carried out as above. The remaining residue was treated with 200 ml. of 1% sodium hydroxide, then extracted with three 150-ml. portions of ether. The combined ether layer was washed twice with 100-ml. portions of 4% sodium hydroxide.[12] Removal of the solvent from the dried ether layer yielded 11.1 g. (65.2%) of slightly impure *o*-hydroxybiphenyl melting at 53–55° which gave a mixed melting point with authentic material (m.p. 57–58°) of 55–57°. The combined alkaline layer was warmed on a steam-bath, filtered hot, cooled in an ice-bath, and acidified with 6 *N* hydrochloric acid. Filtration gave 2.6 g. (15.3%) of nearly pure *o*-hydroxybiphenyl; m.p. and mixed m.p. 56–57°. The total yield of *o*-hydroxybiphenyl was 80.5%.

Run IV.—This run was the same as run III except that the dioxane was replaced with 200 ml. of ether and the total reaction time was 22 hours. Color Test I was positive at the end of 8, 18 and 22 hours. An additional 150 ml. of ether was added at the end of 18 hours to replace the solvent which had been carried off in the slow stream of nitrogen. Carbonation, hydrolysis and isolation of products were carried out as in run III. From the alkaline solution there was obtained 12.6 g. (64.3%) of impure 3,4-benzocoumarin (the lactone of 2'-hydroxy-2-diphenylcarboxylic acid) melting from 80–86°. The product was recrystallized from 150 ml. of dilute ethanol to yield a total of 8.3 g. (47.0%) of 3,4-benzocoumarin; m.p. and mixed m.p. 95–96°.[13] Removal of the solvent from the dried ether layer from the reaction mixture gave 2.5 g. (14.9% recovery) of dibenzofuran melting at 78–81°, identified by the method of mixed melting points. The yield of 3,4-benzocoumarin based on the amount of dibenzofuran which actually reacted was 75.7% crude and 55.2% pure.

Lithium Cleavage of Dibenzothiophene. Run I.—A mixture of 0.1 mole of dibenzothiophene (18.4 g.) which had been well-desiccated over sulfuric acid, 0.22 g. atom (1.5 g.) of lithium and 200 ml. of purified and sodium-dried dioxane was refluxed and stirred vigorously for 12 hours. The reaction flask was closed with a calcium chloride tube. Most of the lithium had disappeared by the end of 8 hours. After cooling overnight a few particles of unreacted lithium were removed mechanically, and the suspension was carefully hydrolyzed with a water–dioxane mixture. Isolation and purification of products as in the dibenzofuran runs above gave a 30.5% yield of biphenyl melting at 69–70° and a 33.2% recovery of dibenzothiophene melting at 98–99°.

Run II.—The same amounts of reagents and conditions of reaction were used in this experiment as in Run I, except that the reaction was conducted under an atmosphere of nitrogen. Color Test I was negative at the end of 4, 8 and 12 hours. Carbonation, hydrolysis and treatment by customary procedures yielded 3.4 g. (18.3%) of *o*-mercaptobiphenyl melting at 38–40°. Purification through the sodium salt gave 3.0 g. (16.1%) of pure material melting at 40–41°.

Anal. Calcd. for $C_{12}H_{10}S$: S, 17.21. Found: S, 17.12, 17.05.

Removal of the solvent from the dried ether layer yielded 13.3 g. of liquid which solidified on standing; m.p. 55–70°. Steam distillation and purification of the materials by customary procedures gave a total yield of biphenyl melting at 66–68° of 3.3 g. (21.4%) and a total recovery of dibenzothiophene melting at 96–98° of 9.0 g. (48.8%). Based on the amount of bibenzothiophene which actually reacted, the yield of *o*-mercaptobiphenyl was 35.8%, and the yield of biphenyl was 41.8%.

Run III.—A stirred suspension of 18.4 g. (0.1 mole) of dibenzothiophene in 150 ml. of ether and 1.75 g. (0.25 g. atom) of lithium was refluxed for 36 hours. Color Test I was negative throughout. Carbonation, hydrolysis and acidification yielded no acidic material. Removal of the solvent from the dried ether layer resulted in a 95.1% recovery of dibenzothiophene; m.p. and mixed 98–99°. A check run gave essentially the same results.

AMES, IOWA

(12) Mr. K. Oita has observed that 1% sodium hydroxide is apparently more effective than a 5% solution for extracting 2-chloro-4-(or 6-) hydroxydibenzofuran.

(13) An authentic sample of 3,4-benzocoumarin was prepared in 18.7% yield by the procedure of reference 7. Cahn reports a m.p. of 94–95° and yields of 20–22%.

