[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Acid Amides as Hypnotics. IV. Barbituric Acids

BY F. F. BLICKE AND M. F. ZIENTY[1,2]

The known 5,5-disubstituted barbituric acids in which one of the substituents is an arylalkyl, cycloalkylalkyl, alkoxyalkyl or aryloxyalkyl are relatively few in number.

5-Ethyl-5-benzylbarbituric acid, although a strong hypnotic, tends to produce convulsions.[3,4] The corresponding propyl and isopropyl compounds seem to be of little or no value.[4] 5-Ethyl-5-β-phenylethylbarbituric acid lacks the convulsive property of the benzyl compound and is an active hypnotic when administered intraperitoneally into mice but is much less active when given orally.[5]

Several representatives of alkyl-α-naphthylmethyl-,[6] alkyl-β-(α-naphthyl)-ethyl- and alkylcyclohexylmethylbarbituric[7] acids have been described but none of them was found to be superior to barbital.

Allylbenzylbarbituric acid[8] and allylbenzylthiobarbituric acid[9] have also been synthesized.

A few disubstituted barbituric acids which contain alkoxyalkyl or aryloxyalkyl groups such as methoxy-,[10] propoxy-,[10] butoxy-[10] and isobutoxymethyl,[10] ethoxyethyl,[11a,b,c] benzyloxymethyl,[10] phenoxyethyl[11b,c, 12a,b] and ethoxyethoxyethyl[13] have been reported in the literature.

In view of the rather limited studies mentioned above, a further investigation of disubstituted barbituric acids in which one of the substituents was an arylalkyl, a cycloalkylalkyl, an alkoxyalkyl or an aryloxyalkyl seemed warranted.

The arylalkyl and cycloalkylalkyl derivatives which we have prepared are listed in Table I, the alkoxyalkyl and aryloxyalkyl derivatives in Table II.

The barbituric acids were examined by Mr. J. Nelson and Dr. G. F. Cartland in The Upjohn Company laboratories and we are indebted to them for the preliminary pharmacological data.

The compounds were injected intraperitoneally, in the form of a 5% aqueous solution of their sodium salts, into rats.[14]

In order to provide a basis for comparison and evaluation, the data for Sodium Barbital and Phenobarbital Sodium, determined under similar but not exactly identical conditions, are reported.

	Mg./kg. M. L. D.	Mg./kg. M. H. D.	M. L. D. / M. H. D.
Sodium Barbital	225	130	1.7
Phenobarbital Sodium	150	80	1.9

It is interesting to note that ethyl-α-phenylethylbarbituric acid, like ethylbenzylbarbituric acid, is a strong convulsant; ethyl-β-phenylethylbarbituric acid, as stated before, is free from this side reaction.

Ethylcinnamyl- (8), ethyl-β-butoxyethyl- (23) and ethyl-γ-phenoxybarbituric acid (28) produce very quiet sleep and probably represent the compounds which possess the most favorable properties.

Experimental Part

The new disubstituted malonic esters (Tables I and II) were prepared from the monosubstituted malonic esters mentioned below: compound 7 from diethyl ethylmalonate[15]; compound 12 from diethyl butylmalonate[16]; compound 13 from diethyl isobutylmalonate[17]; compounds 15, 17, 18, 30, 32 and 42 from diethyl β-phenylethylmalonate[18]; compound 24 from diethyl β-(β′-ethoxyethoxy)-ethylmalonate[19]; compound 29 from diethyl benzylmalonate[20]; compounds 31, 34, 35 and 37 from di-

(1) This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by M. F. Zienty in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(2) The Upjohn Company Fellow.

(3) Dox and Yoder, THIS JOURNAL, **44**, 1141 (1922).

(4) Shonle and Moment, *ibid.*, **45**, 243 (1923).

(5) Dox, *ibid.*, **46**, 2843 (1924).

(6) Keach, *ibid.*, **55**, 2977 (1933).

(7) Katsnel'son and Brodskii, *Compt. rend. acad. sci. U. R. S. S.*, **17**, 477 (1937); *C. A.*, **32**, 2912 (1938); Merkulov, *Bull. med. exptl. U. R. S. S.*, **6**, 64 (1938); *C. A.*, **33**, 2992 (1939).

