[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

CYCLOPROPANES III.[1] CYCLOPROPYLMALONIC ESTER AND RELATED COMPOUNDS

LEE IRVIN SMITH AND SCOTT McKENZIE, JR.[2]

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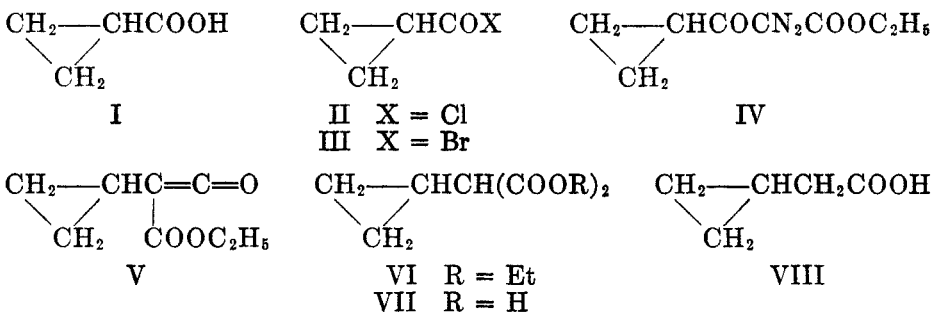
Reactions involving ring closure to form small rings usually cannot be employed for synthesis of compounds containing one or more carbon atoms between the ring and the functional group. This is so because the ring closure itself involves withdrawal of an atom which must be sufficiently activated to react preferentially; this activation is most commonly produced by locating the atom to be withdrawn in the α-position to some functional group such as carbonyl, carbethoxy, etc. Rearrangements involving expansion or contraction of the small ring occur frequently in replacement reactions of a halogen or other group attached either directly to the ring or to an α-carbon atom; this makes difficult the extension of a one-carbon side chain attached to a small ring.

Cyclopropanecarboxylic acid has been converted into cyclopropylacetic acid by a sequence of reactions involving no attack upon the carbon atom joined directly to the ring. The acid (I) was converted into the acid halide (II, III), and the latter was converted, by action of ethyl diazoacetate, into the acyldiazoester (IV) (1). The diazoester (IV), when refluxed in toluene in the presence of silver oxide, lost nitrogen and rearranged into the ketene (V), and the ketene, by action of ethanol, was converted into ethyl cyclopropylmalonate (VI). Basic hydrolysis of VI gave the malonic acid (VII), which, on decarboxylation, gave cyclopropylacetic acid (VIII).



Demjanov and Dojarenko (2) reported the preparation of VIII from cyclopropylcarbinol, but no derivative of VIII was prepared and the substance was characterized only by the boiling point and refractive index. These properties of VIII prepared *via* the ketene (V) agreed well with those given by Demjanov and Dojarenko, but it was decided to prepare VIII from cyclopropylcarbinol for comparison.

Ethyl cyclopropanecarboxylate was reduced to cyclopropylcarbinol by actio

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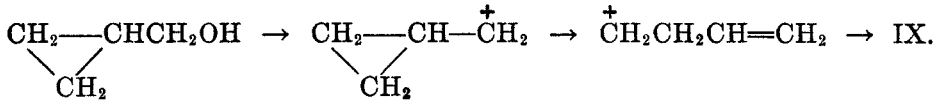
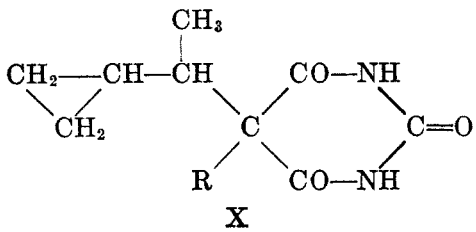
[2] General Mills post-doctorate fellow.

of lithium aluminum hydride;[3] the properties of the carbinol agreed well with those given by Demjanov (3) who reduced the ester by the Bouveault-Blanc procedure. The carbinol was converted into the bromide by action of phosphorus tribromide at 0°; the properties of the bromide agreed with those given by Demjanov (3). However, carbonation of the Grignard reagent from this bromide gave an unsaturated acid (IX) isomeric with VIII. The unsaturated acid reduced permanganate, and gave a *p*-bromophenacyl ester melting at 57–58°; VIII did not reduce permanganate, and gave a *p*-bromophenacyl ester melting at 83°. The most likely structure for IX appeared to be that of allylacetic acid; this acid was accordingly prepared from allylmalonic acid (4) and converted into its *p*-bromophenacyl ester. The ester so prepared melted at 57–58°, alone or when mixed with the *p*-bromophenacyl ester of IX. It followed, therefore, that at some stage in the conversion of cyclopropyl carbinol into IX a rearrangement occurred; this most likely occurred in the first step, when the carbinol was converted into the bromide.