[CONTRIBUTION FROM THE DEPARTMENTS OF PHARMACOLOGY AND CHEMISTRY, VANDERBILT UNIVERSITY]

Alkylated Derivatives of Ethyl *t*-Butylmalonate and the Corresponding Barbituric Acids[1,2]

BY MILTON T. BUSH AND WM. DUDLEY BEAUCHAMP[3]

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Methyl, ethyl and allyl groups have been introduced into ethyl *t*-butylmalonate. The 5-methyl-5-*t*-butyl- and 5-allyl-5-*t*-butylbarbituric acids were prepared from these esters in small yields by condensation with urea. The latter barbituric acid was prepared also (in much better yield) from *t*-butylbarbituric acid and allyl bromide. 5-Ethyl-5-*t*-butylbarbituric acid was obtained in impure form. The anesthetic activities were compared with a known standard (amytal).

The 5,5-dialkyl barbituric acids in which one of the substituents is a *t*-butyl or other tertiary group have apparently not been described in pure form. This is due primarily to the difficulty of synthesis of the corresponding disubstituted malonic esters, which previously has been accomplished, if at all, in yields too small to allow satisfactory characterization of the products.[4,5] Secondarily, certain of the pure *t*-butyl-alkyl-malonic esters condense with urea only very slowly (as we have found), which makes the preparation of the barbituric acids still more difficult.

After the synthesis in relatively good yields of *t*-butylmalonic acid[6] it was hoped that substitution of a second alkyl group, despite the marked hindrance, could be made satisfactorily in the corresponding ester. The preparation in moderately good yields of the allyl, ethyl and methyl derivatives has now been carried out by appropriate modifications of the usual methods. It is the purpose of this report to describe these preparations, and also those of the corresponding barbituric acids.

The condensation of the esters with urea by the usual procedure has yielded minute amounts of 5-allyl-5-*t*-butyl- and of 5-ethyl-5-*t*-butylbarbituric acid, and considerably larger amounts of the 5-methyl derivative. Only the first and last of these have been obtained pure, but the ethyl deriva-

(1) Supported in large part by the Mallinckrodt Chemical Works.

(2) Presented at the XIIth International Congress of Pure and Applied Chemistry, New York, New York, September 10 to 13, 1951.

(3) Taken in part from the Ph.D. thesis of Wm. Dudley Beauchamp, August, 1952.

(4) A. W. Dox and W. G. Bywater, THIS JOURNAL, **58**, 731 (1936).

(5) F. C. Whitmore, private communication (1938).

(6) M. T. Bush, THIS JOURNAL, **61**, 637 (1939); U. S. Patent 2,260,800.

tive has been shown to be present (almost certainly) in the crude product by bio-assay in mice. The allyl derivative was prepared twelve years ago by (M. T. B.) by the reaction of allyl bromide and 5-*t*-butylbarbituric acid, in amounts ample for characterization and bio-assay. This preparation will be described. The product is identical with that obtained from the malonic ester.

Experimental

Ethyl *t*-Butylmalonate.—The preparation of *t*-butylmalonic acid by the method used successfully in 1939[6] was attempted repeatedly during 1947–1949 without success, although it was repeatedly checked during the years 1939–1942, both in this laboratory and by Dr. David M. Jones in the Organic Research Laboratory of the Mallinckrodt Chemical Works. It was finally abandoned in favor of the quite satisfactory method of Wideqvist for preparing the corresponding ethyl ester.[7] This involved reaction of methylmagnesium iodide with ethyl isopropylidenemalonate[8] followed by hydrolysis. The yield of ethyl *t*-butylmalonate was approximately 60% (Wideqvist reported 37%), b.p. 98–101° (10 mm.). It was identified by conversion to the malonic acid by way of the potassium salt[7] in yields of 80–90%. The acid potassium malonate was precipitated from aqueous solution of the dipotassium salt by half-neutralization with hydrochloric acid, as a white crystalline material. This was dissolved by addition of another equivalent of the acid, and the malonic acid was isolated and purified as described earlier.[6] The malonic acid had neutral equivalent 80.9 (theory 80.0), melted with slow gas evolution at 155–157°; decarboxylation gave a crude acid which was converted in good yield to *t*-butylacetamide, identical by mixed m.p. with that described by Homeyer, *et al.*[9] The malonic acid was therefore identical with the product described in 1939.[6]

