[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BRYN MAWR COLLEGE]

Vinylalkylmalonic Esters and Barbituric Acids

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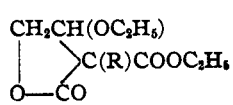
A number of 5-(substituted vinyl)-5-alkyl barbituric acids[2] have been prepared from the corresponding malonic or cyanoacetic esters, which were obtained by the alkylation of alkylidene malonic and cyanoacetic esters.[3] These synthetic methods are quite general and practical, but they cannot be used to prepare the vinyl derivatives themselves. Ethyl ethylidenemalonate was found to polymerize under conditions suitable for alkylation of its higher homologs.[3] Ethyl vinylethylmalonate has been prepared by an indirect method, but this ester proved to be very susceptible to cleavage by alcoholic sodium ethoxide, and its condensation with urea yielded α-ethylcrotonamide instead of vinylethylbarbituric acid.[4] The present paper describes an investigation of methods by which it has been possible to prepare several vinyl alkylmalonic esters and barbituric acids.

Unsuccessful attempts were made to adapt the Boord olefin synthesis[5] to the introduction of vinyl groups into malonic esters and barbituric acids. The product obtained by alkylating ethyl butylmalonate with α,β-dibromoethylethyl ether (presumably the ester, I) decomposed on distillation into ethyl bromide and the lactone, II. Ethyl ethylmalonate also yielded a lactone (IV) under these conditions.

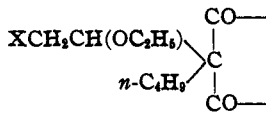


I, X = Br; R = n-C_4H_9
III, X = Cl; R = n-C_4H_9

II, R = n-C_4H_9
IV, R = C_2H_5

It was possible to synthesize the more stable chloro-ester III from ethyl butylmalonate and α,β-dichloroethylethyl ether, but the unsaturated ester XIV could not be obtained from III by reaction with zinc and alcohol under the conditions of the Boord synthesis. Attempts to alkylate 1-methylbutylmalononitrile and ethyl-1-methylbutylcyanoacetate with α,β-dibromoethylethyl ether were unsuccessful.

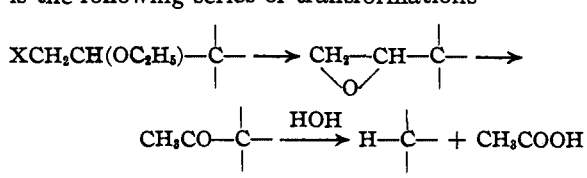
Condensation of the lactone II with urea proved to be a suitable method for preparing the barbituric acid derivative V.



V, X = OH
VI, X = Cl
VII, X = Br

The halogenated derivatives VI and VII were obtained by treating V with thionyl chloride and thionyl bromide, respectively, in the presence of pyridine. Attempts to prepare 5-vinyl-5-butylbarbituric acid from VI and VII by elimination of halogen and ethoxyl were unsuccessful.

In preliminary attempts to prepare VII, V was heated with 48% hydrobromic acid. This treatment resulted in cleavage of the hydroxyl-containing side chain and produced 5-n-butyl barbituric acid. The same product was formed from VI and VII under similar conditions. One possible explanation for this unexpected cleavage is the following series of transformations



Modification of the methods previously used to prepare ethyl vinylethylmalonate[4] resulted in fairly practical syntheses of four vinylalkylmalonic esters. The reactions employed consisted in the alkylation of monoalkylmalonic esters with symmetrical dibromoethylene to give (β-bromovinyl)-alkylmalonic esters (VIII–XI), which were then dehalogenated to vinylalkylmalonic esters (XII–XV). The alkylation of

$(BrCH{=}CH)C(R)(COOC_2H_5)_2$

VIII, R = C_2H_5 X, R = n-C_4H_9
IX, R = i-C_5H_{11} XI, R = C_6H_5

$(CH_2{=}CH)C(R)(COOC_2H_5)_2$

XII, R = C_2H_5 XIV, R = n-C_4H_9
XIII, R = i-C_5H_{11} XV, R = C_6H_5

ethyl isoamylmalonate with symmetrical dibromoethylene gave a better yield of IX when the enolate was prepared from the ester and sodamide

(1) Abstracted from part of a dissertation presented to the Faculty of the Graduate School of Bryn Mawr College by Dorothea Heyl in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Cope, Hartung, Hancock and Crossley, THIS JOURNAL, **62**, 1199 (1940), and preceding papers.

