[Contribution from the Baker Laboratory of Chemistry at Cornell University]

The Reaction of 1,3-Dibromobutane with Sodio Malonic Ester[1]

A. T. BLOMQUIST and JOSEPH WOLINSKY

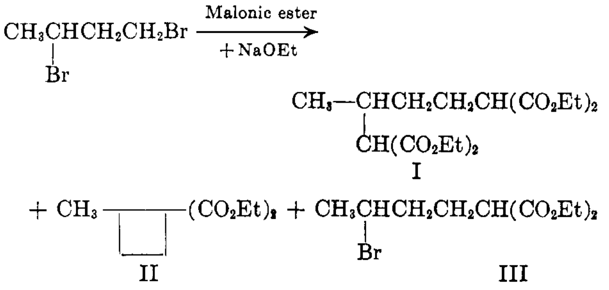
Received May 29, 1956

By using a large excess of malonic ester (200%) in the condensation of 1,3-dibromobutane with sodio malonic ester a fair yield (*ca.* 35%) of tetraethyl 2-methyl-1,1,5,5-pentanetetracarboxylate has been realized. Diethyl 2-methyl-1,1-cyclobutanedicarboxylate and diethyl γ-bromobutylmalonate were isolated as accessory products. The tetraester gave β-methylpimelic acid upon hydrolysis and decarboxylation. Characterization of the cyclobutane product included, among other things, its conversion to *trans*-2-methylcyclobutanecarboxylic acid. The bromoester product was characterized by (1) its conversion to diethyl *n*-butylmalonate and (2) its transformation to diethyl 2-methyl-1,1-cyclobutanedicarboxylate.

Need for tetraethyl 2-methyl-1,1,5,5-pentanetetracarboxylate (I) as an intermediate for the synthesis of 1,2-dimethylene-3-methylcyclopentane[2] prompted us to examine in some detail the reaction of 1,3-dibromobutane with sodio malonic ester. This reaction, similar to that of trimethylene bromide with sodio malonic ester,[3] should afford the desired open-chain tetraester I in fair yield by employing the proper ratio of reactants.

Incomplete studies of the reaction have been reported by earlier workers. Ipatiev and Mikeldase[4] as well as Blackstock and Perkin[5] only described the isolation and characterization of diethyl 2-methyl-1,1-cyclobutanedicarboxylate (II) from the mixture of products obtained in the reaction.

More recently Kazanskii and Lukina[6] reported diethyl γ-bromobutylmalonate (III) and II, containing *ca.* 18% of unsaturated substances arising from III, as being the principal products of the reaction in question. No reference to the tetraester I was made by any of these earlier workers.



The recent work of Cason on the condensation of trimethylene bromide with malonic ester[3] showed that the formation of a dicondensation product such as the tetraester I would be favored by using a large excess of malonic ester. It was found that reaction of 2 moles of 1,3-dibromobutane with 6.2 moles of malonic ester and 4 moles of sodium ethoxide gave a mixture of products from which four principal compounds could be obtained by rapid distillation *in vacuo:* (1) the tetraester I (*ca.* 35%); (2) the crude cyclobutane derivative II (*ca.* 32%); (3) crude bromoester III (*ca.* 12%); and (4) recovered malonic ester. The yield of I decreased to 20% when less malonic ester was used.

The redistilled tetraester I, b.p. 160° (0.5 mm.) n_D^{20} 1.4441, was characterized as its tetraamide, m.p. 276–278°. Basic hydrolysis of I proved to be unsatisfactory but hydrolysis with concentrated hydrochloric acid gave β-methylpimelic acid, m.p. 42–44°, characterized as its diamide.

Careful refractionation of the crude cyclobutanedicarboxylic ester II gave a fairly pure II, b.p. 86–87° (2.8 mm.), n_D^{20} 1.4351, but still contaminated with small amounts of unsaturated compounds. The latter, as indicated by Kazanskii, probably comprised the isomeric butenylmalonic esters IV and V resulting from dehydrobromination of III. Acid hydrolysis of II gave 2-methyl-1,1-cyclobutanedicarboxylic acid (VI) (79%), m.p. 163–164°, which on esterification with ethanol gave a mixture of pure II and the monoester VII in *ca.* a 5:4 ratio. The realization of a substantial amount of VII is probably a consequence of steric hindrance of the carboxyl group *cis* to the methyl group. It is, therefore, reasonable to assign to VII the configuration 2-methyl-*trans*-1-carboethoxy-*cis*-1-cyclobutanecarboxylic acid. Heating VII at 200° gave ethyl *trans*-2-methylcyclobutanecarboxylate (VIII). Decarboxylation of the dicarboxylic acid VI gave *trans*-2-methylcyclobutanecarboxylic acid (IX). The same amide derivative was obtained from both VIII and IX.

