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# Physico-Chemical Characterization of Some 5,5-Disubstituted 1:3-Dimethyl Barbituric Acids

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## Abstract

Infrared spectra and ultraviolet characteristics for nine 5,5disubstituted 1 3-dimethyl barbituric acids are presented. X-ray diffraction powder data are given for 5 of these compounds

As part of a program of research comprising the synthesis of barbituric acid derivatives, a series of 1:3dimethyl analogues was recently prepared in this laboratory. It is the purpose of this report to present the physicochemical constants that were determined for the compounds.

# Experimental Results and Discussion

# Preparation and Purity

The 1:3-dimethyl derivatives of luminal, nembutal, seconal, and veronal were prepared by methylation of the acid in alkaline solution with methyl sulfate, according to the method of Bush and Butler (1). The remaining derivatives were methylated with diazomethane following the method of Dox (2). The barbituric acids used as starting materials were commercial samples obtained from reputable drug houses.

Several of the derivatives separated as oils that could not be induced to crystallize. These oils were dissolved in ether and washed repeatedly with dilute sodium hydroxide and water. The ether layer was filtered, and the solvent evaporated under reduced pressure. The derivatives, which separated as solids, were recrystallized to constant melting point. The melting points obtained for the derivatives of luminal and veronal agreed with those reported in the literature (1,2). The 1:3-dimethyl compounds of cyclopal, evipal, and rutonal, whose melting points had not been reported, were recrystallized from aqueous alcohol. Micro-Kjeldahl nitrogen determinations were performed on these three crystalline compounds and on those compounds which separated as oils. The results are shown in Table I.

#### Infrared Data

Solid samples were prepared by grinding 2.5 mg of the derivative with 997.5 mg of KBr (A.C.S. reagent grade) in a Wig-l-bug amalgamator for 30 sec. Disks were obtained by pressing *in vacuo* 200 mg aliquots of the mixtures in a KBr disk die at 10,000 lbs/sq. in. for about 5 min. A disk containing only KBr was placed in the reference beam, and absorbancies of the disks containing the derivatives were measured over the wave number range of 4000-650 cm<sup>-1</sup>. The spectra of the oils were taken as contact films. The spectra were recorded on a Perkin-Elmer Double Beam Model 21 Spectrophotometer equipped with rock salt optics, under standard conditions. The spectra are presented in Figures 1 and 2.

Marotta and Rosanova (3) have claimed that the N-methyl as well as the O-methyl derivative are generated during the methylation of barbital with diazomethane. Formation of the O-methyl derivative was later

TABLE I. PHYSICO-CHEMICAL CHARACTERISTICS OF 1:3-DIMETHYL DERIVATIVES OF BARBITURIC ACIDS

	N-Methyl Derivative of								
Trade	Chemical	Spa	Spectrum No			% N		Ultraviolet Spectrum	
Name	Name	Fig. 1	F1g. 2	Fig 3	M Pt °C	Found	Calc.	λ <i>max m</i> μ	ε max
Amytal	5-Ethyl-5-isoamylbarbituric acid	3	_	_	oıl	10.60	11.02	224	6.431
Cyclopal	5-Allyl-5-(1-cyclopenten-2-yl) barbituric acid	—	2	1	47.0-47 5	10.64	10.68	224	6.760
Evipal	5-(1-Cyclohexen-1-yl)-3,5-dimethyl barbituric acid		1	2	76.5-77.5	11.16	11 19	225	5.745
Luminal	5-Ethyl-5-phenylbarbituric acid		4	3	88.0-89.0			225	7.156
Nembutal	5-Ethyl-5-(1-methylbutyl) barbituric acid	4	—		oıl	10.64	11.02	225	6.230
Neonal	5-Ethyl-5-n-butylbarbituric acid	2	_	_	oıl	11.09	11.66	224	6.189
Rutonal	5-Methyl-5-phenylbarbituric acid	_	3	4	98 099 0	11 06	11 37	226	7.332
Seconal	5-Allyl-5-(1-methylbutyl) barbituric acid	5			oıl	10 25	10.52	225	5.821
Veronal	5,5-Diethylbarbituric acid	1		5	35.5-36.5	_		225	6,500



Fig. 1. Infrared Spectra of N-methyl Derivatives of Barbituric Acids

questioned by Buch and Butler (1), Dox (2), and Stuckey (4) who reported the formation of N-methyl derivatives only when using diazomethane and/or methyl sulfate as methylating agents. The infrared data presented in Figures 1 and 2 support their findings based on chemical and ultraviolet spectral evidence. The spectra show clearly