Braker, Pribyl, and Lott (5) have recently prepared bromides from cyclopropyl carbinol and ethylcyclopropyl carbinol, and have used these bromides for alkylation of malonic esters; no evidence, other than the method of synthesis, was given to show that the resulting malonic esters actually contained a cyclopropyl group. An attempt was made to degrade the methyl ester of VIII to I by the method of Barbier-Wieland (6) but no I could be obtained; nor could VIII be obtained from methyl cyclopropyl ketone by a Willgerodt reaction.

These reactions show that the product obtained from cyclopropyl carbinol by extension of the side chain is definitely not VIII. Although the structure of VIII has not been confirmed by conversion into a known cyclopropane derivative, the method of synthesis and the lack of reaction with permanganate indicate that VIII is really cyclopropylacetic acid.



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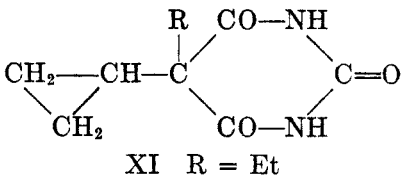

XI R = Et

Many compounds containing the cyclopropyl group are physiologically active. Having in hand cyclopropylmalonic ester (VI), it was of interest to convert it into a barbiturate, and to test the barbiturate for physiological activity. Opie, Seifter, Bruce, and Mueller (7) have prepared a barbiturate of type X; the barbiturate from VI would be one of type XI in which the cyclopropyl group is joined directly

[3] The authors desire to thank Mr. E. Rogier for performing this reduction.

TABLE I

BARBITAL HYPNOTICS IN WHITE MICE

DRUG	DOSE, MG./KG.						
	10	30	50	100	200	300	400
Pentobarbital Sodium Salt	5/10* showed slight depression, others hyperactive	3/5 asleep for 40 min.	10/10 asleep for 45–80 min.	5/5 asleep for 100 min.	10/10 dead		
5-Ethyl-5-cyclopropyl Barbituric Acid Sodium Salt	5/5 showed slight hyperactivity	3/5 asleep for 50 min., others drowsy for 100 min.	5/10 asleep for 120 min., others drowsy for 180 min.	4/5 asleep for 3 hrs.	10/10 asleep for 4 hrs. (marked hypnosis)	5/5 asleep for 24 hrs. 1 dead	4/5 dead
Phenobarbital Sodium Salt		5/5 asleep 120 min.		4/5 sleepy and drowsy at 18 hrs.	1/5 dead		
Phanodorn	at 350 mg. per kg., 4/5 dead.						

* 5/10 is to be read, 5 out of 10 mice showed slight depression, etc.

to the barbituric acid group in the 5-position. Accordingly, VI was ethylated by action of ethyl iodide and alkali, and the resulting ethylcyclopropylmalonic ester was subjected to the action of urea. The barbiturate XI was obtained as colorless needles melting at 173–174°.[4]

EXPERIMENTAL PART

Ethyl diazoacetate. A solution of glycine ethyl ester hydrochloride (500 g.)[5] and sodium acetate (2.5 g.) in water (1000 cc.) was placed in a 3-l. separatory funnel. At room temperature, sodium nitrite (10 g.) in a small amount of water was carefully added; the solution was extracted at once with ether (200 cc.). The ether was removed; sodium nitrite (10 g.), followed by sulfuric acid (2 *N*, 25 cc.) was added to the aqueous layer, which was again extracted with ether (200 cc.). This procedure was repeated until a total of 375 g. of sodium nitrite and 2200 cc. of ether were used. The combined ethereal extracts were washed with saturated aqueous sodium carbonate and dried (magnesium sulfate). Ether was removed and the residue was distilled under reduced pressure (25–35 mm.). The product weighed 300 g. (73%). This procedure is a modification of that of Womack and Nelson (10).