Ethyl Alkyl *t*-Butylmalonates.—The disubstituted malonic esters were prepared by the procedure of Wallingford, Thorpe and Homeyer,[10] with the modification that the reactions with ethyl bromide and methyl iodide were carried out in sealed flasks, to avoid loss of the low boiling reactant. The crude product was refluxed in each instance with about 10% potassium hydroxide in 95% ethanol (approximately 10 ml. per gram of ester) for the purpose of effecting selective saponification of the monosubstituted ester. Ethyl *t*-butylmalonate itself is saponified practically completely under these conditions in 5 hours. The methyl derivative reacted appreciably in 5 hours, but 27% recovery of unsaponified ester was obtained from the crude product after one treatment. Similar treatment of the recovered material left 46% unsaponified. This product was assumed to be free of the monosubstituted ester. The ethyl and allyl derivatives were much more resistant to hydrolysis, and 20% recovery of unsaponified ester was obtained in each instance when the crude product was treated for three to four days with boiling alcoholic potassium hydroxide.

Besides unchanged ester and *t*-butylmalonic acid, the saponification of each of these crude disubstituted esters gave appreciable quantities of liquid product having properties which would be expected of a half-saponified ester. These products have not been characterized. The monosubstituted ester does not give more than traces of such a product.

Ethyl allyl-*t*-butylmalonate was recovered as the unsaponified fraction from a three-day treatment of the crude ester with boiling alcoholic potash. It distilled smoothly at 2 mm. and bath temperature 100°. The yield was 3.0 g. *ca.* 20% based on the ethyl *t*-butylmalonate taken at the start.

Anal.[11] Calcd. for $C_{14}H_{24}O_4$: C, 65.59; H, 9.44. Found: C, 66.04, 65.75; H, 9.27, 9.46.

Ethyl ethyl-*t*-butylmalonate was recovered from the crude product and distilled in the same manner as was the allyl derivative. The yield was 4.0 g. (20%), b.p. 90° (3 mm.), $n^{30}D$ 1.4348.

Anal.[11] Calcd. for $C_{13}H_{24}O_4$: C, 63.89; H, 9.90. Found: C, 63.94, 63.74; H, 9.89, 9.64.

Ethyl methyl-*t*-butylmalonate was obtained pure after putting the crude ester through one 5-hour treatment with alcoholic potash, recovering the unsaponified fraction (recovered 27%) and repeating the hydrolysis procedure for 5 hours (recovered 46%). The yield was 3.5 g. (13%), b.p. 100° (5 mm.); $n^{30}D$ 1.4291. The refractive index was the same for successive fractions.

Anal.[11] Calcd. for $C_{12}H_{22}O_4$: C, 62.57; H, 9.63. Found: C, 62.29, 62.05; H, 9.40, 9.50.

Alkyl *t*-Butylbarbituric Acids.—The condensations of the esters with urea were carried out by a modification of the method of Fischer and Dilthey,[12] that is, by refluxing a mixture of the ester with a slight excess of dry urea in approximately 2.0 *M* sodium ethylate solution (about 6 ml. per gram of ester) for about 24 hours. Most of the alcohol was distilled off, the cooled residue was dissolved in water (10–20 ml. per gram of ester), and the "disubstituted barbituric acid fraction" was obtained by a series of extractions: the aqueous solution (*p*H 11.7) was extracted twice with equal volumes of ether, to remove unchanged ester; the solution was then brought to *p*H 9.0 with 2 *M* NaH_2PO_4, the concentration of HPO_4 ion adjusted to 2.0 *M* with K_2HPO_4, and the volume adjusted to 75 ml. with 2.0 *M* K_2HPO_4; this solution was then put through a systematic multiple fractional extraction[13] between ether and 2.0 *M* K_2HPO_4, using four batches of each solvent and volume ratio 25 ml. ether/75 ml. aqueous. In this system the partition coefficient of 5-allyl-5-*t*-butylbarbituric acid is about 20, of the 5-methyl-5-*t*-butyl derivative about 10, and of the 5-*t*-butylbarbituric acid itself 1.0. The disubstituted barbituric acid accumulates in the ether pool, and any monosubstituted derivative, or other relatively strongly acidic by-product accumulates in the aqueous pool. The desired product was recovered in crude form by evaporating the ether, and recrystallization from methanol usually led to pure material.

5-Methyl-5-*t*-butylbarbituric Acid.—The crude "disubstituted barbituric acid fraction" (164 mg.) as separated by the partition process gave 120 mg. (15% yield) of white crystalline product from methanol; m.p. 268–270° (open or sealed capillary), constant on repeated recrystallization.

