[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES, ELI LILLY AND COMPANY]

A Study of the Effect of Unsaturated Aliphatic Groups in Barbituric Acids[1]

BY H. A. SHONLE AND JOHN H. WALDO

5,5-Dialkyl substituted barbituric acids containing such unsaturated groups as the allyl,[2] bromopropenyl,[3] crotyl,[4] propargyl,[5] isopropenylpropargyl,[5] cyclohexenyl[6] and cyclopentenyl[7] groups have been described and a number of them tested pharmacologically and used clinically.

Since barbituric acids containing the allyl group are, in general, more effective than those containing the propyl group, it was decided to establish experimentally whether barbituric acids containing larger unsaturated groups, such as the secondary pentenyl and secondary hexenyl groups, were more or less effective than barbituric acids containing the corresponding saturated groups. This study has been extended to include a comparison of barbituric acids containing the propargyl, propyl, allyl and bromopropenyl groups.

The saturated and unsaturated secondary alcohols employed in this investigation were prepared by the Grignard reaction. The propargyl alcohol was prepared by the method of Kirrmann.[8]

Since it has been pointed out previously that refluxing secondary alcohols with aqueous hydrobromic acid tends to cause a rearrangement which results in obtaining a mixture of isomeric bromides, we prepared the halides of all of the secondary alcohols used by saturating the cold alcohol with dry gaseous hydrobromic acid.[9] In order to prevent possible rearrangement during distillation, a low vacuum was used with the receiver immersed in liquid air so that distillation could be carried out without warming the flask above room temperature.[10] It was necessary to prepare 4-chloropentene-2 and 4-chlorohexene-2 instead of the bromide due to the instability of the latter. These chlorides were prepared by saturating the cold alcohol with dry hydrochloric gas.

That no rearrangement took place in the preparation of saturated halides by the above methods was experimentally established by the preparation of

(1) Presented before the Division of Medicinal Chemistry at the New Orleans meeting of the American Chemical Society.

(2) T. B. Johnson and A. J. Hill, *Am. Chem. J.*, **46**, 537 (1911); E. Preisewerk and E. Grether, U. S. Patent 1,042,265 (1912); H. Hörlein and W. Kropp, U. S. Patent 1,056,793 (1913); E. H. Volwiler, THIS JOURNAL, **47**, 2236 (1925); A. W. Dox, U. S. Patent 1,615,870 (1927).

(3) F. Boedecker, U. S. Patent 1,622,129 (1927), and 1,739,622 (1929).

(4) L. Taub, L. Schütz and K. Meisenburg, U. S. Patent 1,511,919 (1924).

(5) M. Brockmühl and G. Ehrhart, U. S. Patent 1,682,062 (1928).

(6) W. Schulemann and K. Meisenburg, U. S. Patent 1,690,796 (1928).

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

(8) A. Kirrmann, *Bull. soc. chim.*, [4] **39**, 698 (1926).

(9) M. L. Sherrill, B. Otto and L. W. Pickett, THIS JOURNAL, **51**, 3023 (1929); M. L. Sherrill, C. Baldwin and D. Haas, *ibid.*, **51**, 3034 (1929).

(10) Personal communication from Dr. M. S. Kharasch.

2- and 3-bromopentane, each of which had the refractive index as given by Sherrill.[9] From each of these bromides, barbituric acids were produced which differed from each other.

The mono- and di-substituted malonic esters were prepared and purified as previously described.[11] The barbituric acids were prepared by condensing the di-substituted malonic ester with urea in the presence of sodium ethylate. In one instance, propargyl bromide was condensed with *sec*-butylbarbituric acid to produce *sec*-butylpropargylbarbituric acid. The three tables give some of the constants of the products prepared.

TABLE I

HALIDES

Compound	B. p., °C.	n^{25}
4-Chloropentene-2	58 at 155 mm.	1.4311
4-Chlorohexene-2	73–76 at 136 mm.	1.4356
3-Bromohexane	65.8–67 at 49 mm.	1.4469 (n^{20})

TABLE II

DISUBSTITUTED MALONIC ESTERS[a]

Ethyl malonate derivatives	Boiling point °C.	Mm.	Boiling point °C.	Mm.	n^{25}
Isoamyl propargyl	142	at 11 to 151	at 14		1.4403 to 1.4409
1-Methylbutene-2 ethyl	135	at 15 to 138	at 15		1.4418 to 1.4438
1-Ethylbutene-2 ethyl	143.4	at 15 to 144.6	at 15		1.4437 to 1.4439
1-Ethylbutyl ethyl	135	at 9 to 132.8	at 8.5		1.4363 to 1.4369
sec-Butyl propyl	112	at 6 to 114	at 5		1.4331 to 1.4342

[a] The boiling points and refractive indices given are for the cuts which were found satisfactory for the desired synthesis.

TABLE III

DISUBSTITUTED BARBITURIC ACIDS

Derivative	Melting point °C. (Anschütz)	Nitrogen, % Calcd.	Found	
sec-Butyl propargyl	167 –168	12.61	12.52	12.44
Isoamyl propargyl	163 –164	11.86	12.00	12.20
1-Methylbutene-2 ethyl	114.5–116	12.50	12.51	12.58
1-Ethylbutene-2 ethyl	93 – 94	11.76	11.76	11.76
1-Ethylbutyl ethyl	112 –115	11.67	11.52	11.40
sec-Butyl propyl	136 –138	12.44	12.34	12.55

The several new barbituric acids described above and the known barbituric acids which were used for comparison were evaluated pharmacologically. Experience has indicated that it is unsatisfactory to compare data obtained at different times, or with different colonies of rats. Therefore we injected part of each group of rats with sodium isoamylethylbarbiturate. Freshly prepared two per cent. solutions of the sodium salt of the barbituric acids were injected intraperitoneally into white rats of 100 g. average weight and frequent observations were made until the animals either recovered or died. The pharmacologic data are summarized in

(11) H. A. Shonle, A. K. Keltch and E. E. Swanson, THIS JOURNAL, **52**, 2440 (1930).

