[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES, INDIANAPOLIS, INDIANA]

Studies on Some Optically Active Barbituric Acids[1]

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Many of the naturally occurring drugs which exhibit optical activity have been prepared synthetically in the racemic modifications, and resolved into the optically active enantiomorphs. It has been found in most cases that there exist great differences in the pharmacologic action of the *d*, *l* and *dl* forms.

In 1928 Hsueh and Marvel[2] prepared the *d* and *l* 5,5-*s*-octylethylbarbituric acid, and reported that the *d*, *l* and *dl* forms had practically the same physiologic effect.[3] Since the *s*-octylethylbarbituric acids required such a large dose to produce any effect they were not as ideally suited for study as certain other barbituric derivatives.

In 1932 Sobotka and co-workers[4] prepared *d* and *l* phenylethylhydantoin. In this series of compounds the asymmetry of the molecule was due to an asymmetric carbon atom in the hydantoin ring rather than to an asymmetric carbon atom in one of the alkyl side chains as in the *s*-octylethylbarbituric acids. No very great difference was found between the M. E. D. or the M. L. D. of the three forms. The *d* form was found to be only one-third as toxic as the *dl* form in causing "nirvanol disease," a condition similar to serum sickness, which results from the repeated administration of the *dl* form.

Several investigators, among them Boedecker and Ludwig,[5] have expressed the opinion that the mere presence of an asymmetric center in the side chain of a barbituric acid derivative is enough to increase the efficiency of the drug even though the drug is administered as a racemic modification. Consequently the pharmacologic findings of three primary amyl ethyl and two secondary amylethylbarbituric acids were examined.

From Table I it is seen that the three primary amylethylbarbituric acids have very similar values for the M. A. D. and M. L. D., although one of them, *s*-butylcarbinylethylbarbituric acid, has an asymmetric carbon atom. The two secondary amylethylbarbituric acids are more effective than the primary amylethylbarbituric acids. It is believed that the greater effectiveness is due to the secondary carbinol residue attached to the 5 carbon atom rather than to any asymmetric carbon atom in the group.

TABLE I

ISOMERIC AMYLETHYLBARBITURIC ACIDS

	Configuration of 5 carbon	Pharmacologic data as determined intraperitoneally Injections into white rats M. A. D. mg./kg.	M. L. D. mg./kg.	M. L. D. / M. A. D.
1	*n*-Amyl, ethyl	80	210	2.63
2	Isoamyl, ethyl	72	180	2.50
3	*s*-Butylcarbinyl, ethyl	80	210	2.63
4	*n*-Propylmethylcarbinyl, ethyl	45	110	2.44
5	Diethylcarbinyl, ethyl m. p. 161–161.5° (Anschütz)	60	100	1.66

The present investigation includes two types of optically active barbituric acids, the first of which has an asymmetric carbon atom in the side chain, while the second has an asymmetric carbon atom in the ring. As a representative of the first type, *n*-propylmethylcarbinylethylbarbituric acid was selected because it is effective in low doses and because the sodium salt of the *dl* isomer is in clinical use as pentobarbital sodium. The asymmetric carbon is in the amyl group attached to the 5 carbon atom.

As representatives of the second type 1-methyl-5,5-isoamylethylbarbituric acid (or N-methyl amytal) and 1-methyl-5,5-*n*-butylethylbarbituric acid (or N-methyl neonal)[6] were selected. In this type, the methyl group is substituted for the hydrogen on one of the nitrogens. This makes the 5 carbon atom of the ring asymmetric. These compounds are somewhat analogous to phenylethylhydantoin.

A sufficient quantity of the *dl*, *d* and *l* forms of each of the above barbituric acids was prepared to enable complete pharmacologic study. The pharmacologic findings given in Table III were obtained by injecting solutions of the sodium salts in the tail veins of white rats approximately 100 g. in weight.

(1) Presented before the Division of Medicinal Chemistry at the Chicago Meeting of the American Chemical Society, September, 1933.

(2) Hsueh and Marvel, THIS JOURNAL, **50**, 855 (1928).

(3) M. E. D., *dl* 370, *d* 380, *l* 360 mg./kg. M. L. D., *dl* 1900, *d* 1850, *l* not given, mg./kg.

(4) Sobotka and co-workers, THIS JOURNAL, **54**, 4697 (1932).

(5) Boedecker and Ludwig, *Arch. exper. Path. Pharm.*, **139**, 353 (1926).

(6) Dox and Hjort, *J. Pharm.*, **31**, 455 (1927).