Anal.[11] Calcd. for $C_9H_{14}N_2O_3$: C, 54.52; H, 7.13; N, 14.13. Found: C, 54.30, 54.09; H, 6.71, 6.82; N (Dumas), 14.09, 14.01.

This barbituric acid was tested for anesthetic activity in mice. Doses up to 300 mg./kg., administered intraperitoneally, failed to produce even moderate anesthetic effects or other symptoms. Since there seems to be no doubt of the identity of this product, we are at present at a loss to explain these results. By analogy with closely related compounds we would expect doses this large to be effective.[14]

5-Ethyl-5-*t*-butylbarbituric acid was obtained similarly but could not be gotten pure by crystallization from methanol, or from ethylene dichloride. The crude "disubstituted barbituric acid fraction," total 29 mg. from 1.8 g. of the disubstituted malonic ester (most of which was recovered), was dissolved in a slight excess of 0.48 *N* NaOH, then diluted to 0.1 *N* and tested for hypnotic activity by intraperitoneal injection into 20-gram mice. A dose of 3.0 mg. produced slight ataxia in one mouse. In another mouse a dose of 11.3 mg. caused "light surgical" anesthesia in 10–13 minutes from the time of injection, which lasted for several hours. This is taken by us to be good evidence of the presence of several milligrams (say 2 to 4 mg.) of the sought disubstituted barbituric acid in the 11.3 mg. of crude stuff, because the previous history of the preparation rules out the presence of any other disubstituted barbituric acid, and no known by-product of the synthesis is likely to show appreciable hypnotic activity.

(7) S. Wideqvist, *Arkiv Kemi, Mineral. Geol.*, **B23**, No. 4, 1 (1946); *C. A.*, **41**, 1615 (1947).

(8) Prepared by the method of A. C. Cope and E. M. Hancock, THIS JOURNAL, **60**, 2645 (1938). Saponification of a sample of our product with alcoholic potassium hydroxide gave a good yield of the corresponding malonic acid of m.p. 168–170° (vigorous gas evolution). A. Meyenberg (*Ber.*, **28**, 786 (1895)) gives m.p. 170–171°.

(9) A. H. Homeyer, F. C. Whitmore and V. H. Wallingford, THIS JOURNAL, **55**, 4209 (1933).

(10) V. H. Wallingford, M. A. Thorpe and A. H. Homeyer, *ibid.*, **64**, 580 (1942).

(11) By Clark Microanalytical Laboratory, Urbana, Illinois.

(12) E. Fischer and A. Dilthey, *Ann.*, **335**, 334 (1904).

(13) M. T. Bush and P. M. Densen, *Anal. Chem.*, **20**, 121 (1948).

(14) D. L. Tabern and E. H. Volwiler, THIS JOURNAL, **56**, 1142 (1934).

5-Allyl-5-*t*-butylbarbituric acid was obtained in 1–2% yield (crude "disubstituted barbituric acid fraction") from batches of 2–3 g. of the ester. Most of the ester was recovered. The pure product was obtained by several crystallizations from methanol; yield 0.5%, m.p. 221–222°. This product was identical with that prepared several times in this Laboratory twelve years ago from 5-*t*-butylbarbituric acid and allyl bromide by modification of the method of Volwiler.[15] This method was modified by using an isolation procedure similar to that described above. From 1.84 g. of 5-*t*-butylbarbituric acid (m.p. 235–236°) there was obtained 193 mg. (10% yield) of product thrice crystallized from ethanol, to constant m.p. 221–222°.

Anal.[11] Calcd. for $C_{11}H_{16}N_2O_3$: C, 58.90; H, 7.19; N, 12.49. Found: C, 59.02, 59.29; H, 7.10, 7.23; N (Dumas), 12.69, 12.78.

The anesthetic activity of 5-*t*-butyl-5-allyl-barbituric acid was compared with that of amytal in mice, by intraperitoneal injection of aqueous solutions of the sodium salts (5 mg./ml.). The dose required to produce "surgical anesthesia" in 50% of the animals was about 15% higher for the new compound, and the duration of this anesthesia was about twice as long, as for amytal. The quality of the anesthesias was essentially the same.

Acknowledgment.—The authors are indebted to Professor A. W. Ingersoll for his advice during the course of this work.

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(15) E. H. Volwiler, THIS JOURNAL, **47**, 2236 (1925).

[CONTRIBUTION FROM THE CHEMISTRY DIVISION OF THE OAK RIDGE NATIONAL LABORATORY]

Evidence for a Cyclic Intermediate in the Reaction of Diarylethylamines with Nitrous Acid[1]

BY PHILIP S. BAILEY[2] AND JOHN G. BURR, JR.