(8) Johnson and Hill, *Am. Chem. J.*, **46**, 544 (1911).

(9) Tabern and Volwiler, THIS JOURNAL, **57**, 1963 (1935).

(10) Hill and Keach, *ibid.*, **48**, 261 (1926).

(11) (a) German Patent 285,636; *Chem. Zentr.*, **86**, II, 639 (1915); (b) Dox and Yoder, THIS JOURNAL, **44**, 1578 (1922); (c) Whitmore and Thorpe, U. S. Patent 2,161,212 (1939); *C. A.*, **33**, 7493 (1939).

(12) (a) Hiemenz and Taub, U. S. Patent 1,217,447; *C. A.*, **11**, 1521 (1917); (b) German Patent 295,492; *Chem. Zentr.*, **88**, I, 149 (1917).

(13) Perlog and Hahn, *Collection Czechoslov. Chem. Communications*, **8**, 219 (1936); *C. A.*, **30**, 5721 (1936).

(14) In the case of compounds 15 and 41, a 5% suspension of the free acid in a 5% acacia solution was used.

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

(16) "Organic Syntheses," Vol. 3, p. 12.

(17) Fischer and Schmitz, *Ber.*, **39**, 351 (1906).

(18) Dolique, *Ann. chim.*, [10] **15**, 447 (1931).

(19) B. p. 155–160° (2 mm.); the product was obtained by interaction of diethyl sodiummalonate and β-(β′-ethoxyethoxy)-ethyl bromide (Blicke and Zienty, THIS JOURNAL, **63**, 2780 (1941).

(20) Vogel, *J. Chem. Soc.*, 2031 (1928).

TABLE I

DISUBSTITUTED MALONIC ESTERS AND 5,5-DISUBSTITUTED BARBITURIC ACIDS

Barbituric acid 4 was recrystallized from a mixture of benzene and petroleum ether (30–40°); 8 from a mixture of benzene and petroleum ether (90–100°); 17 from a mixture of acetone and petroleum ether (90–100°); all of the others from dilute alcohol.

		Malonic ester B. p., °C.	Mm.	Barbituric acid M. p., °C.	Formula	Nitrogen, % Calcd.	Found	M. L. D. mg./kg.	M. H. D. mg./kg.	M. L. D. / M. H. D.
1	Ethylbenzyl	198–203	32[a]	211–212[b]	$C_{13}H_{14}O_3N_2$	11.38	11.50	150[i]	...	...
2	Ethyl-α-phenylethyl	....[c]	..	207–208	$C_{14}H_{16}O_3N_2$	10.76	10.93	< 50[i]	< 50	1
3	Ethyl-β-phenylethyl	222–223	45[d]	167–168[d]	$C_{14}H_{16}O_3N_2$	10.76	11.03	300	150	2
4	Ethyl-γ-phenylpropyl	....[e]	..	129–130[f]	$C_{15}H_{18}O_3N_2$	10.21	10.29	300	150	2
5	Ethyl-δ-phenylbutyl	....[e]	..	140–141	$C_{16}H_{20}O_3N_2$	9.72	9.92	200	100	2
6	Ethyl-ζ-phenylhexyl	....[e]	..	94–95	$C_{18}H_{24}O_3N_2$	8.85	8.95	300	>200	<1.5
7	Ethyl-β-cyclohexylethyl	180–185	10[g]	170–171	$C_{14}H_{22}O_3N_2$	10.51	10.55	200	>100	<2
8	Ethylcinnamyl	....[e]	..	94–95	$C_{15}H_{16}O_3N_2$	10.28	10.02	200	75	2.6
9	Propyl-β-phenylethyl	....[e]	..	99–100	$C_{15}H_{18}O_3N_2$	10.21	10.42	400	150	2.5
10	Isopropyl-β-phenylethyl	....[e]	..	191–192	$C_{15}H_{18}O_3N_2$	10.21	10.39	>300	150	>2
11	Allyl-β-phenylethyl	....[e]	..	151–153	$C_{15}H_{16}O_3N_2$	10.30	10.46	250[i]	175	1.4
12	Butyl-β-phenylethyl	220–225	25	150–151	$C_{16}H_{20}O_3N_2$	9.71	9.76	400	>300	<1.3
13	Isobutyl-β-phenylethyl	158–163	2	193–194	$C_{16}H_{20}O_3N_2$	9.71	10.08	300	200–300	>1
14	s-Butyl-β-phenylethyl	....[c]	..	163–164	$C_{16}H_{20}O_3N_2$	9.71	9.78	200	200–360	...
15	β-Cyclopentylethyl-β′-phenylethyl	255–258	27	166–167	$C_{19}H_{24}O_3N_2$	8.53	8.54	300	(>200)[k]	(1.5)
16	β-Cyclohexylethyl-β′-phenylethyl	....	..	163–164	$C_{20}H_{26}O_3N_2$	8.18	8.25	500	>100	...
17	α-Phenylethyl-β′-phenylethyl	270–275	58	241–242	$C_{20}H_{20}O_3N_2$	8.32	8.56	125[i]	>100	<1.2
18	Di-(β-phenylethyl)	248–249	13[h]	148–149	$C_{20}H_{20}O_3N_2$	8.32	8.36	500	>400	<1.2
19	Di-(β-cyclohexylethyl)	....	..[i]	196–197	$C_{20}H_{32}O_3N_2$	8.03	8.06	500	>500	1