Cyclopropanecarboxylic acid (I) *A.* The acid was prepared *via* trimethylene chlorohydrin (11), trimethylene chlorobromide (12), and γ-chlorobutyronitrile (13) as described by McCloskey and Coleman (14). *B.* The acid (55 g., 64%) was prepared from methyl cyclopropyl ketone (84 g.), bromine (480 g.), and sodium hydroxide (320 g.) essentially according to the procedure described by Sandborn and Bourquet (15) for preparation of trimethylacetic acid.

Cyclopropanecarboxylyl chloride (II) (16). A mixture of the acid (I) (21.5 g.) and phosphorus trichloride (22.6 g.) was protected from moisture while it was stirred at 50° for one hour. The product was distilled directly from the reaction mixture, under sufficiently reduced pressure so that the temperature did not exceed 70°. The distillate, redistilled through a short (6″) column packed with glass helices, gave an initial fraction (discarded) boiling at 72–74°/750 mm. The remainder was distilled under reduced pressure; it formed a colorless liquid which boiled at 39°/20–30 mm. and weighed 22 g. (84%). A small portion of the chloride was converted into the anilide (81%) which, crystallized from ethanol, melted at 108.5–110.5°. The reported melting point of this anilide is 110–111° (17). A mixture of this anilide with crotonanilide [m.p. 114° (18)] melted below 90°.

Cyclopropanecarboxylyl bromide (III). The acid (I) (104.3 g.) and phosphorus tribromide (108.5 g.) gave the bromide boiling at 45–47°/20 mm.

Ethyl cyclopropanecarboxylyldiazoacetate (IV). *A. From the acid chloride.* A solution of ethyl diazoacetate (54.5 g.) in dry ether (2500 cc.) was stirred while the chloride (II) (23 g.) was added slowly, and the mixture was allowed to stand for one week at room temperature. Ether was removed and the residue, when distilled under reduced pressure, formed a yellow oil (17.5 g., 44%) boiling at 76°/3 mm.; n_D^{24} 1.4952. The substance must be distilled at as low a temperature as possible, and no column should be used, for prolonged heating causes the substance to decompose vigorously.

Anal. Calc'd for $C_8H_{10}N_2O_3$: C, 52.72; H, 5.53.
Found: C, 52.57; H, 6.08.

B. From the acid bromide. A solution of ethyl diazoacetate (152.4 g.) in dry ether (500 cc.) was stirred while the bromide (III) (85 g.) was added. The mixture, cooled for a few moments until the evolution of nitrogen subsided somewhat, was allowed to stand at room temperature for a day, after which it was refluxed gently for two days. The product, isolated and purified as above, weighed 75 g. (72%).

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[4] The 5-ethyl-5-cyclopropyl barbiturate as the sodium salt was tested pharmacologically by Dr. R. N. Bieter of the Department of Pharmacology, University of Minnesota, whom we wish to thank for his kindness. The results are given in Table I; for comparison, the activities of three other hypnotics are included.

[5] Prepared from methyleneaminoacetonitrile (8) by the method of Marvel (9).

Ethyl cyclopropylmalonate (VI). A mixture of the diazoester (IV) (82 g.), anhydrous toluene (80 cc.), and silver oxide (0.5 g.) was refluxed under an atmosphere of carbon dioxide until evolution of nitrogen ceased (3–4 hours). The toluene was removed (20 mm.) and the residue was distilled under reduced pressure (3 mm.) into cooled (Dry Ice–acetone) ethanol (50 cc.). Distillation was continued until the bath temperature reached 220°. Ethanol was removed from the distillate, and the product was fractionated. The colorless liquid, b.p. 76–80°/3 mm., n_D^{24} 1.4315, weighed 39 g. (43%).

Anal. Calc'd for $C_{10}H_{16}O_4$: C, 59.96; H, 8.05.
Found: C, 60.15; H, 7.88.

Variants of the above procedure included (a) substitution of xylene for the toluene; yield of product, 35.6%; (b) dry ethanol, silver oxide, and IV (10 g.) heated at 130° for four hours in a bomb, yield 4 g.; dry ethanol, IV, and polished platinum refluxed at atmospheric pressure; no VI was obtained.

Cyclopropylmalonic acid (VII). The ester (VI) (4 g.) was heated overnight on the steam-bath with aqueous sodium hydroxide (10 cc., 10%). The cooled mixture was extracted with ether; the aqueous layer was acidified with hydrochloric acid and extracted continuously with ether in an extractor for three days. The ether extract was dried (magnesium sulfate), ether was removed, and the residue was crystallized from nitromethane. The colorless needles (2.4 g., 83%) melted at 174–175° (dec.) (block). The substance did not decolorize aqueous potassium permanganate.