Experimental

dl-n-**Propylmethylcarbinylethylbarbituric Acid.**—The compound used was a commercial preparation of this barbituric acid, purified to a constant melting point of 129.5° (Anschütz).

d **and** *l n*-**Propylmethylcarbinyl Bromide.**—These compounds were prepared from *l* and *d n*-propylmethylcarbinol, respectively, which had been prepared by the method of Picard and Kenyon,[7] by treatment with phosphorus tribromide in the usual manner.

d and *l n*-**Propylmethylcarbinylethylethylmalonate.**—These compounds were prepared by the usual methods employed for preparing substituted ethylmalonic esters.

d **and** *l n*-**Propylmethylcarbinylethylbarbituric Acid.**—The active barbituric acids were prepared by condensing the active malonic ester with urea by means of sodium ethylate in the usual manner.

dl-**Ethylisoamylcyanoethylacetate.**—The *dl*-ethylisoamylcyanoethylacetate was prepared by condensing isoamyl bromide with ethyl cyanoethyl acetate by means of sodium ethylate.

alcohol. Owing to the oily nature of the more soluble salt it was impossible to obtain its rotation.

l-**Ethylisoamylcyanoacetic Acid.**—The free acid was obtained from the less soluble salt by decomposing it with dilute sodium hydroxide. It was a light yellow viscous oil which showed no tendency to crystallize even after being in the ice chest for several months.

d-**Ethylisoamylcyanoacetic Acid.**—The free acid obtained similarly from the more soluble salt was less pure than the *l* isomer.

dl-**Ethylisoamyl-N-methylbarbituric Acid.**—This compound was prepared according to the directions published by Dox and Hjort.[8] The barbituric acid was also prepared, using *dl*-ethylisoamylcyanoethyl acetate, N-methyl urea and sodium ethylate followed by hydrolysis of the imido group. These methods yielded barbituric acids of the same melting point, and mixed melting points showed no depression.

l and *d*-**Ethylisoamyl-N-methylbarbituric Acids.**—The active ethylisoamylcyanoethyl acetates were prepared from the corresponding active ethylisoamylcyanoacetic acids by converting them with thionyl chloride to the corresponding active acid chlorides and treatment of these compounds with absolute ethyl alcohol. The resulting compounds were treated with N-methyl urea and sodium, yielding the corresponding active imidobarbituric acids. When refluxed with hydrochloric acid solution for several hours, the corresponding barbituric acids were obtained. These were purified by crystallization from 50% alcohol.

TABLE II

PHYSICAL CONSTANTS OF BARBITURIC ACID DERIVATIVES

	B. p., °C. (Anschütz)	Mm.	n_D^{20}	$[\alpha]_D^{25}$	d_{20}^{20}
d-n-Propylmethylcarbinyl bromide	116–118		1.4420	+29.90°	
l-n-Propylmethylcarbinyl bromide	116–118		1.4418	−29.00°	
d-n-Propylmethylcarbinylethylethylmalonate	123–124	10	1.4336[a]	+11.62	0.9607[b]
l-n-Propylmethylcarbinylethylethylmalonate	123–124	10	1.4330[a]	−11.02	.9610[b]
dl-Ethylisoamylcyanoethyl acetate	128–131	14	1.4293[a]	0	
dl-Ethylisoamylcyanoacetic acid	153.5	14		0	
l-Ethylisoamylcyanoacetic acid	156–158	14		− 7.73°	.9776
d-Ethylisoamylcyanoacetic acid	156–158	14		+ 6.71°	.9741
dl-Ethyl-*n*-butylcyanoethyl acetate	122–123.5	14		0	
dl-Ethyl-*n*-butylcyanoacetic acid	145–147	14		0	
d-Ethyl-*n*-butylcyanoacetic acid	148–149	14		+ 7.03°	.9634
l-Ethyl-*n*-butylcyanoacetic acid	148–149	14		− 6.85°	.9611

[a] n_D^{25}. [b] d_4^{25}.

TABLE III

PHARMACOLOGICAL DATA

Barbituric acid	Isomer	M. p., °C.	$[\alpha]_D^{25}$	M. A. D. mg./kg.	M. L. D. mg./kg.	M. L. D. / M. A. D.	Nitrogen analyses, % Calcd.	Found	
5,5-*n*-Propylmethylcarbinylethyl	*d*	120–121	4.93	55	110	2.00	12.38	12.50	12.27
	l	120–121	−4.73	35	90	2.57	12.38	12.23	12.45
	dl	129.5	0	35	80	2.28	...	...	...
1-Methyl-5,5-*n*-butylethyl	*d*	99	1.50	None	70	..	11.67	11.53	11.70
	l	107	−1.56	None	85	..	11.67	11.82	11.59
	dl	72	0	None	75	..	11.67	11.58	11.42
1-Methyl-5,5-*n*-butylethyl	*d*	75	3.50	65	120	1.85	12.38	12.37	12.49
	l	74.5	−3.40	55	100	1.82	12.38	12.37	12.27
	dl	73	0	40	70	1.75	...	...	...

dl-**Ethylisoamylcyanoacetic Acid.**—The corresponding cyanoethyl acetate was saponified with alcoholic potassium hydroxide and the free acid purified by distillation.