FIG. 2. INFRARED SPECTRA OF N-METHYL DERIVATIVES OF BARBITURIC ACIDS

that the methylation process does not involve the carbonyl bonds but affects the imino linkages of the molecules (presence of C=O bands throughout 1650-1750 cm<sup>-1</sup> region; absence of N-H vibrations throughout 3100-3200 cm<sup>-1</sup> range). Reappearance of a strong absorption band in the 1360-1380 cm<sup>-1</sup> region affords further evidence for the presence of N-CH<sub>3</sub> bonds in this series of malonyl urea compounds.

# **Ultraviolet Spectral Data**

Solutions of the derivatives, 0.858-1.573 x 10<sup>-4</sup>M, were prepared in alcohol and the ultraviolet spectra (200-360 m $\mu$ ) recorded on a Beckman DK-2 Automatic Spectrophotometer. Immediately after the spectrum was obtained, the cells were transferred to a Beckman DU Manual Spectrophotometer, and the absorbance measured at the wave length of maximum absorption. The data are listed in Table I. Attempts were made to obtain spectra in 0.01 N NaOH. The compounds were not readily soluble in alkalı; however, upon adding 1 cc of alcohol to the sample and diluting to 200 cc with 0.01 N NaOH, the compounds dissolved readily. The spectra were recorded one min after the dilution had been completed. An absorption peak (228 m $\mu$ ) was observed only with the derivatives of nembutal and seconal. Stuckey (4) also noted no absorption peak for 1:3-dimethyl luminal and veronal in 0.01 N NaOH. However, Fox and Shugar (5) reported a peak at 228 m $\mu$  for 1:3-dimethyl veronal, which decreased 50% in 20 min. The  $\varepsilon_{max}$  for 1:3dimethyl nembutal and seconal decreased very rapidly, approximately 40% within 2 min.

# X-Ray Diffraction Data

The x-ray diffraction patterns of the crystalline derivatives at room temperature were obtained. A standard preparation technique, as already reported (6), was used except in the case of the low melting point cyclopal and veronal derivatives whose powders could not be passed through the sieve. Diffraction patterns were obtained using Philips Debye-Scherrer cameras, diam. 114.83 mm, and Cu-K $\alpha$  radiation. A uniform exposure of 9 hrs at 33 kv and 15 ma was employed. Several patterns of the



FIG. 3. X-RAY POWDER DIFFRACTION PATTERNS OF N-METHYL DERIVATIVES OF BARBITURIC ACIDS RECRYSTAL-LIZED FROM EITHER ALCOHOL OR ETHER 1—cyclopal, 2—evipal, 3—luminal, 4—rutonal, 5—veronal