[a] Mohr [*J. prakt. Chem.*, [2] **71**, 330 (1905)], b. p. 173° (12.5 mm.). [b] Ref. 3, m. p. 206–207°. [c] Blicke and Zienty, THIS JOURNAL, **63**, 2780 (1941). [d] Ref. 5, b. p. 148–150° (2 mm.); m. p. 168°. [e] Blicke and Centolella, THIS JOURNAL, **60**, 2923 (1938). [f] Thomas (Dissertation, Kiel, 1937), m. p. 122°. [g] Adams, Ford, Stanley and Peterson [THIS JOURNAL, **49**, 2937 (1927)], b. p. 146–148° (2 mm.). [h] Leuchs and Reinhart (*Ber.*, **57**, 1211 (1924)), b. p. 248° (13 mm.). [i] Davis and Adams, THIS JOURNAL, **50**, 2298 (1928). [j] Convulsant. Barbituric acids 1 and 2 are especially strong convulsants. [k] Estimated value.

TABLE II

DISUBSTITUTED MALONIC ESTERS AND 5,5-DISUBSTITUTED BARBITURIC ACIDS

		Malonic ester B. p., °C.	Mm.	Barbituric acid M. p., °C.	Formula	Nitrogen, % Calcd.	Found	M. L. D. mg./kg.	M. H. D. mg./kg.	M. L. D. / M. H. D.
20	Ethylmethoxymethyl	....[a]	..	185–186[b]	$C_8H_{12}O_4N_2$	14.00	14.13	>900	600	>1.5
21	Ethyl-β-methoxyethyl	....[a]	..	179–180	$C_9H_{14}O_4N_2$	13.07	13.09	500[g]	250	2
22	Ethyl-β-ethoxyethyl	....[a]	..	179–180[c]	$C_{10}H_{16}O_4N_2$	12.27	12.37	400[g]	200	2
23	Ethyl-β-butoxyethyl	....[a]	..	123–124	$C_{12}H_{20}O_4N_2$	10.93	11.21	>200	75	>2.2
24	Ethyl-β-(β′-ethoxyethoxy)-ethyl	138–140	2[d]	96–97[d]	$C_{12}H_{20}O_5N_2$	10.29	10.31	>1000	>1000	1
25	Ethyl-β-(β′-butoxyethoxy)-ethyl	....[a]	..	83–84	$C_{14}H_{24}O_5N_2$	9.33	9.48	420	120	3.5
26	Ethyl-β-benzyloxyethyl	....[a]	..	163–164	$C_{15}H_{18}O_4N_2$	9.65	9.86	<200	55	<3.6
27	Ethyl-β-phenoxyethyl	....[a,e]	..	185–186[e]	$C_{14}H_{16}O_4N_2$	10.14	10.22	125[g]	40	3.1
28	Ethyl-γ-phenoxypropyl	....[a]	..	123–124	$C_{15}H_{18}O_4N_2$	9.65	9.80	250	125	2
29	Methoxymethylbenzyl	189–192	14[f]	175–176	$C_{13}H_{14}O_4N_2$	10.68	10.49	>600[g]	175	>3.4
30	Methoxymethyl-β-phenylethyl	195–200	18	175–176	$C_{14}H_{16}O_4N_2$	10.14	10.06	...		
31	Ethoxymethylphenyl	184–187	14	230–231	$C_{13}H_{14}O_4N_2$	10.68	10.50	...		
32	Ethoxymethyl-β-phenylethyl	215–218	23	180–181	$C_{15}H_{18}O_4N_2$	9.65	9.52	...		
33	Ethoxymethyl-β-phenoxyethyl	225–230	29	189–190	$C_{15}H_{18}O_5N_2$	9.15	9.02	...		
34	Butoxymethylphenyl	195–200	15	182–183	$C_{15}H_{18}O_4N_2$	9.65	9.72	...		
35	β-Methoxyethylphenyl	160–165	6	210–211	$C_{13}H_{14}O_4N_2$	10.77	10.89	550	225	2