$CH_3CH{=}CHCH_2CH(CO_2Et)_2$

IV

$CH_2{=}CHCH_2CH_2CH(CO_2Et)_2$

V

Refractionation of the bromoester III gave a liquid

---

[1] The work reported here was done as part of a research project at the Baker Laboratory of Chemistry, Cornell University, sponsored by the B. F. Goodrich Company.

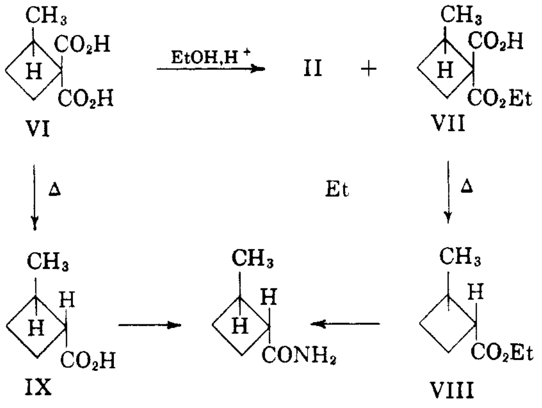
[2] A. T. Blomquist, J. Wolinsky, Y. C. Meinwald, and D. T. Longone, *J. Am. Chem. Soc.*, **78**, 6057 (1956).

[3] J. Cason and C. F. Allen, *J. Org. Chem.*, **14**, 1036 (1949).

[4] W. Ipatiev and M. Mikeldase, *Chem. Cent.*, **11**, 106 (1902).

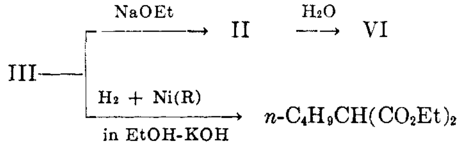
[5] G. Blackstock and W. H. Perkin, *Proc. Chem. Soc.*, **29**, 76 (1913).

[6] B. A. Kazanskii and N. Y. Lukina, *Doklady Akad. Nauk S.S.S.R.*, **83**, 693 (1952); *Chem. Abstr.*, **47**, 2712 (1953).



with b.p. 121° (1.5 mm.), n_D^{20} 1.4568. Although the elementary analysis of this III was not satisfactory, the properties were in accord with the proposed structure, diethyl γ-bromobutylmalonate (III). It gave a negative test for unsaturation with bromine in carbon tetrachloride. With alcoholic silver nitrate reagent and with sodium iodide in acetone it gave positive and negative tests respectively, indicative of a secondary bromide. Attempts to convert III to a solid derivative by treatment with trimethylamine followed by reaction with picric acid[7] gave only triethylamine picrate. Upon heating with hydrazine hydrate only hydrazine hydrobromide was obtained. Refluxing the ester with pyridine gave an unsaturated ester whose infrared spectrum indicated it was a mixture of the two possible isomeric esters IV and V.

Treatment of the bromoester III with sodium ethoxide gave a liquid whose properties were identical with those of the cyclobutane dicarboxylic ester II. Further, the acid obtained on hydrolysis of this II was identical with VI. Hydrogenation of III with Raney nickel in alkaline ethanol gave diethyl n-butylmalonate, characterized as its diamide derivative.



$$\text{III}\begin{cases}\xrightarrow{\text{NaOEt}} \text{II} \xrightarrow{\text{H}_2\text{O}} \text{VI}\\ \xrightarrow[\text{in EtOH-KOH}]{\text{H}_2 + \text{Ni(R)}} n\text{-C}_4\text{H}_9\text{CH(CO}_2\text{Et)}_2\end{cases}$$

EXPERIMENTAL PART

Reaction of sodio malonic ester with 1,3-dibromobutane. Following the procedure described earlier[2] from 1000 g. (6.2 moles) of diethyl malonate and 432 g. (2 moles) of 1,3-dibromobutane there was obtained: (1) 473.5 g. of diethylmalonate, b.p. 64–77° (0.2 mm.), n_D^{20} 1.4157–1.4194; (2) 138.8 g. (32%) of a mixture of diethyl malonate and II, b.p. 76–79° (0.2–0.5 mm.), n_D^{20} 1.4258–1.4349; (3) 68.5 g. (12%) of crude III, b.p. 77–168° (0.5–2.0 mm.), n_D^{20} 1.4420–1.4518; and (4) 312 g. (41.5%) of I, b.p. 171–185° (1.0–2.0 mm.), n_D^{20} 1.4440–1.4490. Characterization of fractions 2, 3, and 4 is described in the succeeding paragraphs.