Су	clopal	Εı	vipal	Lu	mınal	Rui	tonal	Ver	onal
d.A	1/1.	d A	- I/L.	d A	1/1.	d A	1/1.	d A	1/I.
	1/10	<i>w</i> ,11	1/10		1/10	<b>W</b> ,22	1/10	4,11	1/10
8.22	2	15.2	1	13.1	1	10.1	1	16.8	5
7.04	-	1.7.0					-	10.0	
/.8)	1	13.)	33	11.5	30	915	60	13.5	1
747	100	11.6	15	10.3	1	8.65	5	12.9	1
	100	11.0	.,	10.5		0.0)	,	12.0	1
/.01	1 w	9.88	2 W	8.86	1	7.9I	1 w	9.17	1
6 6 6	40	9.11	60	8 1 0	70	7 10	2 107	8 63	5
		2.11		0.10		7.10	- **	0.05	
6.39	l w	8.23	2 W	7.31	2 w	6.61	60	811	100
610	100	7 25	25	657	95	637	100	756	28
010	100	/.2)	2)	0.)/		0.57	100	7.50	20
584	Iw	6.63	100 w	6.35	20	6.16	2	7.20	55
\$ 61	50	637	5	611	100	5 9 4	80 m	601	15
5 01		0 57	,	0.11	100	J.0 <del>1</del>	80 W	0.24	1)
534	1	6.15	40	5.76	2 w	5.59	1	6.65	2
\$ 19	1	5 89	50	5 4 2	60	\$ 42	1	6 28	50
		, .,	,,,	1.42	00	J.72	1	0.20	,,
4.97	35	5.34	2 w	5.22	2	5.30	1	6.00	100
471	1	4 8 2	100	5 01	25	\$ 10	2	6 70	2
4.71	1	7.02	100	1.01	,,	5.10	,	)./0	2
4.64	1	4 60	40	492	8	4.84	8	5.59	60 w
4 4 8	75	4 46	50	4 72	2	1 60	70	520	2
1.10	<i>'</i> ,	7.70	,,	4.72	,	7.00	70	).)0	2
4.37	1	4.31	2	4 62	10	4.47	80	518	15
4 27	1	4 1 0	2	4 47	75	1 2 4	40	4.05	25
7 27	T	4.17	3	4.4/	1)	4.34	40	4.9)	2) W
4 1 4	20	4.04	1	4 27	10	4 22		4 70	10
4.14	20	4.04	1	4 27	30	4.22	1	4.72	10
3.99	25	3,90	45	4.07	2	4.09	15	4 62	10
2.04	05	1 70	1.0	2 0 4		1 0 1	26		
374	7)	3/8	1)	3.94	>>	2 21	3) W	4.43	20
3.83	1	3,70	s	3.86	2	3 80	25	4.27	40
	, .			2.00	<u>-</u>	2 00			
5/3	55	5.61	55	\$ 77	85	3.72	35	4.04	2 d
3 62	5	352	28	3.65	2	3 65	20	3 9 6	30
3 52					4	5.05	20	5.70	50
3.56	1	3.45	5	3.54	15	3.56	30	3.84	25
3 4 4	1	3 3 3	35	3 47	15	2 / 9	80	1 70	1
2.77		5.55	,,	J. T/	1)	540	80	3.79	T
341	5	327	1	3.36	15	3.37	1	3.65	35
2 2 2	90	1 22	2	2 2 2	1 6	2 2 2	-	1 (0	-
5 55	80	3.22	2	5.52	1)	3.32	1	5.60	4
325	2	3.15	2	3.22	50	3 2 4	35	3.50	30
2 1 0	2	1 00	-	1 10					
2 10	2	5.09	1	3.12	8	3.17	T	3.42	30
3.10	20	3 01	25	3.04	3	3.12	40	3.30	70
2.00	1	2.02	10	2.00		2.04			, ,
3 06	1	2.92	10	2.99	2	3.04	2 w	3.22	5
3.01	1	2.85	50	2.94	10 w	2 96	40	3 1 6	20
2.00	-	2.07	20			2 /0	10	5.10	20
290	4	2./9	20 w	2.85	1	289	20	3.10	1
286	1	2.72	15	2.81	50	2 84	5	3 04	1
2 00	-	2.7 2	1)	2.01	,0	2.04	,	J.04	I
2 8 2	1	2 67	10	2 7 9	2	2 7 9	3.0	2 00	2
2.02	1	2.07	10	2.75	5	219	50	2.99	4
2.77	10	259	10 w	2.71	8	2.74	20	2.92	15 w
2 7 2	10	256	10 m	266	Q	269	2	2 94	10
2/2	10	2 ) 0	10 w	2.00	0	2 00	2	2 84	10
266	1	249	2	2.63	8	2.62	20	279	5
2 61	25	2 4 4	15	257	1	250	1	2 74	15
2.01	2)	2.77	1)	2.37	1	2.)0	,	2./4	1)
2.56	1	240	15	251	20	253	20	2.69	5
250	30 W	2 3 3	2	2 47	0	2 4 9	1 5	261	
2.70	90 w	2 ) )	2	2.4/	0	2.40	1)	2.04	) a
2.44	15	2.30	10	2.41	1 w	2 4 3	10	255	5 d
242	15	226	10	226	1	2 40	101	2	~ <del>~</del>
4.74	17	4 20	10	2 30	1	2 <del>4</del> 0	10 a	د ( ۷	ð
236	10 d	2.23	2	2.31	1	2 37	5	2.48	5
2 34	3 4	2 1 0	10	2 20	1	220	10.1	2 4 4	1 6
2 27	Ju	4.17	10	4.40	1 W	4.33	10 a	2.44	1)
2.29	2 w	2.15	5	2 2 2	10	2 30	1	2.41	10
2 24	5	2 10	1	2 20	10	2 20	1	220	·
	<i>.</i>	2.10	1	2.20	10	2.20	1	2.30	) W
2.23	5	208	8	2 17	۶w	2.24	20	2.32	15
2 1 9	1	2 04	ç	2 1 3	۲.	2 22	1	226	ć
		A.C.	,	2.17	ر د	2.23	1	2.20	,
216	10	2.00	5	2.09	2	2.19	15	2.24	10
2.14	2	1.97	10 11	2 05	۲	2 1 7	1	2 20	ç
~·· T	-	1.77	10 W	20)	,	21/	1	2.20	,
2.09	2	1 94	٢	2 00	2	211	12	2 1 0	e
2.07	-	1 27	,	2 00	2	4.14	14	2.10	,
2.08	5	1.91	5	1.98	10 w	2.11	10 w	213	10
2.03	20	1 2 9	10 d	1 0 2	10	2 00	1	2 1 2	
2.00	40	1.07	ivu	1.73	10	4.Uð	1	4.12	4
1.99	7	1.82	1	1.90	4 w	2 0 5	35	2 0 9	1
1 97	5	1 90	15	1 07	1	2 01	1	2 07	- 0
1.77	,	1 90	1)	1.0/	T	2 01	1	2.07	ð
195	2	178	2	184	3	199	1	2.03	10
1 0 2	1	1 74	10	1 0 1	Å	1 07	÷	2.00	
1 7 )	1	1./0	10	1.01	4	1.9/	)	∠.00	2
1.90	3 d	1.74	10	1.78	2	1.95	2	1,97	1
1 07	1	1 71	,	1 76	2 1	1.01	-	1	ċ
1.0/	2	1./1	1	1./)	3 a	1.93	∠0 w	196	8
1.84	2	1.70	1	1.73	3 d	1.88	2	1,92	8
1 9 1	1	1 (7		1 10	0	1.0.	~	1 0 0	ĉ
1 91	1	10/	Z	1.69	8	1.86	) w	1.90	8
179	2	166	2	1.66	1	1.83	2	1.89	2
1 77	2	1 / 2	-	1 / 1	÷	1.00	-	1.07	-
1//	2	1.03	2	163	2 w	1.80	1	1.85	1
174	1	159	1	1.55	1	1 7 8	10	1.81	1
1 7 1	÷	1	÷		ź	. / 0	10	1.01	1
1/5	1	128	1	154	2	1.77	1	1.76	2 w
1.70	5	1.53	1 w	1.52	1	1.75	2	1 74	1
1 /-	<i>,</i>		1 W	1.74	<u>,</u>	1/)	4	1.74	1
1.67	δW	1.451	2	1.50	1	1.73	8	1.71	2