36	β-Methoxyethyl-β′-phenylethyl	....[a]	..	164–165	$C_{15}H_{18}O_4N_2$	9.65	9.61	>500[g]	200–500	...
37	β-Ethoxyethylphenyl	190–193	14	196–197	$C_{14}H_{16}O_4N_2$	10.14	10.16	550	175	3.1
38	β-Ethoxyethyl-β′-phenylethyl	....[a]	..	169–170	$C_{16}H_{20}O_4N_2$	9.25	9.29	450[g]	250	1.8
39	β-Butoxyethyl-β′-phenylethyl	....[a]	..	160–161	$C_{18}H_{24}O_4N_2$	8.43	8.76	350	.....	...
40	β-Phenoxyethyl-β′-phenylethyl	....[a]	..	210–211	$C_{20}H_{20}O_4N_2$	7.95	8.01	500	>400	<1.2
41	Di-(γ-phenoxypropyl)	....[a]	..	143–144	$C_{22}H_{24}O_5N_2$	7.06	7.13	300	.....	...
42	γ-Phenoxypropyl-β′-phenylethyl	298–300	38	124–125	$C_{21}H_{22}O_4N_2$	7.64	7.83	250	.....	...

[a] Blicke and Zienty, THIS JOURNAL, **63**, 2780 (1941). [b] Ref. 10, m. p. 184°. [c] Ref. 11(a), m. p. 182–184°. [d] Ref. 13, b. p. 173–175.5° (10 mm.); m. p. 96.5–97°. [e] Ref. 12(a), no b. p. reported; m. p. 185°. [f] Simonsen [*J. Chem. Soc.*, **117**, 566 (1920)], b. p. 194–195° (19 mm.). [g] Convulsant.

ethyl phenylmalonate[21] and compound 33 from diethyl β-phenoxyethylmalonate.[22]

The 5-alkoxyalkyl-5-phenylbarbituric acids (compounds 31, 34, 35 and 37, Table II) were obtained, in the manner illustrated below, by the use of magnesium methylate[23] as a condensation agent; all other barbituric acids were prepared by the usual procedure with the aid of sodium ethylate in the presence of toluene.

5-(β-Methoxyethyl)-5-phenylbarbituric Acid.—Magnesium methoxide was obtained when 0.94 g. (0.040 mole) of magnesium ribbon, which had been cleaned with steel wool and cut into small pieces, was refluxed with 50 cc. of absolute methyl alcohol until all of the metal had reacted. After the addition of 10 g. (0.039 mole) of diethyl β-methoxyethylphenylmalonate and 3.3 g. (0.055 mole) of urea, the mixture was refluxed for twenty-four hours, the alcohol removed and the residue acidified with 18% hydrochloric acid. A small amount of unchanged malonic ester was removed by extraction with low boiling petroleum ether. The barbituric acid weighed 7.5 g. (73%).

(21) "Organic Syntheses," Vol. 16, p. 34.

(22) Bentley, Haworth and Perkin (*J. Chem. Soc.*, **69**, 167 (1896)) did not report the boiling point; we found the latter to be 215–218° (30 mm.).