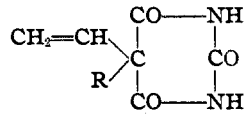
(3) Cope, Hartung, Hancock and Crossley, *ibid.*, **62**, 314 (1940), and preceding papers.

(4) Cope and McElvain, *ibid.*, **54**, 4311, 4319 (1932).

(5) Soday and Boord, *ibid.*, **55**, 3293 (1933), and preceding papers.

rather than powdered sodium, provided 0.2 molar equivalent of absolute alcohol was added to the enolate. If alcohol was not added to the enolate, little if any alkylation occurred.[6] In the previous work, ethyl (β-bromovinyl)-ethylmalonate was converted to ethyl vinylethylmalonate through reaction with zinc dust and alcohol at 170° in sealed tubes or a steel bomb. It was found possible to dehalogenate the (β-bromovinyl)-alkylmalonic esters much more simply and in better yield by heating them with zinc dust and acetamide. The principal advantage of this procedure is the fact that the high boiling point of acetamide makes it possible to operate at atmospheric pressure. The acetamide was separated from the dehalogenated esters simply by washing them with dilute hydrochloric acid. The dehalogenation of α-bromonaphthalene, which was investigated first as a model substance containing an inert halogen atom, also proceeded smoothly by this method.

Barbituric acids were prepared from the vinylalkylmalonic esters by condensing them with guanidine rather than urea. The condensations were carried out in the absence of excess sodium ethoxide, in order to minimize cleavage. The resulting di-iminobarbituric acids were not isolated, but were hydrolyzed directly. The structure of each of the vinyl alkyl barbituric acids (XVI, XVII and XVIII) was established by quantitative reduction to the corresponding 5-ethyl-5-alkylbarbituric acid.



XVI, R = C_2H_5
XVII, R = i-C_5H_{11}
XVIII, R = n-C_4H_9

Ethyl (β-bromovinyl)-allylmalonate (XI) might be expected to rearrange on heating, since rearrangement with migration of the allyl group occurs when other (substituted vinyl)-allylmalonic and cyanoacetic esters are heated.[7] Consequently the structure of XI was established by hydrogenation, and conversion of the resulting ethyl ethylpropylmalonate into ethylpropylmaonic acid and 5-ethyl-5-propylbarbituric acid as solid derivatives. Attempts at rearrangement showed that XI could not be isomerized into the alkylidene ester, $C_3H_5CHBrCH{=}C(COOC_2H_5)_2$, by heating. At 200° extensive polymerization and at 170° slight polymerization occurred, and the portion of the ester which was not polymerized was recovered unchanged at both temperatures. XI would be expected to resist rearrangement because of the size and electron attraction of the bromine atom.[8]

The relatively low yield of ethyl vinylallylmalonate, XV, obtained from XI is probably due to partial rearrangement of XV during the dehalogenation, and decomposition of the rearrangement product. XV was rearranged on heating at 170° into ethyl (4-pentenylidene)-malonate, $CH_2{=}CHCH_2CH_2CH{=}C(COOC_2H_5)_2$ (XIX). The structure of XIX was established by hydrogenation and conversion of the resulting ethyl n-amylmalonate into n-amylmalonamide.

Experimental Part[9]

α-Butyl-α-carbethoxy-β-ethoxy-γ-butyrolactone (II).—Sodium (5.75 g., powdered under xylene) and 300 cc. of dry ether were placed in a 500-cc. three-necked flask equipped with a stirrer, reflux condenser and drying tube, and a dropping funnel. Ethyl butylmalonate (54 g.) was added dropwise, and the mixture was stirred until all of the sodium had reacted. The solution was cooled to −10° and 70 g. of α,β-dibromoethylethyl ether[10] was added rapidly. Sodium bromide precipitated immediately. After twenty minutes the ether solution was washed three times with water and concentrated *in vacuo*. Partial decomposition with evolution of ethyl bromide and a resulting increase in pressure occurred when the residue was distilled *in vacuo*. Three distillations through a Widmer column gave the lactone (II) free from halogen; yield 36.1 g. (56%), b. p. 129–130° (2 mm.); $n^{25}D$ 1.4459; d^{25}_{25} 1.0579. M_D calcd. 65.00, found 65.29.