Tetraethyl 2-methyl-1,1,5,5-pentanetetracarboxylate (I). This ester was obtained in 31–41% yield from the reaction of sodio malonic ester with 1,3-dibromobutane as described earlier.[2] Pure I, obtained by redistillation of fraction No. 4 above, showed b.p. 160° (0.5 mm.) and n_D^{20} 1.4441.

The tetraamide of I was obtained by shaking I with concentrated aqueous ammonia for two weeks. The pure amide had m.p. 276–278° after several recrystallizations from ethanol.

Anal. Calc'd for $C_{10}H_{18}N_4O_4$: C, 46.50; H, 7.01. Found: C, 46.85, 46.80; H, 7.02, 6.94.

Hydrolysis of I was achieved by boiling with concentrated hydrochloric acid. The resulting liquid was placed on a 1:1 Magnesol-Celite column, the column was washed thoroughly with hexane, and finally was eluted with ether. The residual solid from the ether eluate showed m.p. 42–44° after several recrystallizations from chloroform-hexane (reported for β-methylpimelic acid m.p. 45–48°[8,9] and m.p. 48–50°).[10] This acid was converted to its amide which showed m.p. 142–145° after several recrystallizations from benzene–methanol (reported for the diamide of β-methylpimelic acid, m.p. 144–145°).[11]

Diethyl 2-methyl-1,1-cyclobutanedicarboxylate (II). Careful fractional distillation of the combined low-boiling fractions (fraction No. 2) obtained from several runs of the malonic ester–1,3-dibromobutane reaction gave relatively pure II showing b.p. 68–70° (0.65 mm.), 86–87° (2.8 mm.), n_D^{20} 1.4349–1.4351. Ipatiev[4] reported b.p. 155–165° (15 mm.); Kazinskii[6] reported b.p. 113–114° (13 mm.), n_D^{20} 1.4358, d_4^{20} 1.0282. This II contained trace amounts of isomeric unsaturated open-chain esters. The ester II free of these trace impurities is described subsequently.

Anal. Calc'd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.87, 61.62; H, 8.47, 8.36.

The *dihydrazide derivative of II* was prepared and showed m.p. 118–120° (rapid heating) after recrystallization from ethanol–pentane.

Anal. Calc'd for $C_7H_{14}N_4O_2$: C, 45.15; H, 7.58. Found: C, 45.08, 45.31; H, 7.56, 7.48.

Addition of a concentrated ethanolic solution of picric acid to a solution of the dihydrazide gave an immediate yellow precipitate. This *picrate derivative* was obtained as long yellow needles from ethanol, m.p. 195–198° (sintering at 180°).

Anal. Calc'd for $C_{19}H_{20}N_{10}O_6$: C, 27.53; H, 3.35. Found: C, 27.40, 27.35; H, 3.32, 3.27.

From II the *barbiturate derivative* was obtained in 50% yield following the method of Dox and Yoder.[12] Recrystallized from water it was obtained as long white needles which softened at 190–210°, appeared to resolidify and finally melted at 223–227°.

Anal. $C_8H_{10}N_2O_3$: C, 52.73; H, 5.53; N, 15.37. Found: C, 52.87; H, 5.47; N, 15.21.

Treatment of II with concentrated aqueous ammonia at room temperature for 3 weeks gave the *diamide* derivative. This showed m.p. 213–214° after several recrystallizations from chloroform (Kazanskii[6] reported m.p. 196.5°).

Anal. Calc'd for $C_7H_{12}N_2O_2$: C, 53.83; H, 7.75; N, 17.94. Found: C, 53.93, 53.97; H, 7.68, 7.80; N, 17.75.

2-Methyl-1,1-cyclobutanedicarboxylic acid (VI). A mixture of 50 g. of II, 150 ml. of conc'd hydrochloric acid, and 75 ml. of water was refluxed with stirring for 2 days. From the cooled concentrated solution 29 g. (79%) of crude VI was obtained. Pure VI, m.p. 163–164°, was obtained after several recrystallizations from chloroform.

Anal. Calc'd for $C_7H_{10}O_4$: C, 53.16; H, 6.37; N.E. 79.1. Found: C, 53.11, 53.33; H, 6.26, 6.34; N. E. 79.6, 79.3.

---

[7] H. M. Walborsky, *J. Am. Chem. Soc.*, **71**, 2941 (1949).

[8] R. D. Haworth and J. D. Hobson, *J. Chem. Soc.*, 561 (1951).