Anal. Calc'd for $C_6H_8O_4$: C, 50.00; H, 5.55.
Found: C, 49.69; H, 5.69.

Cyclopropylacetic acid (VIII). The acid (VII) (4 g.) was decomposed and distilled by heating it in a 20-cc. Claisen flask with a flame until evolution of carbon dioxide ceased. The distillate was a colorless liquid, yield 2.5 g. (90%); b.p. 189–191°/750 mm., n_D^{23} 1.4330, n_D^{25} 1.4320. Demjanov and Dojarenko (2) reported for their acid b.p., 189–190°/740 mm., n_D^{21} 1.4343. The *p-bromophenacyl ester*, prepared in the usual way and crystallized from ethanol, melted at 83°.

Anal. Calc'd for $C_{13}H_{13}BrO_3$: C, 52.52; H, 4.38.
Found: C, 52.36; H, 4.57.

The *methyl ester* (4.5 g., 79%) prepared from the acid (5 g.) by action of ethereal diazomethane, had b.p. 132°/745 mm., n_D^{23} 1.4175.

Anal. Calc'd for $C_6H_{10}O_2$: C, 63.16; H, 8.77.
Found: C, 63.32; H, 9.22.

A mixture of methyl cyclopropyl ketone (8.4 g.), sulfur (16 g.), ammonium hydroxide (25 cc.), and pyridine (15 cc.) was heated in a sealed tube at 165° for four hours (19). No acidic material was obtained when the product was processed in the usual manner. Methyl cyclopropyl ketone (8.4 g.) and sulfur (5 g.) were heated at 200° for four hours in a sealed tube with ammonium hydroxide (50 cc.) which had been saturated with hydrogen sulfide. No cyclopropylacetic acid could be isolated from the product. Methylcyclopropyl ketone (42 g.) in carbon tetrachloride (50 cc.) containing sulfuryl chloride (75 g.) was stirred and heated to 45° for one hour (20). The solution was washed with water and dried (calcium chloride). Solvent was removed, and the residue, when distilled, formed a colorless, lachrymatory liquid, b.p. 60–62°/20 mm., n_D^{16} 1.4840. The product was a mixture of chloro compounds which could not be separated; the composition approximated that of the dichloro ketone.

Anal. Calc'd for C_5H_7ClO: C, 50.63; H, 5.97.
Calc'd for $C_5H_6Cl_2O$: C, 39.3; H, 3.93.
Calc'd for $C_5H_5Cl_2O$: C, 38.71, H, 4.84.
Found: C, 41.08; H, 4.84.

Attempted degradation of methyl cyclopropylacetate. The ester (4 g.) in dry ether (50 cc.) was added, with stirring, to a solution of phenylmagnesium bromide (from bromobenzene, 23.6 g., magnesium, 3.65 g., and ether, 100 cc.). The product, isolated in the usual way and

distilled, gave a small fore-run (0.5 g.) boiling at 75°/7–8 mm., followed by the main product (6 g.), an oil boiling at 125°/7–8 mm. The oil could not be purified further.

Anal. Calc'd for $C_{17}H_{16}$: C, 92.73; H, 7.27.
Calc'd for $C_{17}H_{18}O$: C, 85.71; H, 7.56.
Found: C, 90.87; H, 7.44.

A solution of potassium permanganate (1.92 g.) in water (60 cc.) containing pyridine (80 cc.) was added to a solution of the above oil (1 g.) in pyridine (80 cc.) and the solution was allowed to stand for three days, with occasional shaking. Sodium sulfite (solid) was added until the color was discharged; then the manganese dioxide was removed and washed with water. The combined filtrates and washings were evaporated under reduced pressure to a volume of 150 cc., then cooled and extracted several times with ether. The aqueous layer was concentrated to a volume of 20 cc., acidified with hydrochloric acid, and extracted with ether. No acidic material was found in the ether extract. Action of permanganate in acetone upon the oil likewise led to no acidic material.

Cyclopropyl carbinol[3]. Ethyl cyclopropanecarboxylate (22.4 g.), reduced by the action of lithium aluminum hydride (2.2 g.) according to the procedure of Nystrom and Brown (21) gave the carbinol (8.3 g., 58%); b.p. 122–123°, n_D^{20} 1.426. The carbinol did not react with a solution of bromine in chloroform, nor with permanganate. The *phenylurethane*, prepared in the usual way and crystallized from benzene-petroleum ether or from aqueous ethanol had m.p. 75.5–76°.

