[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

The Resolution of 5-Allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric Acid

WILBUR J. DORAN

Received March 11, 1960

Condensation of diethyl allyl(1-methyl-2-pentynyl)malonate with methylurea gave a mixture of the α- and β-forms of 5-allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid. The α-form was conveniently prepared by condensation of ethyl allyl(1-methyl-2-pentynyl)cyanoacetate with methylurea, followed by acid hydrolysis of the imino derivative (I). The β-form was prepared by acid hydrolysis of 5-allyl-4-imino-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid, which was prepared by N^1-methylation of 5-allyl-4-imino-5-(1-methyl-2-pentynyl)barbituric acid. The α-racemate was resolved at the imino stage, while the β-stereoisomers were obtained by allylation of *d*- and *l*-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid. A study was made of the anesthetic activity of the enantiomorphs in relation to their chemical structure.

In the synthesis of a group of barbituric acids substituted at the 5-carbon with an acetylene containing side-chain, one was chosen for more extensive study.[1] This compound has undergone broad clinical investigation, and for this reason its chemistry is being reported.

The present work describes the preparation of 5-allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid, and the resolution of its α- and β-forms into their enantiomorphs. Specific methods have been found for the preparation of the higher melting form, designated the α-form, and for the lower melting form, called the β-form.

Condensation of diethyl allyl(1-methyl-2-pentynyl)malonate with methylurea or the allylation of *dl*-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (VIII) gave an oily mixture consisting of the two racemic forms. However, condensation of ethyl allyl(1-methyl-2-pentynyl)cyanoacetate with methylurea formed a relatively pure imino derivative (I), which is designated as α-*dl*-5-allyl-6-imino-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (see Chart 1). The yield of I after one recrystallization from dilute ethanol was 75%, melting at 86–88°, whereas the pure material melts at 92–94°. From I there was obtained by hydrolysis with dilute acid compound II, which has been designated as α-*dl*-5-allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid; when pure, II melts at 96°.

The exclusive formation of the α-*dl*-imino derivative (I) and the resulting α-*dl*-barbituric acid (II) results because the reaction of disubstituted cyanoacetic acid esters with alkylureas gives iminobarbituric acids in which the imino group is attached to a carbon atom of the ring which is adjacent to the alkylated nitrogen atom.[2]

Also, in the reaction of the sodium derivative of ethyl(1-methyl-2-pentynyl)cyanoacetate with allyl bromide, the composition of the resulting ester must be predominantly of one form.

However, the reaction of 5,5-disubstituted 4-iminobarbituric acids with methyl iodide in a solution of sodium in ethanol gives 5,5-disubstituted 4-imino-1-methyl barbituric acids.[2]

α-Forms. When α-*dl*-5-allyl-6-imino-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (I) was treated with *d*-10-camphorsulfonic acid, the less soluble α-*d*-iminobarbituric acid-*d*-10-camphorsulfonic acid salt (III) was obtained. Treatment with sodium bicarbonate solution gave the α-*d*-iminobarbituric acid (IV) (m.p. 96–100°, $[\alpha]_D^{25}$ +113.5°) which was hydrolyzed to the α-*d*-barbituric acid (V) (m.p. 104–106.5°, $[\alpha]_D^{31}$ +40.6°).

Filtrates from the recrystallization of the less soluble salt III were allowed to evaporate on the steam bath. Instead of obtaining the expected α-*l*-imino base-*d*-10-camphorsulfonic acid salt, the α-*l*-barbituric acid (Va) was isolated (m.p. 104–107°, $[\alpha]_D^{28}$ −40.0°). This obviously resulted from the hydrolysis of the imino compound and demonstrates its lability in strongly acid solution.

However, the α-*l*-imino base (IVa) was obtained by treating the α-*dl*-iminobarbituric acid (I) with half a molecular equivalent of *d*-10-camphorsulfonic acid thereby separating the less soluble α-*d*-imino salt (III). The filtrate was treated with *dl*-10-camphorsulfonic acid and the resulting α-*l*-imino base-*l*-10-camphorsulfonic acid salt (VI) was isolated. The α-*l*-imino base (IVa) could also be purified by preparation of its hydrochloride salt (VIIa).

