# cyclo*Octatetraene Derivatives. Part VI.* Preparation of Barbituric Acids.*

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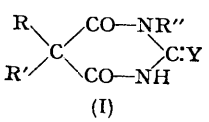
Some barbituric and thiobarbituric acids containing a *cyclo*octyl or a *cyclo*oct-2-enyl group in the 5-position have been prepared and their narcotic actions examined.

Some barbiturates and thiobarbiturates possessing a *cyclo*alkyl or a *cyclo*alkenyl group in the 5-position have high narcotic activity. Representatives carrying a five-membered (Pentenal) (I; R = $C_5H_7$, R′ = $C_2H_5$, R″ = H, Y = O) or a six-membered ring (*e.g.*, Thialbarbitone) (I; R = $C_6H_9$, R′ = $C_3H_5$, R″ = H, Y = S) have been used in pharmacy, and it was therefore of interest to prepare and examine analogous barbituric acid derivatives containing an eight-membered ring.



(I)

A high yield (85%) of *cyclo*octylmalonic ester obtained from ethyl malonate and *cyclo*octyl bromide was unexpected because of the usual tendency of *cyclo*alkyl halides to lose hydrogen halide in alkali: in analogous reactions with *cyclo*pentyl iodide and *cyclo*hexyl bromide, the highest recorded yields of *cyclo*alkylmalonic esters are 50% (Verwey, *Ber.*, 1896, **29**, 1996) and 44% (Hiers and Adams, *J. Amer. Chem. Soc.*, 1926, **48**, 2385) respectively. In the preparation of *cyclo*octylmalonic acid (m. p. 124°) by alkaline hydrolysis it was essential to make the product strongly acid, for at pH 5—6 the crystals (m. p. 176°) which separated proved to be potassium trihydrogen bis*cyclo*octylmalonate,

$$[C_8H_{15}\cdot CH(CO_2H)_2,C_8H_{15}\cdot CH(CO_2H)(CO_2K)]$$

Malonic acid itself forms a similar salt.

Attempts to methylate *cyclo*octylmalonic ester gave extremely low yields (about 4%), and provide another example of the difficulty of introducing a second alkyl group into a monosubstituted malonic ester (cf. Dox and Yoder, *ibid.*, 1922, **44**, 1566; Schoule, Keltch, and Suranson, *ibid.*, 1930, **52**, 2440), particularly when the larger of the two groups has been introduced first. It has recently been claimed (B.P. 649,682/1951) that the difficulty can be overcome by a modified procedure but it was not successful when applied to dibutyl *cyclo*octylmalonate. The required *cyclo*octylmethylmalonic ester was ultimately obtained in 55% yield by inverting the order of alkylation.

*cyclo*Octen-2-ylmalonic ester was prepared by treating sodiomalonic ester with 3-bromo*cyclo*octene or 1 : 2-dibromo*cyclo*octane (cf. Mousseron, Manon, and Combes, *Bull. Soc. chim.*, 1949, 396), identity of the products being confirmed by hydrolysis to *cyclo*oct-2-enylmalonic acid. 1-Bromo*cyclo*octene did not react with sodiomalonic ester.

Several barbituric and thiobarbituric acids containing a *cyclo*octyl or a *cyclo*oct-2-enyl group have been prepared by standard methods. The products containing a 5-allyl group were prepared by direct allylation of the 5-monosubstituted barbituric acid (cf. Volwiler, *J. Amer. Chem. Soc.*, 1925, **47**, 2236) and not through the corresponding allylmalonic ester, but an attempt to introduce a methyl group into the 5-position of 5-*cyclo*octylbarbituric acid failed.

Sodium salts of the 5 : 5-disubstituted barbituric and thiobarbituric acids were all less toxic than Hexobarbitone, but the therapeutic ratio was usually much lower, the best

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product being 5-methyl-5-*cyclo*octylbarbituric acid with a therapeutic ratio about equal to that of Hexobarbitone (I; R = $C_6H_9$, R′ = R″ = $CH_3$, Y = O).

It is known that two substituents (preferably having together 6—8 carbon atoms) on the 5-position of barbituric acids appear to be essential for narcotic action (Dox and Yoder, *loc. cit.*, p. 1141). To test the possibility that one bulky eight-carbon substituent would have the same effect, 5-*cyclo*oct-2′-enylbarbituric acid was also examined, but it was devoid of narcotic action.