Anal. Calc'd for $C_{11}H_{13}NO_2$: C, 69.10; H, 6.85.
Found: C, 69.31; H, 6.81.

Bromide from cyclopropyl carbinol. The carbinol (5.5 g.) was added dropwise, with stirring and cooling (0°) to phosphorus tribromide (6.3 g.). The mixture was stirred for thirty minutes; the product was washed twice with cold water, dried (calcium chloride) and distilled. The distillate (7.3 g., 66%) had b.p. 105–108°, n_D^{25} 1.4700. Demjanov (3) reported that his bromide, obtained from cyclopropyl carbinol, boiled at 105–106° and had $n_D^{19.5}$ 1.475.

Carbonation of the Grignard reagent from the above bromide. A solution of the bromide (6 g.) in ether (50 cc.) was added dropwise and with stirring to magnesium (1.22 g.) and ether (40 cc.). The reaction mixture was poured over solid carbon dioxide (20 g., small pieces) and then processed in the usual way. The product (2 g., 50%) was a colorless liquid, b.p. 175–180°, n_D^{25} 1.4274; it readily decolorized permanganate. The *p-bromophenacyl ester*, prepared in the usual way and crystallized from aqueous ethanol, melted at 57–58°. A mixture of this ester and the *p*-bromophenacyl ester of VII (m.p. 83°) melted at 52–75°. A mixture of this ester and the *p*-bromophenacyl ester of allylacetic acid (IX) (4) melted at 57–58°.

Anal. Calc'd for $C_{13}H_{13}BrO_3$: C, 52.52; H, 4.38.
Found: C, 52.84; H, 4.68.

5-Ethyl-5-cyclopropylbarbituric acid (XI). Ethyl cyclopropylmalonate (VI) (28 g.) was added, with stirring, to a solution of sodium ethoxide [from sodium (3.26 g.) in dry ethanol (100 cc.)]. The solution was stirred for one hour, then ethyl iodide (23.5 g.) was added and the solution was stirred at 50° for two hours, after which it was allowed to stand overnight. The product was diluted with water (1000 cc.) and extracted several times with ether. The extracts were washed with aqueous sodium bisulfite, dried (magnesium sulfate), and the solvent was removed. The residual oil gave a main fraction (24 g.) boiling at 83–87°/3 mm. Analysis indicated that ethylation was not complete, but the material, ethylated again as above, was not of improved purity, nor did extraction with aqueous sodium hydroxide (10%) give a better product.

Anal. Calc'd for $C_{12}H_{20}O_4$: C, 63.16; H, 8.77.
Found: C, 62.05; H, 8.84.

The above ester (XI) (5 g.) was added to a warm solution of sodium ethoxide [from sodium (0.7 g.) in dry ethanol (50 cc.)]. Urea (3 g.) was added, and the mixture was heated on the steam-bath until the solvent was removed; the residue was heated for one hour on

the bath. Water (15 cc.) was added and the solution was extracted with ether. The aqueous layer was warmed to remove ether, then cooled and acidified with hydrochloric acid (5 cc.). The solid was removed and recrystallized three times from water, when it formed colorless needles (1.5 g., 26%) melting at 173–175° (block).

Anal. Calc'd for $C_9H_{12}N_2O_3$: C, 55.10; H, 6.12.
Found: C, 55.15; H, 6.14.

SUMMARY

1. Cyclopropylmalonic ester (VI) has been synthesized from cyclopropanecarboxylic acid (I) by a method which does not involve an attack upon the carbon atom joined to the ring. From the malonic ester (VI), the malonic acid (VII) has been obtained by hydrolysis; the malonic acid (VII) has been decarboxylated to cyclopropylacetic acid (VIII).

2. The cyclopropylacetic acid so obtained differs from the product prepared by Demjanov and Dojarenko *via* cyclopropyl carbinol, "cyclopropylmethylbromide", and the Grignard reagent from this bromide, and it is shown that the synthesis of Demjanov and Dojarenko actually leads to allylacetic acid, not cyclopropylacetic acid.

3. From the malonic ester (VI), by ethylation followed by condensation with urea, 5-ethyl-5-cyclopropylbarbituric acid (XI) has been prepared. This is a barbiturate of low toxicity.

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