Table IV, in which the minimum hypnotic dose, the minimum anesthetic dose, and the minimum lethal dose are given in milligrams per kilogram body weight.

TABLE IV

PHARMACOLOGICAL DATA

Barbituric acid	M. H. D. mg./kg.	M. A. D. mg./kg.	M. L. D. mg./kg.	Therap. index M. L. D./M. A. D.
1-Ethylbutyl ethyl	30	50	80	1.60
1-Ethylbutenyl-2 ethyl	50[a]	..	60[a]	..
1-Methylbutyl allyl	20	45	100	2.22
1-Methylbutyl ethyl	40	50	120	2.40
1-Methylbutenyl-2 ethyl	50[a]	90[a]	100	1.10
sec-Butyl allyl	40	60	110	1.84
Isoamyl propargyl	80	140	300	2.14
sec-Butyl propargyl	50	80	180	2.25
sec-Butyl bromopropenyl	70	..	120	..
sec-Butyl *n*-propyl	50	80	180	2.25

[a] Caused convulsions.

Discussion

The pharmacologic summary shows that when a saturated secondary pentyl or hexyl group in alkylethylbarbituric acid is replaced by an unsaturated group having the same carbon skeleton, a product having less satisfactory hypnotic properties is obtained. Both of the unsaturated secondary groups produced convulsions in white rats when low doses were given, and with higher doses either gave an unsatisfactory state of anesthesia or no anesthesia at all. The barbituric acids containing these unsaturated secondary groups were more toxic than the corresponding barbituric acids containing saturated groups and were also more toxic than the isomeric secondary alkyl allyl barbituric acids. The toxicity increased with the increasing molecular weight.

The isoamylpropargylbarbituric acid was less effective and less toxic than the *sec*-butylpropargyl. In this instance the derivative having the lower molecular weight was the more toxic. This increase of toxicity with the decrease in molecular weight is probably due to the presence of the more effective and the more toxic secondary butyl group. The *sec*-butylpropargyl and *sec*-butylpropylbarbituric acids were equally effective. It will be noted that the *sec*-butylallyl was the most effective of this series and the *sec*-butylbromopropenyl was the least satisfactory as shown by animal tests. There would appear therefore to be little correlation between the degree of unsaturation in the three carbon atom chain and the physiologic properties.

A more detailed report of other physiologic effects of these barbituric acids will be published in another journal.

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Wilbur J. Doran for the micro-chemical nitrogen analyses reported in this investigation, and for his assistance in the preparation of some of the products.

Conclusion

1. Alkenylethylbarbituric acids containing the unsaturated secondary pentyl or hexyl group have less hypnotic action than corresponding barbituric acids with saturated alkyl groups and cause convulsions at low doses.

2. Two propargylalkylbarbituric acids were investigated and found to have hypnotic action which was not more effective than the corresponding barbituric acids containing the allyl or propyl group.

3. The following new products were prepared—isoamylpropargylmalonic ester, 1-methylbutenyl-2-ethylmalonic ester, 1-ethylbutenyl-2-ethylmalonic ester, 1-ethylbutylethylmalonic ester, *sec*-butyl-*n*-propylmalonic ester, *sec*-butylpropargylbarbituric acid, isoamylpropargylbarbituric acid, 1-methylbutenyl-2-ethylbarbituric acid, 1-ethylbutenyl-2-ethylbarbituric acid, 1-ethylbutylethylbarbituric acid and *sec*-butyl-*n*-propylbarbituric acid.

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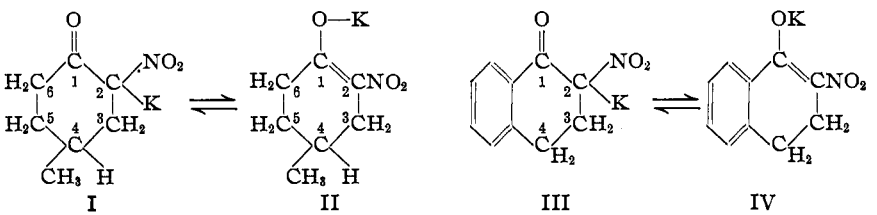
Asymmetric Syntheses. III. The Action of Optically Active Nitrates on α-Tetralone

BY W. H. HORNE AND R. L. SHRINER

The formation of an optically active product as the result of the reaction between 4-methylcyclohexanone and *d* or *l*-2-octyl nitrate[1] left undecided the location of the optically active center of the molecule and the exact structure of the salts of these nitro compounds. The presence of the asymmetric carbon atom at position 4 prevents any distinction between structures I and II since both forms would be optically active.



I II III IV

In order to avoid the complicating effect of the asymmetric carbon atom at position 4, a study was made of the action of *d*- and *l*-2-octyl nitrates

(1) Shriner and Parker, THIS JOURNAL, **55**, 766 (1933).