[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

The Perkin Synthesis of Five- and Six-membered Rings

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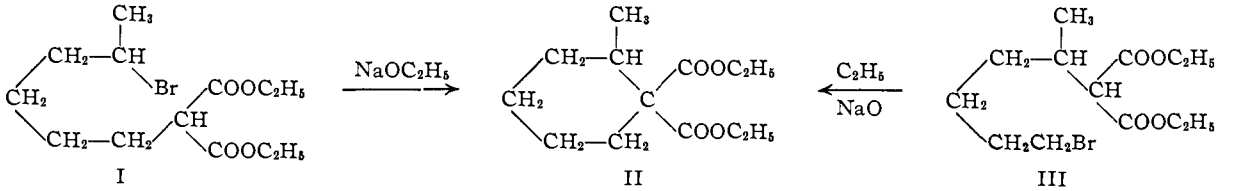
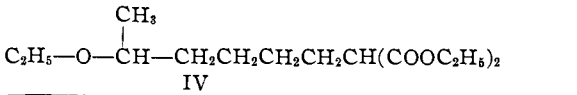
The preparation of substituted cyclohexane and cyclopentane rings by a modified Perkin synthesis has been successfully accomplished in good yield.

In the course of the synthesis of some barbituric acids an adequate preparation was desired for some 2,6-dialkylsubstituted-1,1-dicarbethoxycyclohexanes and 2,2,5-trialkylsubstituted-1,1-dicarbethoxycyclopentanes. The customary Perkin synthesis from an alkyl dihalide and malonic ester was considered to be inapplicable for these compounds for the following reasons. As a general rule, simply substituted cyclopentane rings are formed easily by a Perkin synthesis. However, the synthesis of cyclopentanes of the type desired would require alkylating malonic ester with what are essentially secondary and tertiary halides. The easy elimination of hydrogen halide from tertiary halides in such alkylations along with the undoubted steric inhibition of the second alkylation argues against the use of the normal Perkin reaction for the preparation of the cyclopentanes. Apparently the use of this method for the cyclohexane series is likewise prohibited according to the following evidence. Using a slight modification of Perkin's technique, Dox and Yoder[1] prepared the unsubstituted 1,1-dicarbethoxycyclohexane in 33% yield. Perkin[2] originally prepared the 1-methyl homolog in a very poor yield which he failed to report. The obvious deduction from this limited information is that the conditions for six-membered ring closure are highly unfavorable under Perkin's conditions when even only one of the groups alkylating the malonic ester is a secondary group.

It was hoped, however, that the ring closure could be effected if the bromoalkyl ester, which is the product of the first alkylation in the Perkin reaction, could be first formed and then cyclized. Some recent work by Golmov,[3] reported after the present work was completed, makes use of this method. Golmov elaborated the mechanism of the synthesis performed by Perkin which is mentioned above. He prepared I and III and cyclized them to II in 5% and 70% yields, respectively. I is the initial product from the condensation of malonic ester with the dibromide.