TABLE	II.	DIFFRACT	TION	ΔΑΤΑ	OF	1:3-DIMETHYL
	Dei	RIVATIVES	OF	BARBIT	URIC	Acids <sup>a</sup>

Cyclopal		Evipal		Lumınal		Rutonal		Veronal	
d,A	1/1.	d,A	1/I.	d,A	$I/I_o$	d,A	I/I <sub>o</sub>	d,A	I/I <sub>o</sub>
1 64	6	1.432	2	1.486	1	170	2	1.68	1
1.63	6	1.428	2	1.468	1	1 69	8	1.66	1
1.62	2			1.446	1	166	1	163	2 w
1.61	2			1 426	2	1.65	1	158	1
1.59	1			1.389	1	164	1 w	1.56	1
156	3			1.375	1	1.62	2	1.54	1
1.54	1			1.352	1	1.61	2	1.53	1
1.53	1					1.59	2	1.51	1
1.49	1 w					1.58	2		
1 47	1					1.56	1		
						1.55	2		
						1.53	5		
						151	1		
						1 493	12		
						1.467	1		
						1.462	1		
						1.456	1		
						1.445	1 w		
						1.430	1		
						1.418	1		
						1 402	1		
						1 394	1		
						1.362	1		
						1.314	1		
						1.296	1		
						1.267	1		
						1 251	1 w		
						1.240	1		
						1.232	1		
						1.216	I		
						1.204	3		
						1.181	1		
						1.512	1		
						1 1 3 6	1		

<sup>a</sup> d, diffuse and w, wide

Cu-K $\alpha$ ,  $\lambda = 1.54050$  A

derivatives recrystallized from 2 different solvents, alcohol and ether, were obtained to ascertain the reproducibility of the experimental data presented in Table II. No variation in the patterns shown in Figure 3 was observed.

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