## Experimental

*Diethyl* cyclo*Octylmalonate*.—Ethyl malonate (185 g.) was added to a solution of sodium ethoxide (26·5 g. of sodium in 600 ml. of absolute ethanol), and most of the ethanol (410 ml.) was distilled off. *cyclo*Octyl bromide (220 g.) was added to the pasty residue and heating continued (107° internal temp.) for 50 hr., most of the remaining ethanol (120 ml.) being allowed to distil away. The cooled mixture was treated with water, extracted with ether, and dried. On evaporation and fractionation, apart from a fraction (22 g.; *cyclo*octene), the whole product distilled at 132°/0·7 mm., having $n_D^{24}$ 1·4628. The colourless oil obtained (198 g., 85%) was the required *ester* (Found: C, 66·7; H, 9·6. $C_{15}H_{26}O_4$ requires C, 66·7; H, 9·6%). Hydrolysis with alcoholic potassium hydroxide, followed by acidification with hydrochloric acid to Congo-red, yielded cyclo*octylmalonic acid*, plates (from water), m. p. 123—124° (decomp.) (Found: C, 61·3; H, 8·3%; equiv., 107·5. $C_{11}H_{18}O_4$ requires C, 61·7; H, 8·4%; equiv., 107). When the hydrolysis solution was acidified to pH 6 only, *potassium trihydrogen bis*cyclo*octylmalonate* separated in rhombs, m. p. 176—177° (decomp.) (Found: C, 56·7; H, 7·5%; equiv., 156. $C_{22}H_{35}O_8K$ requires C, 56·6; H, 7·5%; equiv., 155).

*Di*-n-*butyl* cyclo*Octylmalonate* (cf. B.P. 649,682).—Di-*n*-butyl malonate (108 g.) and *cyclo*octyl bromide (115 g.) were stirred together at 100°, and a solution of sodium butoxide in butanol (from 12·65 g. of sodium and 228 g. of *n*-butanol) was added dropwise during 70 hr. Water was added to the cooled mixture and the oil was taken up in benzene, dried, and fractionated. The required *ester* (51 g., 31%) had b. p. 116°/0·15 mm., $n_D^{23}$ 1·4641 (Found: C, 69·2; H, 10·4. $C_{19}H_{34}O_4$ requires C, 69·9; H, 10·4%).

*Diethyl Methyl*cyclo*octylmalonate*.—Ethyl sodiomethylmalonate (from 87 g. of ester) was heated for 60 hr. at 100—104° (internal) with *cyclo*octyl bromide (95 g.), and the product isolated in the normal manner. The disubstituted malonic *ester* (78 g., 55%) had b. p. 140—142°/2 mm., $n_D^{20}$ 1·4652 (Found: C, 67·5; H, 9·8. $C_{16}H_{28}O_4$ requires C, 67·6; H, 9·9%). On hydrolysis it gave *methyl*cyclo*octylmalonic acid*, colourless plates (from water), m. p. 176° (decomp.) (Found: C, 63·3; H, 8·8. $C_{12}H_{20}O_4$ requires C, 63·2; H, 8·8%).

*Attempts to Alkylate* cyclo*Octylmalonic Esters*.—(*a*) Diethyl *cyclo*octylmalonate (13·5 g.) was heated with methyl iodide (8·0 g.) in the presence of sodium ethoxide in absolute ethanol until the mixture no longer gave an alkaline reaction with litmus paper (62 hr.). The resulting ester (11·8 g.), b. p. 107—109°/0·02—0·03 mm., $n_D^{21}$ 1·4637, was mainly unchanged *cyclo*octylmalonic ester since the main product on hydrolysis was *cyclo*octylmalonic acid. A very small amount (4%) of methyl*cyclo*octylmalonic acid, m. p. and mixed m. p. 176° (decomp.), was also isolated.

(*b*) The method of achieving the reverse order of alkylation described in B.P. 649,682 yielded no disubstituted malonic derivative from di-*n*-butyl *cyclo*octylmalonate and methyl sulphate, the great majority of the original ester being recovered.