[9] H. Pistor and H. Plieninger, *Ann.*, **562**, 244 (1949).

[10] A. Einhorn, *Ann.*, **295**, 180 (1897).

[11] M. Mousseron and J. Jullien, *Compt. rend.*, **231**, 410 (1952).

[12] A. W. Dox and L. Yoder, *J. Am. Chem. Soc.*, **43**, 677 (1921).

A solution of 78 g. of VI and 2 g. of *p*-toluenesulfonic acid in absolute ethanol and toluene was refluxed one week with occasional removal, drying, and re-addition of solvent. There was obtained on distillation 50 g. of pure II (free of unsaturation) having b.p. 70–72.5° (1.0 mm.), n_D^{25} 1.4340, d_4^{25} 1.0245 and 40 g. of the ester-acid VII, b.p. 103–104° (0.75 mm.), n_D^{25} 1.4480, d_{25}^{25} 1.101.

Anal. Calc'd for $C_9H_{14}O_4$: C, 58.05; H, 7.57. Found: C, 57.74; H, 7.70.

Ethyl trans-2-methylcyclobutanecarboxylate (VIII). Distillation at atmospheric pressure of 4.8 g. of VII gave 3.0 g. (84%) of the ester VIII, b.p. 161–164° (atm.), n_D^{25} 1.4238, d_{25}^{25} 0.9349.

Anal. Calc'd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.15; H, 10.01

The *amide* derivative of VIII was prepared: m.p. 130–131.5° from benzene–pentane.

Anal. Calc'd for $C_6H_{11}NO$: C, 63.68; H, 9.80. Found: C, 63.80; H, 9.82.

trans-2-Methylcyclobutanecarboxylic acid (IX). Upon distillation at atmospheric pressure of 19.5 g. of VI, with the heating bath at 220°, there was obtained 12.5 g. (89%) of a yellowish liquid of indefinite b.p. Upon redistillation a sample of IX was obtained showing b.p. 200° (atm.), n_D^{20} 1.4394 and having an unpleasant cheese-like odor.

Anal. Calc'd for $C_6H_{10}O_2$: C, 63.13; H, 8.83. Found: C, 63.35, 63.16; H, 8.76, 8.71.

This IX after refluxing with thionyl chloride was poured into aqueous ammonia to give an amide, m.p. 130–131.2°, which did not depress the m.p. of the amide obtained previously from the *trans*-ester VIII.

Diethyl γ-bromobutylmalonate (III). Fractional distillation *in vacuo* of the combined intermediate fractions (fraction no. 3) from several runs of the malonic ester-dibromobutane reaction gave a colorless liquid product, impure III, having b.p. 121° (1.5 mm.), n_D^{20} 1.4568. This III did not give a completely satisfactory elementary analysis.

Anal. Calc'd for $C_{11}H_{19}BrO_4$: C, 44.75; H, 6.49. Found: C, 46.73, 46.81; H, 6.57, 6.47.

This III (10 g., 0.034 mole) was refluxed 3 hours with a solution of 0.9 g. (0.04 g.-atom) of sodium in 60 ml. of absolute ethanol. After 50 ml. of water had been added to the concentrated reaction mixture it was extracted with ether. From the ether extract there was obtained 3.6 g. of II, b.p. 94–97° (4 mm.), n_D^{20} 1.4350–1.4356. Hydrolysis of a portion of this II gave VI, m.p. 163–164°, which did not depress the m.p. of VI obtained previously.

A mixture of 14 g. (0.047 mole) of III, 2.8 g. (0.05 mole) of potassium hydroxide, 50 ml. of absolute ethanol, and 8 g. of Raney nickel was hydrogenated in a Parr apparatus. After filtration of the catalyst and distillation of the ethanol, water and ether were added. From the ether extract there was obtained 6.1 g. of diethyl *n*-butylmalonate, b.p. 95–98° (3 mm.), n_D^{20} 1.4240–1.4248 [reported for diethyl *n*-butylmalonate, b.p. 122° (12 mm.), n_D^{20} 1.4222;[13] b.p. 136–137° (21 mm.), n_D^{20} 1.4250].[14] The *amide* derivative of this ester, m.p. 197–199°, did not depress the m.p. of the amide prepared from authentic diethyl *n*-butylmalonate. The infrared spectra of the two samples of *n*-butylmalonamide were identical.

ITHACA, N. Y.

---

(13) P. A. Levene and F. A. Tayler, *J. Biol. Chem.*, **54**, 358 (1922).

(14) V. H. Wallingford, A. H. Homeyer, and D. M. Jones, *J. Am. Chem. Soc.*, **63**, 2058 (1941).