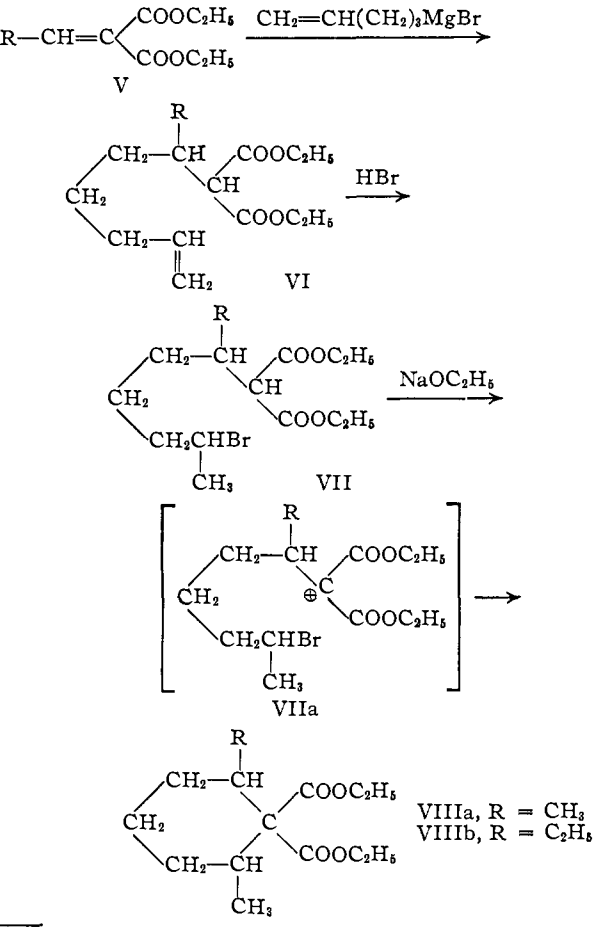
I II III



IV

Golmov raised the yield of II from I to 43% by the slow addition of the ester to the ethoxide solution. However, there was quite a large amount of the ethyl ether IV formed through replacement of the bromine in the bromoester by ethoxide ion.

The method of cyclization presently employed was designed to reduce the concentration of the ethoxide ion to a minimum, helping thereby to minimize the ether formation and elimination reactions. This was accomplished by the slow addition of the sodium ethoxide to the bromoester in refluxing alcohol, the malonate ion forming quickly and the cyclization then occurring more slowly in the near absence of ethoxide ion.



V VI VII VIIa VIIIa, R = CH_3 VIIIb, R = C_2H_5

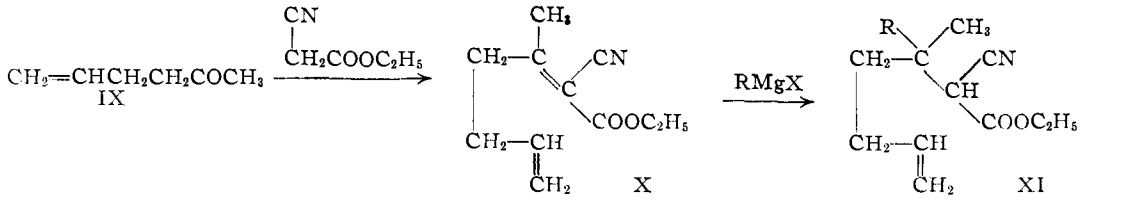
(1) A. W. Dox and L. Yoder, THIS JOURNAL, **43**, 1366 (1921).

(2) P. C. Freer and W. H. Perkin, Jr., *J. Chem. Soc.*, **53**, 202 (1888).

(3) V. P. Golmov, *J. Gen. Chem.* (*U.S.S.R.*), **22**, 1162 (1953).

In the synthesis of the cyclohexane compounds 4-pentenylmagnesium bromide was added 1,4 to an alkylidenemalonic ester V. The resulting unsaturated ester VI was converted with hydrogen bromide in acetic acid–chloroform into a bromoester VII, which was then cyclized as previously described. In this manner VIIIa and VIIIb were obtained in yields of 79% and of 62 and 79%, respectively.

In the cyclopentane series the problem was not only to effect ring closure in good yield but to substitute the malonic ester with a quaternary carbon atom. The readily accessible alkylidenecyanoacetic ester X when treated with a Grignard reagent gives the required quaternary carbon on a cyanoacetic ester. Since for the synthesis of barbituric acids the cyanoacetic esters are as useful as the malonic esters, this was the route chosen. The addition of hydrogen bromide to the ester XI and subsequent ring closure was likewise similar to the reactions in the cyclohexane series.



The cyclic esters XIIIa and XIIIb were thus obtained in 75% and 60% yields, respectively.

The barbituric acids that were formed from several of the above esters give substantial proof that cyclization has actually occurred. 5,5-Disubstituted barbituric acids are precipitated from basic solution by carbon dioxide, whereas 5-monosubstituted barbituric acids are not. All the derivatives prepared were precipitated under these conditions.