Anal. Calcd. for $C_{13}H_{22}O_5$: C, 60.44; H, 8.59. Found: C, 60.56; H, 8.44.

Ethyl butylmalonate (15 g., 27%) was recovered as a fore-run in the distillation.

Variations of the above preparation in which the reaction time and temperature were modified, or the ester enolate was added to the alkylating agent, or sodamide was used in place of sodium, gave similar results. Partial loss of ethyl bromide occurred when the product from a similar preparation was distilled at an initial pressure of 1×10^{-4} mm. Treatment of this distillate (probably a mixture of I and II) or the crude undistilled ester (I) with zinc dust and boiling alcohol followed by distillation, also yielded the lactone (II).

Ethyl (α-Ethoxy-β-chloroethyl)-butylmalonate (III).—α,β-Dichloroethylethyl ether[11] (75.8 g.) was added rapidly to a solution of the sodium enolate prepared from 9.2 g. of powdered sodium and 86.4 g. of ethyl butyl-

(6) The function of the alcohol is uncertain. Some alcohol is present in sodium enolates prepared from esters and metallic sodium in ether, because of partial reduction of the ester; see ref. 4.

(7) Cope, Hoyle and Heyl, *ibid.*, **63**, 1843 (1941); Cope and Hardy, *ibid.*, **62**, 441 (1940).

(8) See ref. 7 and Cope, Hofmann and Hardy, *ibid.*, **63**, 1852 (1941), concerning the mechanism of the rearrangement.

(9) All boiling and melting points are uncorrected.

(10) Swallen and Boord, THIS JOURNAL, **52**, 654 (1930).

(11) Wildman and Gray, *ibid.*, **41**, 1122 (1919).

malonate in 350 cc. of dry ether and cooled to −10°. The mixture was stirred for twelve hours at 0°, washed, and distilled as described above. The yield of III was 88 g. (68%); b. p. 119° (2 mm.); $n^{25}D$ 1.4448; d^{25}_{25} 1.0573; M_D calcd. 81.30, found 81.47.

Anal. Calcd. for $C_{12}H_{17}O_5Cl$: C, 55.80; H, 8.43. Found: C, 55.87; H, 8.37.

α - Ethyl - α - carbethoxy - β - ethoxy - γ - butyrolactone (IV).—Ethyl ethylmalonate (47 g.) was added to an equivalent quantity of freshly prepared sodamide suspended in 500 cc. of dry ether. After the ammonia formed was removed by heating, the suspension was cooled to 0°, α,β-dibromoethylethylether (69.6 g.) was added, and the mixture was stirred for sixteen hours at 0°. The product isolated according to the procedure described under (II) above was the lactone, IV; yield 37.7 g. (66%); b. p. 149.5° (8.5 mm.); $n^{25}D$ 1.4443; d^{25}_{25} 1.1022; M_D calcd. 55.76, found 55.69.

Anal. Calcd. for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.32; H, 7.84.

1-Methylbutylmalononitrile.—1-Methylbutylidene malononitrile[12] (68 g.) in approximately 200 cc. of alcohol was shaken with 2 g. of palladinized charcoal catalyst[13] and hydrogen at 1–2 atmospheres pressure until the absorption of hydrogen became very slow (twenty-four hours). After filtering from the catalyst the alcohol was removed *in vacuo*, and the residue was washed with dilute hydrochloric acid and water. Distillation yielded a liquid product contaminated with a white solid, which was removed by centrifugation and additional washing with dilute hydrochloric acid and water. Redistillation through a Widmer column gave 46.3 g. (67%) of 1-methylbutylmalononitrile; b. p. 99–100° (8 mm.); $n^{25}D$ 1.4324; d^{25}_{25} 0.9086; M_D calcd. 38.80, found 39.02.

Anal. Calcd. for $C_8H_{12}N_2$: N, 20.57. Found: N, 20.75.

Alkylation of the sodium derivative prepared from 34 g. of the above nitrile with α,β-dibromoethylethyl ether under conditions described for the preparation of IV resulted in recovery of 13.3 g. of 1-methylbutylmalononitrile, while the remainder was converted into high boiling material. Trial showed that 1-methylbutylmalononitrile could be converted into its sodium derivative under these conditions and recovered on acidification with hydrochloric acid without appreciable loss. Consequently the reaction failed in the alkylation phase. An attempt to alkylate ethyl 1-methylbutylcyanoacetate with α,β-dibromoethylethyl ether under similar conditions also failed, 90% of the ester being recovered.