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The rearrangement at 70° of 2-phenyl-2-(*p*-tolyl)-ethylammonium-1-C^{14} nitrite in either dry ligroin or in water has been found to give a mixture of carbinols. The same rearrangement in dry butanol at 70° has been found to give a mixture consisting of *55% carbinols*, about 35–40% of the corresponding butyl ethers and 5–10% 4-methylstilbene. The per cent. migration of the *p*-tolyl group in this nitrite has been found to be independent of the acidity or the nitrite ion concentration in water. The reaction of 2-phenyl-2-(*p*-tolyl)-ethylamine hydrochloride with nitrous acid has been found to be an over-all second-order reaction at 74°, corresponding to the reaction of other aliphatic amines with nitrous acid. The rearrangement of 2-phenyl-2-(*o*-tolyl)-ethylamine-1-C^{14} with nitrous acid proceeded with 42% *o*-tolyl migration. The facts are discussed in terms of a concerted process for rearrangement step of the conventional mechanism for amine–nitrous acid reactions.

Introduction

Aliphatic amines react with nitrous acid by a presumed mechanism which can be summarized in the steps

$$RNH_2 + HNO_2 \longrightarrow RN_2^+ + OH^- + H_2O \quad (1)$$

$$RN_2^+ \begin{cases} \longrightarrow R^+ + N_2 \\ \xrightarrow{X^-} R{-}X + N_2 \end{cases} \quad (2)$$

Investigation of the reaction kinetics of this system[3] has shown that it is over-all second order in very weak acid. It has been usually assumed that the rearrangement step is fast and not rate-determining and that the final products of the reaction are those resulting from the known modes of reaction and rearrangement of carbonium ions, such as R^+; or from nucleophilic displacement of the diazonium ion by a base, X^-, as shown.[4]

It has been shown recently[5] that the migration ratios observed in the reactions of 2,2-diarylethylamines with nitrous acid are not the same as those observed in the acid-catalyzed rearrangement of the corresponding 2,2-diarylethanols. In fact, very little selectivity between phenyl and substituted phenyl was observed in the amine–nitrous acid rearrangement, although the reaction is usually written as proceeding through the same carbonium ion intermediate as does the carbinol rearrangement. It is thus evident that, at least in the case of these amines, the second step of the reaction cannot be set down so assuredly as a simple displacement or rearrangement reaction. It is shown in this paper that not only the migration ratios but also the reaction products are not those which would be expected from such a simple picture.

Here are reported the results of a more detailed examination of the reaction of several of these amines with nitrous acid. Three aspects of the reaction have been investigated: (1) the effect upon the migration ratio of the acidity, nitrite ion concentration and the nature of the reaction medium; (2) the nature of the reaction products in several different types of reaction medium (3) the over-all kinetic order observed in the reaction of these amines with nitrous acid.

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(2) Member of the Research Participation program sponsored jointly by the Oak Ridge National Laboratory and the Oak Ridge Institute of Nuclear Studies; permanent address, University of Texas, Austin, Texas.

(3) Recent conclusions regarding these kinetics are well summarized in two papers by C. K. Ingold, E. D. Hughes and their co-workers, THIS JOURNAL, **74**, 555 (1952); *Nature*, **166**, 642 (1950). The reactions of amines with nitrous acid are over-all second order in very weak acid, and over-all third order in stronger acid. A good survey of earlier work is found in L. P. Hammett, "Physical Organic Chemistry," 1st Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 294–296.

(4) There has been relatively little systematic examination, such as D. W. Adamson and J. Kenner, *J. Chem. Soc.*, 838 (1934), of the reaction products of aliphatic amines and nitrous acid. This lack of information of the reaction products sometimes brings a certain element of doubt into otherwise excellent work. For example, F. C. Whitmore and R. S. Thorpe reported (THIS JOURNAL, **63**, 1118 (1941)) that the reaction of methylamine with nitrous acid did not give any methanol (nor anything else that they could isolate except recovered methylamine). Nevertheless, a number of investigators have studied the kinetics of this reaction on the assumption that the reaction product is methanol; *cf.*, Taylor, *J. Chem. Soc.*, 1099 (1928); Euler, *Ann.*, **330**, 280 (1903), and more recently Dusenbury and Powell, THIS JOURNAL, **73**, 3269 (1951).

(5) J. G. Burr, Jr., and L. S. Ciereszko, *ibid.*, **74**, 4526 (1952); L. S. Ciereszko and J. G. Burr, Jr., *ibid.*, **74**, 5431 (1952).