Experimental[4]

Diethyl 1-Methyl-5-*n*-hexenylmalonate.—The starting materials for this preparation were obtained by following directions in the literature. Thus, 4-pentenol[5] (n^{25}D 1.4524, b.p. 40–42° (9 mm.), 71%) was converted to 4-pentenyl bromide[6] by the use of phosphorus tribromide and pyridine (n^{25}D 1.4642, b.p. 124.5–128° (atm.), 66.5%). The diethyl ethylidenemalonate was prepared by the method of Cope[7] (n^{25}D 1.4398, b.p. 70° (1 mm.), 64%). Then, to the Grignard reagent, prepared from 19.0 g. (0.78 atom) of magnesium in 500 ml. of dry ether and 106.5 g. (0.71 mole) of 4-pentenyl bromide, 132.0 g. (0.71 mole) of diethyl ethylidenemalonate was added dropwise with cooling in an ice-bath. After the two hour addition period the reaction mixture was stirred overnight, and then decomposed with ice and dilute hydrochloric acid. The product was extracted with ether. The ether layer was washed with water and sodium bicarbonate solution, dried with magnesium sulfate and then evaporated. The residue was distilled; b.p. 113–116° (1.4 mm.), yield 72.3 g. (0.282 mole, 40%).

Anal. Calcd. for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.84; H, 9.35.

Diethyl 1-Methyl-5-bromo-*n*-hexylmalonate.—An ice-cooled solution of 72.3 g. (0.282 mole) of diethyl 1-methyl-5-hexenylmalonate in 100 ml. of chloroform and 18.0 ml. of glacial acetic acid was saturated with anhydrous hydrogen bromide. The reaction was allowed to warm to room temperature and stand for 12 hr. It was then poured onto ice and water and extracted with chloroform. The chloroform solution was washed with water, sodium bicarbonate solution, water and then dried with magnesium sulfate. The chloroform was evaporated and the product was distilled; b.p. 132–135° (0.7 mm.), n^{25}D 1.4596, yield 79.9 g. (0.237 mole, 84%).

Anal. Calcd. for $C_{14}H_{25}O_4Br$: C, 49.85; H, 7.47. Found: C, 49.73; H, 7.35.

Cyclization to 2,6-Dimethyl-1,1-dicarbethoxycyclohexane.—A solution of sodium ethoxide prepared from 5.5 g. (0.239 atom) of sodium in 135 ml. of absolute ethanol, was added dropwise over 5 hr. to a refluxing solution of 79.9 g. (0.237 mole) of the bromoester in 100 ml. of absolute ethanol. The solution was allowed to reflux for 2 hr. more. The alcohol was then removed by evaporation in vacuum. The salt was dissolved in water, the ester was extracted with ether, the ether layer was dried with magnesium sulfate and the ether was finally removed. Distillation yielded the ester, b.p. 93–95° (0.8 mm.), n^{25}D 1.4510, yield 48.2 g. (0.188 mole, 79%).

XIIIa, R = CH_3
XIIIb, R = C_2H_5

Anal. Calcd. for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.38; H, 9.28.

In the synthesis of the following compounds the methods described above for their next lower homolog were used.

Diethyl 1-Ethyl-5-*n*-hexenylmalonate.—The reaction of 4-pentenylmagnesium bromide (207.4 g. of bromide) with diethyl *n*-propylidenemalonate (276.0 g.) produced 180.3 g. of the desired ester, b.p. 103–107° (0.65 mm.), n^{25}D 1.4420, 48.3% yield.

Anal. Calcd. for $C_{15}H_{26}O_4$: C, 66.63; H, 9.69. Found: C, 66.86; H, 9.84.

Diethyl 1-Ethyl-5-bromo-*n*-hexylmalonate.—The addition of hydrogen bromide to the unsaturated ester (73.0 g.) yielded 76.3 g. of the bromoester, b.p. 150–153° (1 mm.), n^{25}D 1.4610, 80.0% yield.

Anal. Calcd. for $C_{15}H_{27}O_4Br$: C, 51.28; H, 7.75. Found: C, 51.46; H, 8.14.

Cyclization to 2-Methyl-6-ethyl-1,1-dicarbethoxycyclohexane.—Cyclization of the bromoester (76.3 g.) yielded 36.2 g. of the cyclohexane ester, b.p. 105–107° (0.85 mm.), n^{25}D 1.4534, 62.0% yield. Another preparation yielded the ester in 79% yield.

Anal. Calcd. for $C_{15}H_{26}O_4$: C, 66.63; H, 9.69. Found: C, 66.68; H, 9.85.