5-*n*-Butyl-5-(α-ethoxy-β-hydroxyethyl)-barbituric Acid (V).—Urea (10.6 g.) and the lactone II (45.5 g.) were added to a solution of sodium (8.1 g.) in 250 cc. of absolute alcohol. The solution was refluxed for seventeen hours, after which the alcohol was removed *in vacuo*. The residue was dissolved in water, extracted three times with ether to remove neutral impurities, and acidified with concd. hydrochloric acid. The sticky precipitate was dissolved in ether and washed with four 50-cc. portions of saturated sodium bicarbonate solution and with water. The ether was evaporated and the residue crystallized, first from benzene, then from a mixture of benzene and pentane. The yield of V was 28.8 g. (60%); m. p. 127–127.5°.

Anal. Calcd. for $C_{12}H_{20}O_5N_2$: N, 10.29. Found: N, 10.20.

V (1 g.) and 10 cc. of constant boiling hydrobromic acid were heated at 50–110° for forty-five minutes. A black solid was formed, which was washed with water and dried by boiling with benzene. The solid was placed in a Soxhlet extractor and extracted with benzene. 5-*n*-Butylbarbituric acid (0.3 g.) was obtained from the extract by recrystallization from dilute alcohol; m. p. and mixed m. p. with a known sample 206.5–207°.

5 - *n* - Butyl - 5 - (α - ethoxy - β - chloroethyl) - barbituric Acid (VI).—Thionyl chloride (1.3 cc.) was added in small portions to a mixture of 4.17 g. of V, 1.2 g. of dry pyridine, and 10 cc. of carbon tetrachloride, with cooling. After standing for ten minutes, the mixture was heated at 75° for forty-five minutes. Ether was added to the mixture, which was washed with dilute hydrochloric acid, sodium bicarbonate solution and water. After removal of the ether, the product was crystallized from benzene; yield 4.3 g. (95%); m. p. 158.5–159°.

Anal. Calcd. for $C_{12}H_{19}O_4N_2Cl$: N, 9.64. Found: N, 9.58.

VI (1.0 g.) was boiled with 8 cc. of 48% hydrobromic acid for twenty minutes. The solution was diluted with ten volumes of water, filtered to remove dark insoluble material, and extracted with ether. Evaporation of the ether and recrystallization of the residue from water gave 0.25 g. of 5-*n*-butylbarbituric acid; m. p. and mixed m. p. with a known sample 206–207°.

5-*n*-Butyl-5-(α-ethoxy-β-bromoethyl)-barbituric Acid (VII).—Thionyl bromide (1.8 cc.) was added to V (6.0 g.), pyridine (1.8 g.), and 10 cc. of benzene. The reaction and purification were carried out as described above for VI. The yield of VII was 5.9 g. (80%): m. p. 166–167°.

Anal. Calcd. for $C_{12}H_{19}O_4N_2Br$: N, 8.36. Found: N, 8.17.

VII (0.3 g.) was suspended in 48% hydrobromic acid. After boiling for twenty minutes, the hydrobromic acid was removed *in vacuo* and the residue recrystallized from dilute alcohol. 5-*n*-Butylbarbituric acid (0.07 g.) was obtained; m. p. and mixed m. p. with a known sample 206–207°.

Dehalogenation of α-Bromonaphthalene with Zinc and Acetamide.—α-Bromonaphthalene (15 g.), acetamide (12.9 g.), and zinc dust (15 g.) were placed in a flask equipped with a stirrer and an air condenser. The mixture was heated in a bath at 230° for three hours. Ether and 20% hydrochloric acid were added to the mixture. Filtration to remove zinc and evaporation of the ether yielded 6.5 g. (69%) of naphthalene, m. p. 80–80.5°.