(23) This agent was first employed in the barbituric acid synthesis by Lund (*Kgl. Dan. Vid. Selsk. Math.-fys. Medd.*, **13**, 13 (1935)); *Ber.*, **69**, 1621 (1936).

Summary

The preparation and hypnotic activity of a number of 5,5-disubstituted barbituric acids which contain an arylalkyl, cycloalkylalkyl, alkoxyalkyl or aryloxyalkyl group have been described.

ANN ARBOR, MICHIGAN RECEIVED AUGUST 4, 1941

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF DELAWARE]

Barbiturates Containing Large Radicals

BY GLENN S. SKINNER AND A. P. STUART[1]

It has been reported that α-alkyl-α-carbethoxy-γ-butyric lactones[2] condense very easily with urea to give excellent yields of 5-alkyl-5-β-hydroxyethylbarbiturates. This observation encouraged us to try the condensation of such lactones containing large radicals where solvent effects might be expected to interfere.

These experiments were successful, but some experimental items deserve especial mention. In fractionally distilling the higher lactones under diminished pressure it is quite necessary to release the vacuum very slowly when changing receivers. Otherwise a violent explosion may occur as the rarefied vapor is heated above its spontaneous ignition temperature. After removal of the bulk of the unchanged alkylmalonic ester, it is highly desirable to distill the remainder from a flask the neck of which is immersed in the bath up to the side tube. During the condensation with urea the object to be attained is the solution of the maximum amount of the lactone while some of the urea is still undissolved.

Experimental Part

Lauryl,[3] cetyl[4] and octadecylmalonic esters[5] were synthesized by standard procedures using the corresponding alcohols and malonic ester as starting materials. It may be noted that the yield of the alkyl malonic ester may be increased from about 75% to about 85% by the simple expedient of gradually adding the alkyl bromide dissolved in a second mole of malonic ester: lauryl ester, b. p. 170–172° (2 mm.); cetyl ester, b. p. 195–200° (1 mm.); octadecyl ester, b. p. 200–205° (1 mm.).

Lactones.—The lactones were prepared by the procedure previously described.[2] The desirability of using two equivalents of the alkylmalonic ester was checked. If only one mole of the lauryl ester is used, the yield of the lactone drops from 81 to 55%.

LACTONES $C_2H_5O_2C-\underset{\displaystyle R}{\overset{\displaystyle |}{C}}(-CH_2-CH_2-O-)-C(=O)$

R—	B. p., °C.	Mm.	M. p., °C.	Yield, %	Found, % C	Found, % H	Calculated, % C	Calculated, % H
n-$C_{12}H_{25}$-[a]	192–194		43.5	81	70.5	10.6	70.1	10.5
n-$C_{16}H_{33}$-	225–230	0.3	49	84	72.3	11.1	72.3	11.1
n-$C_{18}H_{37}$-	233–238	0.4	55–56	73	72.4	11.3	73.1	11.3

[a] d^{25}_4 0.9680 (supercooled liquid); d^{50}_4 0.9505; d^{75}_4 0.9325.

5-Alkyl-5-β-hydroxyethyl Barbiturates.—Since unsatisfactory results are likely to be obtained without close attention to experimental details, the procedure for the preparation of 5-octadecyl-5-(β-hydroxyethyl)-barbituric acid is recorded. In a typical run, 3.45 g. (0.15 mole) of sodium is dissolved in 40 cc. of absolute alcohol, and the solution is cooled to 10–15° with stirring as part of the sodium ethoxide crystallizes. The stirring is continued at a rate to avoid splashing while 20.5 g. (0.05 mole) of α-octadecyl-α-carbethoxy-γ-butyric lactone and 6.05 g. (0.10 mole) of urea are added at once in the order named at the point of the stirrer. The water surrounding the reaction flask is heated at such a rate that after an hour the

(1) Present address: Sun Oil Company, Norwood, Pa.

(2) Skinner, THIS JOURNAL, **59**, 322 (1937).

(3) Rothstein, *Bull. soc. chim.*, [5] **2**, 80–90 (1935).

(4) Phillips and Mumford, *J. Chem. Soc.*, 1736 (1931).

(5) Bleyberg and Ulrich, *Ber.*, **64**, 2509 (1931).