Ethyl 1-Methyl-4-*n*-pentenylidenecyanoacetate.—The method of Cope[8] was employed. A mixture of 185.0 g. (1.65 moles) of ethyl cyanoacetate, 193.0 g. (1.97 moles) of allylacetone, 40.0 g. (0.68 mole) of acetamide and 500 ml. of glacial acetic acid was slowly distilled under a partial take-off still-head so that the distillate boiled at 112–115°. After 10 hr. of distillation the product was isolated by di-

(4) All melting points and boiling points are uncorrected. Analyses were performed by Messrs. W. L. Brown, H. L. Hunter and W. J. Schenck.

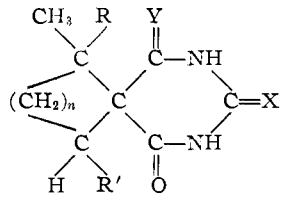
(5) L. A. Brooks and H. R. Snyder, *Org. Syntheses*, **25**, 85 (1945).

(6) P. Gaubert, R. P. Linstead and H. N. Rydon, *J. Chem. Soc.*, 1971 (1937).

(7) A. C. Cope, C. M. Hofmann, C. Wyckoff and E. Hardenbergh, THIS JOURNAL, **63**, 3452 (1941).

(8) A. C. Cope, *ibid.*, **59**, 2327 (1937).

TABLE I



Barbituric acid										
n	R	R′	X	Y	Yield, %	M.p., °C.	Formula	Nitrogen, % Calcd.	Found	Recovery of ester, %
3	H	CH_3	O	S	20	208–210	$C_{11}H_{16}N_2O_2S$	11.66	11.75	37.4
3	H	C_2H_5	O	O	10	142–144	$C_{12}H_{18}N_2O_3$	11.76	12.13	53
3	H	C_2H_5	O	S	12	193–194	$C_{12}H_{18}N_2O_2S$	11.02	11.35	70
2	CH_3	CH_3	NH	O	14	239–241	$C_{11}H_{17}N_3O_2$	18.83	18.00	..
2	CH_3	CH_3	NH	S	15	210	$C_{11}H_{17}N_3OS$	17.56	17.53	25
2	CH_3	CH_3	O	O	50[a]	172–173	$C_{11}H_{16}N_2O_3$	12.49	12.39	..
2	CH_3	CH_3	O	S	60[a]	178–179.5	$C_{11}H_{16}N_2O_2S$	11.66	11.66	..

[a] Based on iminobarbituric acid.

luting the reaction mixture with benzene and washing with water, drying with magnesium sulfate and removing the benzene. The product was distilled, b.p. 82–83° (0.5 mm.), $n^{25}D$ 1.4782. The yield was 152.4 g. (0.79 mole, 48%).

Anal. Calcd. for $C_{11}H_{15}NO_2$: N, 7.25. Found: N, 7.28.

Ethyl 1,1-Dimethyl-4-*n*-pentenylcyanoacetate.—Methylmagnesium iodide was prepared in 1000 ml. of dry ether from 114.0 g. (0.80 mole) of methyl iodide and 19.5 g. (0.80 atom) of magnesium. Then, 152.4 g. (0.79 mole) of ethyl 1-methyl-4-*n*-pentenylcyanoacetate in 300 ml. of dry ether was added to the Grignard reagent at such a rate as to maintain a gentle reflux of the ether. The reaction was stirred 0.25 hr. after complete addition and then decomposed by pouring on ice and dilute hydrochloric acid. The product was extracted with ether which was then washed with water and dried with magnesium sulfate. After removing the ether by evaporation, the product was distilled; b.p. 87–89° (0.8 mm.), $n^{25}D$ 1.4508, yield 128.5 g. (0.615 mole, 77%) of a light yellow liquid.

Anal. Calcd. for $C_{12}H_{19}NO_2$: N, 6.69. Found: N, 6.57.

Ethyl 1,1-Dimethyl-4-bromo-*n*-pentylcyanoacetate.—Dry hydrogen bromide was bubbled through a solution of 75.0 g. (0.359 mole) of ethyl 1,1-dimethyl-4-*n*-pentenylcyanoacetate in 20 ml. of glacial acetic acid and 100 ml. of chloroform while keeping the temperature at 5 to 10° with an ice-bath. When the solution was saturated, it was allowed to warm to room temperature and then poured on ice, washed with water and sodium bicarbonate solution and dried with magnesium sulfate. The chloroform was evaporated and the product distilled; b.p. 132–136° (0.7 mm.), $n^{25}D$ 1.4742, yield 84.3 g. (0.29 mole, 81%).