*Diethyl* cyclo*Oct-2-enylmalonate*.—(*a*) 3-Bromo*cyclo*octene (51 g.) was added during 20 min. to sodiomalonic ester (from 6·3 g. of sodium, 150 ml. of ethanol, and 28·6 g. of ethyl malonate). Titration of a 1-ml. sample 10 min. later showed that the reaction was 75% complete. The mixture was then heated on the steam-bath for 2 hr. Most of the ethanol was removed, the residue was treated with water and extracted with ether, and the extract was dried, and fractionated. The crude *ester* (36·3 g., 50%) on redistillation formed a colourless oil, b. p. 125—126°/1·5 mm., $n_D^{22}$ 1·4691 (Found: C, 66·7; H, 8·8. $C_{15}H_{24}O_4$ requires C, 67·1; H, 9·0%).

(*b*) 1 : 2-Dibromo*cyclo*octane (176 g.) was added to sodiomalonic ester (from 30 g. of sodium, 400 ml. of ethanol, and 104 g. of ethyl malonate), and the whole stirred under reflux for 5 days. The ethanol was distilled off, the residue was diluted with water, and the product isolated in the usual manner. The yield of ester was 39%. A by-product (m. p. 76°) obtained in this reaction was ethanetetracarboxylic ester. Hydrolysis of either sample of *cyclo*oct-2-enylmalonic ester gave cyclo*oct-2-enylmalonic acid*, colourless needles (from water), m. p. 164—165° (decomp.) (Found: C, 62·3; H, 7·7%; equiv., 107. $C_{11}H_{16}O_4$ requires C, 62·3; H, 7·6%; equiv., 106).

Corresponding *cyclo*oct-1-enylmalonic esters could not be obtained from 1-bromo*cyclo*octene

and sodiomalonic esters by the methods used in the above preparations. From one of these experiments was isolated a small quantity of diethyl phloroglucinoldicarboxylate, m. p. 106—107° (Found : C, 53·2; H, 5·4; equiv., 273. Calc. for $C_{12}H_{14}O_7$ : C, 53·3; H, 5·2%; equiv., 270), which is known to be formed from malonic ester and sodium ethoxide under certain conditions.

*Barbituric Acid Derivatives.*—The tabulated *compounds* (I) were prepared by standard methods.

| | | | | | Found, % | | | | Required, % | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. | R′ | R″ | Y | M. p. | C | H | N | S | C | H | N | S |
| | | R = *cyclo*octyl. | | | | | | | | | | |
| 1 | H | H | O | 254° | 60·6 | 7·7 | 11·7 | — | 60·5 | 7·6 | 11·8 | — |
| 2 | Me | H | O | 262—263 | 62·2 | 8·0 | 10·9 | — | 61·9 | 8·0 | 11·1 | — |
| 3 | Allyl | H | O | 169—170 | 65·0 | 8·1 | 10·0 | — | 64·8 | 7·9 | 10·1 | — |
| 4 | Me | Me | O | 138 | 62·9 | 8·4 | 10·6 | — | 63·2 | 8·3 | 10·5 | — |
| 5 | Me | H | S | 166—167 | 57·9 | 7·1 | 10·5 | 12·0 | 58·2 | 7·5 | 10·5 | 11·9 |
| | | R = *cyclo*oct-2-enyl. | | | | | | | | | | |
| 6 | H | H | O | 225 | 60·9 | 6·9 | 11·8 | — | 61·0 | 6·8 | 11·9 | — |
| 7 | H | H | S | 246 | 57·6 | 6·4 | — | — | 57·1 | 6·4 | — | — |
| 8 | Allyl | H | S | 225—226 | 62·1 | 6·9 | — | 10·9 | 61·7 | 6·9 | — | 11·0 |

Compounds 3 and 8 were prepared from 1 and 7 respectively by shaking a solution of the barbituric acid in aqueous sodium hydroxide with allyl bromide for 48 hr. No. 2 could not be prepared from no. 1 under similar conditions with methyl iodide.

The sodio-derivatives were prepared by addition of the calculated amounts of alcoholic sodium hydroxide. Those of nos. 2, 6, and 8 were insoluble in ethanol and were isolated by filtration, whilst those of nos. 4, 5, and 7 were soluble and were isolated by evaporation *in vacuo*.

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