Ethyl Vinylethylmalonate (XII).—Ethyl (β-bromovinyl)-ethylmalonate[4] (36 g.), acetamide (27.2 g.), and zinc dust (24 g.) were heated in a bath at 180° and stirred for three hours. Ether and 20% hydrochloric acid were added and the mixture was filtered. The ether layer was separated, combined with ether washings of the zinc and of the aqueous layer, and distilled through a Widmer column. The yield of XII was 18.8 g. (71%); b. p. 117.5–118° (22 mm.); $n^{25}D$ 1.4318; d^{25}_{25} 0.9997; M_D calcd. 55.85, found 55.73.

(12) Cope and Hoyle, THIS JOURNAL, **63**, 733 (1941).

(13) Hartung, *ibid.*, **50**, 3372 (1928).

Similar procedures were used for dehalogenation of the other ethyl (β-bromovinyl)-alkylmalonates.

5-Vinyl-5-ethylbarbituric Acid (XVI).—Guanidine carbonate (27.2 g.) was added to a solution of sodium (6.18 g.) in 220 cc. of absolute alcohol. The mixture was refluxed for fifteen minutes, ethyl vinylethylmalonate (35.9 g.) was added, and refluxing was continued for five hours. The alcohol was removed *in vacuo*, and 300 cc. of water and 270 cc. of concd. hydrochloric acid were added. The mixture was boiled for three hours, during which time approximately 30 cc. of alcohol and water were distilled. The oil which separated on cooling was extracted with ether and crystallized from benzene; yield 4.2 g. The hydrochloric acid solution was neutralized to litmus by adding sodium hydroxide, distilled to dryness in vacuum, and dried by distilling benzene from the residue. An additional 5.2 g. of XVI was obtained from this residue by repeated extractions with boiling ether and crystallization from benzene; total yield 9.4 g. (29%), m. p. 172.5–173°.

Anal. Calcd. for $C_8H_{10}O_3N_2$: N, 15.38. Found: N, 15.34.

In quantitative hydrogenations of approximately 0.3-g. samples of XVI in 25 cc. of alcohol in the presence of 0.5 g. of palladinized charcoal, 100.8 and 100.2% of the theoretical quantity of hydrogen was absorbed. The reduction product was crystallized from dilute alcohol and identified as 5,5-diethylbarbituric acid; m. p. and mixed m. p. with a known sample 186–187°.

Ethyl (β-Bromovinyl)-isoamylmalonate (IX).—Sodamide was prepared in the usual manner from 8.37 g. of sodium and anhydrous ammonia in a 1-liter three-necked flask.[14] The ammonia was replaced by 350 cc. of dry ether, and ethyl isoamylmalonate (83.6 g.) was added rapidly. The ammonia formed was removed by refluxing and distilling a portion of the ether, and 3.3 g. of absolute alcohol was added. *sym*-Dibromoethylene (135 g.) was added, and the mixture was refluxed for eight hours and stirred at room temperature for eighty hours. The ether solution was washed with cold dilute hydrochloric acid and water, and the ester was distilled. Ethyl isoamylmalonate (17.7 g.), IX (46.7 g., 38%), and a residue (26 g.) of higher boiling material which was not investigated were separated. The properties of IX are: b. p. 158° (11 mm.); $n^{25}D$ 1.4628; d^{25}_{25} 1.1926; M_D calcd. 77.47, found 77.62.

Anal. Calcd. for $C_{14}H_{23}O_4Br$: C, 50.16; H, 6.92. Found: C, 50.27; H, 6.78.

From a similar preparation in which no alcohol was added, 56% of the ethyl isoamylmalonate was recovered, and the yield of IX was 5%. Preparations in which powdered sodium was used to form the enolate (as in ref. 4) yielded 20–27% of IX.

Ethyl Vinylisoamylmalonate (XIII).—A mixture of 46.3 g. of IX, 27.2 g. of zinc dust, and 24.6 g. of acetamide was refluxed and stirred for three and one-half hours. Extraction and distillation according to the procedure described for XII yielded 25.7 g. (72%) of XIII; b. p. 125–126° (10 mm.); $n^{25}D$ 1.4358; d^{25}_{25} 0.9643; M_D calcd. 69.71, found 69.68.

(14) See Cope and Hancock, THIS JOURNAL, **60**, 2644 (1938), for general procedure.

Anal. Calcd. for $C_{14}H_{24}O_4$: C, 65.59; H, 9.44. Found: C, 65.58; H, 9.37.