Anal. Calcd. for $C_{12}H_{20}NO_2Br$: N, 4.83. Found: N, 5.10.

Cyclization to 2,2,5-Trimethyl-1-carbethoxy-1-cyanocyclopentane.—Ethyl 1,1-dimethyl-4-bromo-*n*-pentylcyanoacetate (84.3 g., 0.29 mole) was dissolved in 50 ml. of absolute ethanol and heated to reflux. Then a solution of sodium ethoxide (6.9 g. (0.3 atom) of sodium in 125 ml. of absolute ethanol) was added dropwise over one hour. The reaction was refluxed for 4 hr., then evaporated. The sodium bromide was dissolved in water and the product extracted with ether. The ether solution was dried and evaporated. The product was distilled to yield 45.5 g. (0.218 mole) of material, b.p. 70–71° (0.8 mm.), $n^{25}D$ 1.4540, 75%.

Anal. Calcd. for $C_{12}H_{19}NO_2$: N, 6.69. Found: N, 6.85.

The intermediates in the synthesis of 2-ethyl-2,5-dimethyl-1-cyano-1-carbethoxycyclopentane were prepared by the same procedures as those used for the intermediates of the trimethyl homolog.

Ethyl 1-Methyl-1-ethyl-4-*n*-pentenylcyanoacetate.—By the addition of the Grignard reagent from 164 g. of ethyl iodide to 192 g. of ethyl 1-methyl-4-*n*-pentenylidenecyanoacetate, an 83% yield of the ester was obtained; b.p. 101–102° (0.95 mm.), $n^{25}D$ 1.4543.

Anal. Calcd. for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48. Found: C, 69.66; H, 9.52.

2,5-Dimethyl-2-ethyl-1-cyano-1-carbethoxycyclopentane.—The crude ethyl 1-ethyl-1-methyl-4-bromopentylcyanoacetate prepared by the action of hydrogen bromide on 158 g. of the unsaturated ester could not be distilled without decomposition so it was cyclized in ethanolic sodium ethoxide (0.7 mole). The product distilled at 103–108° (1.7 mm.), $n^{25}D$ 1.4582, yield 60%.

Anal. Calcd. for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.98; H, 9.37; N, 6.22.

The Preparation of Barbituric Acid Derivatives.—The syntheses of the barbituric acids were similar in all cases, so only one example from each series will be given. Physical data and yields are in Table I.

Spiro-(2,2,5-trimethylcyclopentane-1,5′-2′-thiobarbituric Acid).—To a solution of 3.5 g. (0.152 atom) of sodium in 60 ml. of dry ethanol were added 7.6 g. (0.10 mole) of thiourea and 15.0 g. (0.0718 mole) of 2,2,5-trimethyl-1-cyano-1-carbethoxycyclopentane. The mixture was refluxed for 11 hr., then evaporated, dissolved in water and extracted with ether. Evaporation of the ether gave an oil, $n^{26.5}D$ 1.4550 (starting ester $n^{25}D$ 1.4525), recovery 3.3 g. The water solution was treated with CO_2 to precipitate a yellow solid which was recrystallized from water in 2.6 g. yield. This iminothiobarbituric acid (2.0 g.) was hydrolyzed by refluxing in 100 ml. of 3 *N* hydrochloric acid for 2.5 hr. The white precipitate was recrystallized from alcohol–water; yield 1.2 g.

Spiro-(2,6-dimethylcyclohexane-1,5′,2′-thiobarbituric Acid).—A solution of 4.2 g. (0.182 atom) of sodium in 70 ml. of dry methanol was mixed with 7.6 g. (0.10 mole) of thiourea and 15.0 g. (0.0585 mole) of 2,6-dimethyl-1,1-dicarbethoxycyclohexane, refluxed for 20 hr. and then evaporated. The residue was dissolved in water and extracted with ether. The ether solution on evaporation yielded an oil, $n^{25}D$ 1.4540 (starting ester, $n^{25}D$ 1.4510), 5.6 g. or 37% recovery. The water solution was treated with CO_2 to precipitate a yellow compound which on purification from alcohol–water gave 2.8 g. of pure product.

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