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Barbiturates Containing the Δ^2-Cyclopentenyl Group[1]

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Prior to the use of the duration of action of hypnotic drugs as a basis of classification[2] it was recognized that the barbiturates differed in this respect. Vogt[3] spoke of some as slow in induction of action and long in duration, others as rapid in action with quick recovery and still others as permitting a very rapid recovery. It was only after the publication of the method of Fitch and Tatum, however, that this classification of the barbiturates was put on a sound scientific basis.

Studies made since the adoption of this method demonstrate that in general the desirable therapeutic properties of a short induction period and a hypnosis of moderate duration with a minimum of post-hypnotic effects are found in those derivatives bearing a five-carbon group and either ethyl or allyl in the five position of the barbituric acid. Modification of this structure by the addition of an N alkyl group[4,5] or substitution of sulfur for oxygen[6] in the 2-position has yielded compounds possessing interesting and valuable therapeutic properties.

These considerations have made it desirable and the recent commercial availability of dicyclopentadiene has made it possible to undertake a critical and comprehensive investigation of barbiturates containing the Δ^2-cyclopentenyl group as one of the substituents. Some of these have been reported previously[7,8] but are included herein for the sake of completeness.

Chemical

All of the malonic esters in Table I were prepared by conventional methods with the exception of the propenyl and isopropenyl members. These were made by the elegant method of Cope and Hancock,[9] *i. e.*, condensation of Δ^2-cyclopentenyl chloride with the appropriate alkylidene malonic ester in the presence of sodamide. They were also obtained in poorer yields by the condensation of Δ^2-cyclopentenyl chloride with the alkylidene malonic esters by means of sodium ethoxide in benzene solution.

TABLE I

ETHYL R-Δ^2-CYCLOPENTENYLMALONATES

R	B. p., °C.	Mm.	Yield, %
CH_3	138–142	19	24
CH_3CH_2—	141–146	12	42, 66[a]
$CH_3CH_2CH_2$—	158–163	25	26, 58[a]
$(CH_3)_2CHCH_2$—	158–163	7	45
CH_2=$CHCH_2$—	149–155	16	60, 63[a]
CH_2=$C(CH_3)$—	138–140	7	52
CH_3CH=CH—	146–152	11	24
CH_2=$C(CH_3)CH_2$—	157–161	18	66

[a] Δ^2-Cyclopentenyl group introduced first.

Since the completion of this work an improved method of preparing primary 1-alkenyl disubstituted malonic esters has been published by Cope and co-workers.[10]

The Δ^2-cyclopentenyl chloride used in this work was prepared by a modification of the method noted by Arvin and Adams.[11]

This modification consisted of adding one mole freshly distilled cyclopentadiene to slightly less than one mole of hydrogen chloride dissolved in ether at $-5°$. The mixture was maintained at this temperature for twenty-four hours after which the ether was removed and the cyclopentenyl chloride distilled. While this method does not give any better yields than that described by Arvin and Adams, it proved more convenient in our hands.

All of the barbiturates listed in Table II were prepared by the reaction of the disubstituted malonic esters with the appropriate urea in the presence of sodium ethoxide[12] or in the case of the β-bromo-allyl derivatives by the action of β-bromo-allyl bromide on the sodium salt of the monosubstituted barbituric acid in water at 100°.[13]

The barbiturates were crystallized from dilute alcohol except as noted in Table II.

Pharmacology

As a preliminary survey to pick the more promising members for detailed pharmacological study, the minimum effective dose and the minimum lethal dose of the Δ^2-cyclopentenyl barbiturates as the sodium salts were determined by intraperitoneal injection in rats. The rats were not starved in these experiments since the drugs were administered by intraperitoneal injection and starving would have little effect on the calculated dose per kilo. Mature male Wistar strain rats weighing 200–350 *g.* were used and the rats were not used a second time except in a few cases for preliminary experiments. The time of dosage, time of beginning sleep and time of waking, were noted so that it was possible to measure the average time for induction of sleep (promptness of action) and also the average duration of sleep at various dosage levels. Sleep is defined as the period during which the rats could not be aroused by pinching the tail. Results of this preliminary survey are summarized in Table II. These results are expressed in terms of the free acids.

Certain of the thio and N-methyl derivatives in the form of their sodium salts were evaluated by intravenous injection in rats. The results obtained by this mode of administration are noted in Table II. While the compounds appear more

(1) Presented before the Division of Medicinal Chemistry at the Saint Louis meeting of the American Chemical Society, April 10, 1941.

(2) Fitch and Tatum, *J. Pharmacol.*, **44**, 325 (1932).

(3) Vogt, *Arch. Exptl. Path. Pharm.*, **152**, 341 (1930).

(4) Tabern and Volwiler, THIS JOURNAL, **58**, 1354 (1936).

(5) Shonle and Doran, *ibid.*, **58**, 1358 (1936).

(6) Tabern and Volwiler, *ibid.*, **57**, 1961 (1935).

(7) Chaux, *Compt. rend.*, **194**, 1193 (1932).

(8) Horclois, *Chemie & industrie*, Special No. 357–363 (April, 1934).