5-Vinyl-5-isoamylbarbituric Acid (XVII).—XIII (25.7 g.) was added to a solution of guanidine prepared by adding 16.2 g. of guanidine carbonate to a solution of 3.68 g. of sodium in 130 cc. of absolute alcohol. The mixture was refluxed for five hours, concentrated, and the imino compound formed on acidification was hydrolyzed by the procedure described for XVI. XVII was isolated by three extractions of the aqueous hydrochloric acid solution with ether, and purified by recrystallization from benzene and a mixture of alcohol and water; yield 7.0 g. (32%); m. p. 129.5–130°.

Anal. Calcd. for $C_{11}H_{16}O_3N_2$: N, 12.49. Found: N, 12.43.

XVII was characterized in the same manner as XVI by a quantitative reduction in which 99% of the theoretical quantity of hydrogen was absorbed. The product was 5-ethyl-5-isoamylbarbituric acid; m. p. and mixed m. p. with a known sample 156–157°.

Ethyl (β-Bromovinyl)-butylmalonate (X).—Ethyl butylmalonate (113.2 g.) was added to 12.1 g. of powdered sodium suspended in 450 cc. of dry ether. The mixture was refluxed until all of the sodium had reacted. *sym*-Dibromoethylene (195 g.) was added, and the mixture was refluxed for seven hours and stirred at room temperature for eighty-four hours. On extraction and distillation by the procedure described for IX, ethyl butylmalonate (21 g.), X (44.8 g., 26%) and higher boiling material (42 g.) were separated. Analyses of X purified by refractionation indicated the presence of traces of impurities: b. p. 149° (10 mm.); $n^{25}D$ 1.4638; d^{25}_{25} 1.2184; M_D calcd. 72.85, found 72.93.

Anal. Calcd. for $C_{13}H_{21}O_4Br$: C, 48.61; H, 6.59. Found: C, 49.04; H, 6.53.

Ethyl Vinylbutylmalonate (XIV).—A mixture of X (41.1 g.), zinc dust (25.1 g.), and acetamide (22.7 g.) was refluxed and stirred for three hours. XIV (21.8 g., 70%) was isolated by the procedure described for XII; b. p. 116–117° (9 mm.); $n^{25}D$ 1.4352; d^{25}_{25} 0.9758; M_D calcd. 65.09, found 65.02.

Anal. Calcd. for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.19; H, 9.14.

5-Vinyl-5-butylbarbituric Acid (XVIII).—XIV (14.3 g.) was added to the guanidine prepared from a solution of 2.17 g. of sodium in 60 cc. of absolute alcohol, and 9.6 g. of guanidine carbonate. The mixture was refluxed for five hours. Hydrolysis and extraction by the procedure described for XVII and recrystallization from dilute alcohol yielded 4.9 g. (40%) of XVIII, m. p. 84–85°.

Anal. Calcd. for $C_{10}H_{14}O_3N_2$: N, 13.33. Found: N, 13.44.

On quantitative reduction approximately 0.1 g. of XVIII absorbed 100.6% of the theoretical quantity of hydrogen. The product was 5-ethyl-5-butylbarbituric acid, m. p. and mixed m. p. with a known sample 122.5–123°.

Ethyl (β-Bromovinyl)-allylmalonate (XI).—The sodium enolate was prepared from 100 g. of ethyl allylmalonate and 0.5 mole of sodamide in 500 cc. of dry ether. Absolute alcohol (4.6 g.) and *sym*-dibromoethylene (186 g.) were

TABLE I

RESULTS OF PHARMACOLOGICAL TESTS IN WHITE MICE[a,b]

Barbituric acid derivative	AD50,[c] mg./kg.	AD100, mg./kg.	LD50, mg./kg.	Ratio, LD50/AD50	Duration at AD100 Induction, min.	Duration at AD100 Anesthesia, hours
5-Vinyl-5-ethyl (XVI)	380	500	1050	2.8	60	>4.8
5-Vinyl-5-isoamyl (XVII)	310	400	480	1.5	8	3.2
5-Ethyl-5-(1-isopentenyl)	260	350	500	1.9	8	>1.4
5-Vinyl-5-butyl (XVIII)	245	350	550	2.2	11	>4.8
5-Ethyl-5-(1-butenyl)	140	250	470	3.4	15	>2.3
5-Ethyl-5-isoamyl	210	450	415	2.0	3	1