Resolution of *dl*-**Ethylisoamylcyanoacetic Acid.**—This acid was resolved by the method of Fischer and Flatau.[8] The less soluble salt had the rotation $[\alpha]_D^{25}$ −17.50° in

(7) Picard and Kenyon, *J. Chem. Soc.*, **99**, 45 (1911).

(8) Fischer and Flatau, *Ber.*, **42**, 2986 (1909).

dl-**Ethyl-*n*-butylcyanoethyl Acetate.**—This ester was prepared in a manner similar to that used for the isoamyl compound.

dl-**Ethyl-*n*-butylcyanoacetic Acid.**—This acid was prepared from the corresponding ethyl ester in a manner similar to that used for the *dl*-ethylisoamylcyanoacetic acid.

Resolution of *dl*-Ethyl-*n*-butylcyanoacetic Acid.—The method followed in the resolution of this compound was essentially the same as that for the isoamyl compound, using strychnine. The less soluble salt in alcohol gave $[\alpha]_D^{25}$ −25.5° in alcohol. Owing to the oily nature of the more soluble salt a rotation could not be obtained upon the pure material.

d-**Ethyl-*n*-butylcyanoacetic Acid.**—The less soluble salt was decomposed and purified, as in the case of the ethylisoamylcyanoacetic acid.

l-**Ethyl-*n*-butylcyanoacetic Acid.**—The solution of the more soluble salt was decomposed and purified as in the case of the *d*-ethylisoamylcyanoacetic acid.

dl-**Ethyl-*n*-butyl-N-methylbarbituric Acid.**—This compound was prepared according to the directions published by Dox and Hjort.[6] It was also prepared, using *dl*-ethyl-*n*-butylcyanoethyl acetate, N-methyl urea and sodium followed by hydrolysis of the imido group. Both methods yielded barbituric acids of the same melting point, and mixed melting points of these compounds showed no depression.

d and *l*-**Ethyl-*n*-butyl-N-methylbarbituric Acids.**—These compounds were prepared from the corresponding cyanoethyl acetates in the manner described for the ethyl isoamyl-N-methylbarbituric acids.

The *d* form of 5,5-*n*-propylmethylcarbinylethylbarbituric acid was less effective and less toxic than the *l* or the *dl* forms, but the ratio or margin of safety was lower. Preanesthetic excitement was marked with the *d*, present with the *dl* form and absent with the *l* form.

The *d*, *l* and *dl* forms of the 1-methyl-5,5-isoamylbarbituric acid showed no anesthetic action, the *d* form being slightly more toxic than the *dl* or *l* forms. The *d* isomer in sublethal doses, in contrast to the *l* or the *dl* isomer, caused difficulty in breathing and severe convulsive contractions of the thorax, head and neck.

The *d*, *l* and *dl* forms of the 1-methyl-5,5-*n*-butylethylbarbituric acid were found to have anesthetic properties. The *dl* form had a lower M. A. D. and M. L. D. than either the *d* or *l* forms and caused severe convulsions before and after anesthesia, an effect which was not noticed in the case of the *d* or the *l* isomer.

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Conclusions

1. The dextro and levo forms of 5,5-*n*-propylmethylcarbinylethylbarbituric acid, 1-methyl-5,5-isoamylethylbarbituric acid and 1-methyl-5,5-*n*-butylethylbarbituric acid were prepared.

2. These compounds were tested pharmacologically and the effective and the lethal doses were determined. Moderate differences were noted between the doses and the effects produced by the active and racemic forms.

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The 1,2-Dibenzoylcyclobutanes

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Three different 1,2-dibenzoylcyclobutanes have been reported although only two are theoretically possible. This structure has been definitely proved only for the so-called *alpha* form.[1] However, in a parallel study it has been possible to show that the supposititious 1,2-dibenzoylcyclobutane of Conant and Lutz[2] is really a cyclopentane derivative.[3] The lack of evidence upon which to assign the *cis* and *trans* configurations to the two remaining diketones made it desirable to synthesize the so-called β-diketone by a clearcut method. This has now been accomplished, and the identification of the α- and β-diketones of Kao and Fuson as the *trans* and *cis* isomers, respectively, has been completed.

A repetition of the work of Kao and Fuson, undertaken with the hope of isolating a larger amount of the *cis* diketone, was carried out; but instead of the pure *trans*-1,2-cyclobutanedicarboxylic acid there were used (1) the mixture obtained from the decarboxylation of 1,1,2-cyclobutanetricarboxylic acid, and (2) the pure *cis* acid.

(1) Kao and Fuson, THIS JOURNAL, **54**, 1120 (1932).
(2) Conant and Lutz, *ibid.*, **49**, 1090 (1927).
(3) Fuson and Farlow, *ibid.*, **56**, 1593 (1934).