The β-enantiomorphs were obtained by resolution of *dl*-1-methyl-5-[1-methyl-2-pentynyl)-barbituric acid (VIII) by treatment with brucine, followed by reaction of the *d*- and *l*-isomers with allyl bromide (see Chart 2). The β-*d*- and β-*l*-acids prepared in this manner were slightly contaminated with α-*d*- and α-*l*-isomers respectively, and recrystallization of the reaction products gave the pure β-*d*- and β-*l*-acids.

Neither β-*dl*-5-allyl-4-imino-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (XII) nor *dl*-5-allyl-4-imino-5-(1-methyl-2-pentynyl)barbituric acid (XIII), from which XII was prepared, formed a crystalline salt with *d*-10-camphorsulfonic acid.

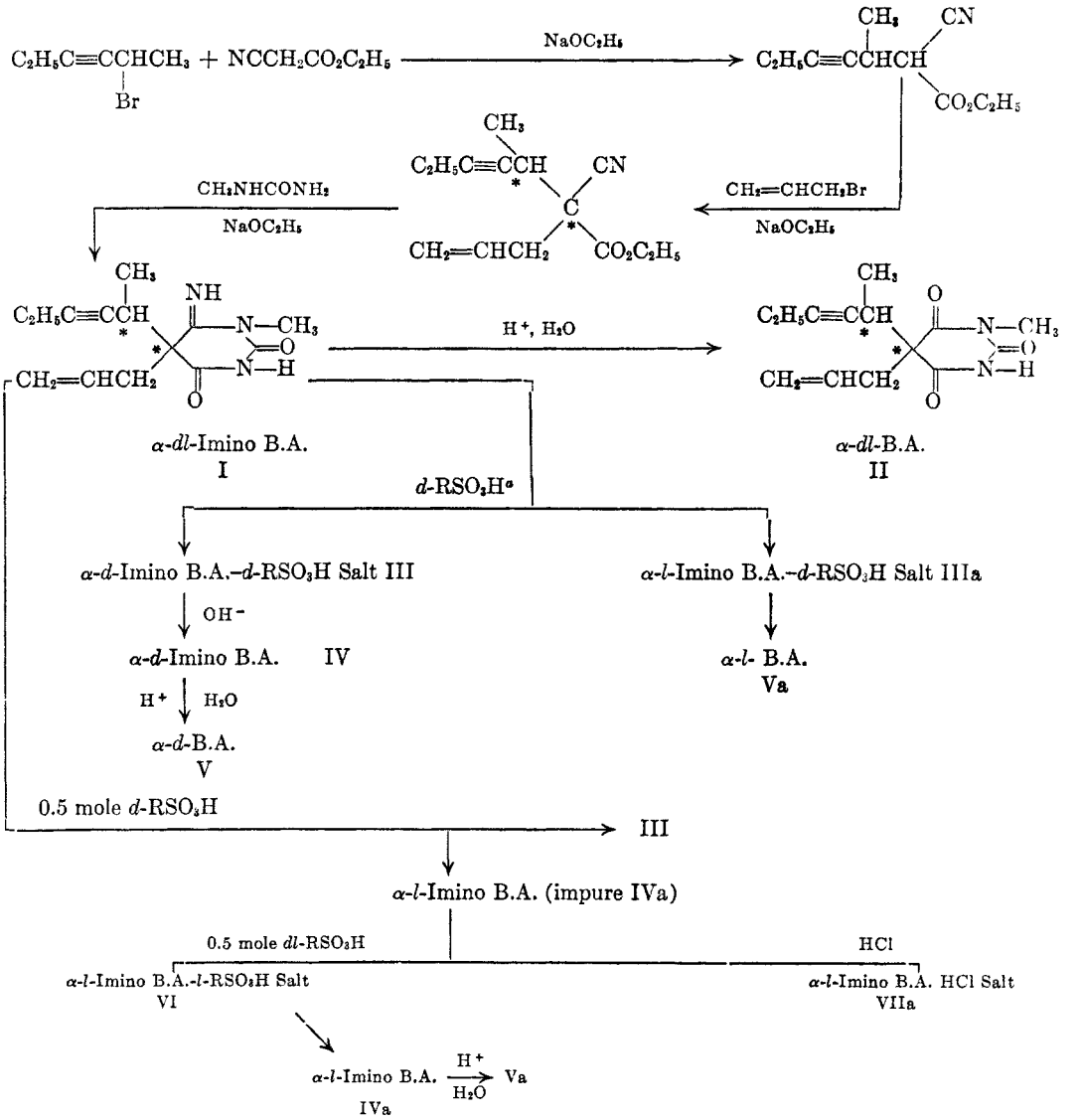
Although the resolution of barbituric acids con-

(1) W. R. Gibson, W. J. Doran, W. C. Wood, and E. E. Swanson, *J. Pharmacol. Exp. Therap.*, **125**, 23 (1959).