[a] We are indebted to Dr. Arnold D. Welch for advice and to Sharp and Dohme, Inc., for providing facilities for pharmacological testing. [b] These data are not directly comparable with previous results (ref. 3), because food was not withdrawn from the mice. [c] For explanation of terms and methods of testing see Cope and Hancock, THIS JOURNAL, **61**, 96 (1939). Clear water solutions of the sodium salts of the barbituric acid derivatives were administered to the mice by stomach tube.

added. The mixture was refluxed for nine hours and stirred at room temperature for eighty hours. Following the procedure described for IX, ethyl allylmalonate (17 g.), XI (40.4 g., 26%), and higher boiling material (42 g.) were separated. The properties of XI are: b. p. 101° (2 mm.); $n^{25}D$ 1.4751; d^{25}_{25} 1.2764; M_D calcd. 67.76, found 67.53.

Anal. Calcd. for $C_{12}H_{17}O_4Br$: C, 47.23; H, 5.62. Found: C, 47.21; H. 5.53.

XI (5.5 g.) was hydrogenated in alcohol solution in the presence of a total of 4 g. of palladinized charcoal, added in portions in order to complete the reduction. Distillation yielded 3.2 g. of ethyl ethylpropylmalonate, b. p. 114–115° (10 mm.). This ester was identified by saponification to ethylpropylmalonic acid, m. p. 118–119°,[15] and condensation with urea to form 5-ethyl-5-propylbarbituric acid, m. p. 147–148°.[16]

XI (16.4 g.) was refluxed at a pressure regulated so that the temperature of the liquid was 200° for seventy-five minutes, and then distilled. XI (10.8 g.) was recovered, while the distillation residue was a brittle polymer. Similar results were obtained by heating XI to 170° for five hours.

Ethyl Vinylallylmalonate (XV).—XI (50 g.), zinc dust (32 g.), and acetamide (29 g.) were heated at 130 to 170° for one and one-half hours. XV (14.4 g., 39%) was isolated by the procedure described for XII; b. p. 112–113° (11 mm.); $n^{25}D$ 1.4450; d^{25}_{25} 1.0079; M_D calcd. 60.00, found 59.93.

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.94; H, 8.07.

Rearrangement of XV to Ethyl (4-Pentenylidene)-malonate (XIX).—When XV was refluxed at 200° under diminished pressure, a mixture was formed, while at 140° no rearrangement occurred. When XV (16 g.) was heated at 170° for eight hours, the distillate (13.8 g.) had reached constant refractive index, indicating complete rearrangement (see ref. 7 for procedure). Fractionation showed that the product was a mixture, however, from which 5.2 g. of fairly pure XIX was obtained; b. p. 140–143° (16 mm.); $n^{25}D$ 1.4530; d^{25}_{25} 1.0141; M_D calcd. 60.00, found 60.48 (exaltation 0.48).

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.43; H, 7.70.

XIX (6.3 g.) was hydrogenated in the presence of 1 g. of palladinized charcoal in alcohol solution. On distillation 5 g. of ethyl *n*-amylmalonate was obtained, b. p. 148–150° (30 mm.). This ester was characterized by shaking a sample with concd. aqueous ammonia. The solid amide formed was recrystallized from alcohol; m. p. and mixed m. p. with a known sample of *n*-amylmalonamide, 198–199°.

(15) Rasetti, *Bull. soc. chim.*, [3] **33**, 684 (1905).

(16) Fischer and Dilthey, *Ann.*, **335**, 346 (1904).

Pharmacological Data

The results of pharmacological tests of the three vinyl alkyl barbituric acids by oral administration to white mice are recorded in Table I. Similar data for the 5-ethyl-5-(substituted vinyl) barbituric acids which differ from XVII and XVIII only in the position of the double bond are included for comparison. The vinyl derivatives proved to be slightly less effective and had slightly poorer therapeutic ratios than their isomers. Compounds V, VI and VII were found to be non-toxic and had no hypnotic action when given to mice orally in tragacanth suspension at 800 mg./kg.

Summary

Methods have been described by which four vinylalkylmalonic esters and three 5-vinyl-5-alkyl barbituric acids have been prepared. Pharmacological tests of the barbiturates have been made. Ethyl vinylallylmalonate has been observed to rearrange into ethyl (4-pentenylidene)-malonate on heating.

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