5211, n^{25}_D 1.5187; d^{20}_4 1.191, d^{25}_4 1.188; b. p. 145° (1 mm.).

β-Hydroxyethyl Barbiturates.—According to the following procedure the yield of β-hydroxyethyl-isoamylbarbituric acid has been increased from 75 to 89%. To a solution of sodium ethoxide prepared from 0.60 at. of sodium and 300 cc. of absolute alcohol is added 0.120 mol of lactone ester and then 0.40 mol of finely powdered urea. The flask is surrounded by a bath of water at room temperature and the stirrer is run until the urea dissolves. After standing until the next day a considerable amount of solid will have separated. A glassy residue remains after removal of the alcohol through a column under diminished pressure from a bath not heated above 50°. The aqueous solution is extracted with chloroform and the acid is precipitated with cooling by hydrochloric acid. An additional amount is obtained by extracting the filtrate with chloroform.

The yield of the *n*-butyl compound at the reflux temperature in six runs was 61–78% where the time of refluxing was one to five hours and the alcohol was distilled under diminished or ordinary pressure, the best yield being for a one-hour reflux. In one experiment where the alcohol was distilled at once and then under reduced pressure the yield was 75%. The yield was increased to 93% by mechanical stirring at a water-bath temperature of 45° to solution of the urea followed by distillation of the alcohol under reduced pressure. The acid melted at 147–148° which agrees with the value for the acid obtained by a different method.[5]

β-Halogenethyl Barbiturates.—β-Hydroxyethyl-isoamylbarbituric acid (0.20 mol) is heated with 200 cc. of fuming hydrobromic acid (55–60%) in 6 oz. (120 cc.) soda water bottles at a water-bath temperature of 55–60° for two hours with occasional shaking. The bottles are capped with crowns in which the cork has been replaced by disks of thin red gasket rubber. Bottles with wired well-ground glass stoppers also may be used. After standing at room temperature until the next day, 59 g. of crude product is obtained by suction filtration through sintered glass. One gram more is obtained by distillation of the filtrate under diminished pressure. The material is purified by dissolving in about three times its weight of warm alcohol, allowing to cool somewhat and stirring in an equal volume of ice water.

The preparation of the chlorides is more tedious, especially for the isoamyl derivative on account of its lesser solubility in the fuming acid. Here refluxing with four mols of thionyl chloride followed by the fuming acid treatment and repeated crystallization gives a pure product. The *n*-butyl derivative (0.050 mol) largely dissolves in 60 cc. of hydrochloric acid (1.19) at 60° with a current of hydrogen chloride passing through the mixture. The passage of the gas is continued while cooling in ice. After standing for two days at room temperature the material is filtered on sintered glass and washed with fuming acid. The crude material weighs 11.4 g. and melts at 138–139°. It must be crystallized repeatedly in the above manner in order to secure a sample melting sharply at 140°.

To prepare the iodide it is better to dissolve the hydroxy acid (0.19 mol) in 1.4 mol of ice-cold fuming 70% hydriodic acid. The solution is then allowed to stand for one day in a brown glass-stoppered bottle in the ice box, two days in a dark place at room temperature and finally one day in the ice box. The crude β-iodoethylisoamylbarbituric acid so obtained weighs 61 g. The filtrate heated to 50–60° for two hours and allowed to stand in the ice box gives 3 g. more. The material is crystallized from hot alcohol for the analysis. Two more crops melting at the same temperature (167°) are obtained by dilution, bringing the total yield of purified product to 58.5 g.

TABLE I

$RR'C(CONH)_2CO$

R	R'	M. p., °C.	Halogen, % Found	Halogen, % Calcd.	Yield, %
n-Butyl	β-Chloroethyl	140	14.28	14.38	92
n-Butyl	β-Bromoethyl	153.5	27.46	27.46	92
n-Butyl	β-Iodoethyl	192	37.53	37.55	92
Isoamyl	β-Chloroethyl	138.5	13.83	13.61	
Isoamyl	β-Bromoethyl	159.5	26.34	26.20	96
Isoamyl	β-Iodoethyl	167	36.18	36.05	91
Isoamyl	γ-Bromopropyl	150.5	24.73	25.05	40

γ-Bromopropyl-isoamylbarbituric Acid.—γ-Bromopropyl-isoamylmalonic ester (0.138 mol) when condensed with urea in the above manner gives 35.5 g. of a very viscous material which could not be induced to crystallize satisfactorily. This material when heated repeatedly with 100-cc. portions of 60% hydrobromic acid followed by the removal of the crystalline portion gives 25 g. of material melting at 143–147°. Repeated crystallization from chloroform did not give a pure product until after heating in an oven at its melting point (Table I). Further work is in progress.

Summary

1. The formation of 5-β-hydroxyethyl barbiturates is favored by lower temperatures than those heretofore employed for this reaction.

2. β-Bromoethyl and β-iodoethyl barbiturates are formed smoothly in excellent yields by the action of the fuming acids on the hydroxy compounds. The chloro compounds are also obtained but with more difficulty. γ-Bromopropyl-isoamylbarbituric acid was made although the desired intermediate lactone ester was not formed in the usual manner.

3. The use of two equivalents of malonate to one of sodium in making the desired halogenalkyl malonate is highly advantageous.

4. By the use of potassium and the adjustment of the mass relationships the yield of phenylmalonic ester is decidedly increased when either ethyl carbonate or ethyl oxalate is used.

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[5] Cretcher, Koch and Pittenger, THIS JOURNAL, **47**, 3084 (1925).