(9) Cope and Hancock, THIS JOURNAL, **60**, 2644 (1938).

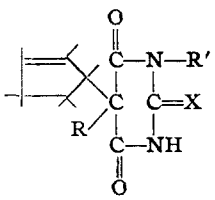
(10) Cope, Hartung, Hancock and Crossley, *ibid.*, **62**, 314 (1940).

(11) Arvin and Adams, *ibid.*, **49**, 2940 (1927).

(12) Fischer and Dilthey, *Ann.*, **335**, 334 (1904).

(13) Dox and Jones, THIS JOURNAL, **51**, 316 (1929).

TABLE II
R-Δ^2-CYCLOPENTENYLBARBITURIC ACIDS



R	R′	X	M. p., °C., uncor.	Nitrogen, % Calcd.	Found	Intraperitoneal injection in rats: MED$_{50}$ mgm./kilo	MLD$_{50}$ mgm./kilo	Induction (min.) at approximately 60% MLD$_{50}$	Duration (min.) at approximately 60% MLD$_{50}$
$CH_3—CH_2—$	H	O	160-161(C)[7,8]	12.61	12.80	100	>150	8[a]	70[a]
$CH_3—CH_2—CH_2—$	H	O	147-148(C)[7,8]	11.86	11.79	45	>125	7[b]	150[b]
$CH_3—CH=CH—$	H	O	186-188	11.96	12.08	175	175	...	...
$CH_2=CH—CH_2—$	H	O	139-140(C)[7,8]	11.96	11.89	30	90	6	110
$CH_2=C(CH_3)$	H	O	136-137	11.96	11.90	70	>175	15	90
$CH_2=CBrCH_2—$	H	O	192-193(C)[7,8]	8.94	8.68	135	350	9	60
$CH_2=C(CH_3)CH_2—$	H	O	168-169	11.29	11.48	60	200	5	90
$(CH_3)_2CH—CH_2—$	H	O	171-172	11.20	11.38	60	200	3	180
$CH_3CH_2—$	H	S	194-195	11.76	12.00	50	>125	4	>180
						30[c]	110[c]		
$CH_3—CH_2—CH_2$	H	S	126-127	11.11	11.29	75	250	4	120
$CH_2=CH—CH_2$	H	S	150-151	11.20	11.46	50	100	10	70
						20[c]	100[c]		
$CH_2=C(CH_3)$	H	S	Dec.	11.20	10.98	100	175	10	150
$CH_2=CBrCH_2—$	H	S	206-207	8.51	8.35	500	500	...	...
$CH_2=C(CH_3)—CH_2—$	H	S	178-180	10.60	10.81	60	60	...	...
$(CH_3)_2CH—CH_2—$	H	S	150-151	10.52	10.75	100	300	3	240
CH_3	CH_3	O	138-139	12.61	12.59	>1000	>1000	...	...
						> 500[c]	> 500[c]		
$CH_3—CH_2$	CH_3	O	117-118	11.86	12.11	75	250	2	>60
$CH_3—CH_2—CH_2$	CH_3	O	104-105(A)	11.20	11.11	125	>300	5	45
$CH_2=CH—CH_2$	CH_3	O	96-97(B)	11.29	11.49	75	275	3	180
						25[c]	90[c]		
$CH_2=C(CH_3)$	CH_3	O	137-139	11.29	11 41	90	200	3	30
$CH_2=CBrCH_2$	CH_3	O	139-141	8.32	8.56	150	350	5	45
$CH_2=C(CH_3)—CH_2—$	CH_3	O	132-133	10.68	10.91	115	>500	4	90
$(CH_3)_2CHCH_2—$	CH_3	O	150-151	10.53	10.70	175	400	7	120

[a] At 125 mgm. [b] At 100 mgm. [c] By intravenous injection. (A) From petroleum ether. (B) U. S. Patent 1,947,944. (C) U. S. Patent 1,869,666.

active by this route of administration, they have about the same margin of safety.

As is evident from Table II, allyl-Δ^2-cyclopentenylbarbituric acid showed promise of being the most effective member of the series and was chosen on the basis of the preliminary intraperitoneal tests for more detailed pharmacological study. This study which includes extensive work in other species is now complete and will appear elsewhere.

Since in general the most satisfactory compounds among the N-alkyl barbiturates are those in which the N-alkyl group is methyl and the groups attached to the 5-carbon are methyl and a secondary group containing five or six carbon atoms, it was surprising to find methyl-Δ^2-cyclopentenyl-N-methylbarbituric acid devoid of hypnotic activity in rats in the large doses employed. Another interesting point is the inactivity of the propenyl derivative as compared to the highly active allyl compound. No explanation is offered for the loss of activity accompanying this shift in the position of the double bond.

Summary

A series of twenty-three barbituric acids containing the Δ^2-cyclopentenyl group has been prepared and characterized. Preliminary pharmacological studies indicate that allyl-Δ^2-cyclopentenylbarbituric acid is the most effective hypnotic of the series. A more detailed pharmacological study of this compound will be reported elsewhere.

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