(2) M. Conrad and A. Zart, *Ann.*, **340**, 326 (1905).

CHART 1

SYNTHESIS OF α-ISOMERS



[a] RSO_3H is 10-camphorsulfonic acid.

taining on asymmetric carbon has been reported,[3,4] the pharmacological data show only minor differences in the anesthetic potency of the enantiomorphs. However, in the compounds reported in this publication considerable differences were found in their anesthetic potencies (see Table I).

As mentioned above, the allylation of *d*-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (Xa) gave a mixture of *β-l-* and *α-l*-acids, while *l*-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (X) gave a mixture of *β-d-* and *α-d*-acids. This then shows that the configuration of the (1-methyl-2-pentynyl) side-chain is the same in the *β-l-* and *α-l*-acids (and in the *β-d-* and *α-d*-acids), and the difference between these two compounds must be at the 5-carbon atom of the ring.

TABLE I

ANESTHETIC POTENCIES OF THE ISOMERS OF 5-ALLYL-1-METHYL-5-(1-METHYL-2-PENTYNYL)BARBITURIC ACID (SODIUM SALT) IV IN RATS

Compound No.	Isomer	AD_{50}, Mg./Kg.	LD_{50}, Mg./Kg.	Duration, Min
V	*α-d*-B.A.	11	18	13
Va	*α-l*-B.A.	35	47	14
II	*α-dl*-B.A.	15	28	14
XI	*β-d*-B.A.	17	23	12
XIa	*β-l*-B.A.	7	15	13[a]
IIa	*β-dl*-B.A.	10	19	14

[a] Postanesthetic stimulant activity.

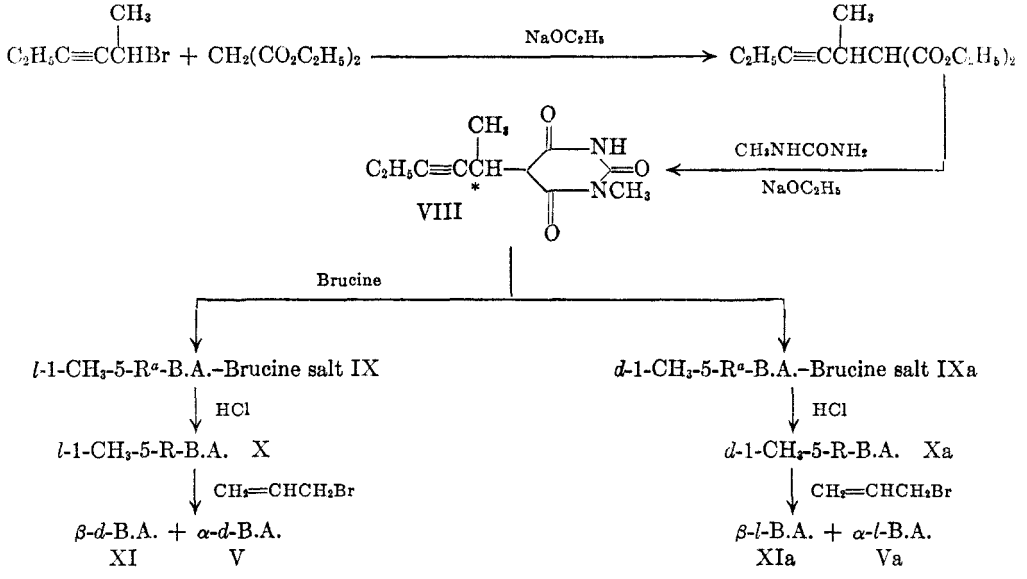
(3) C.-M. Hsueh and C. S. Marvel, *J. Am. Chem. Soc.*, 50, 855 (1928).

(4) E. C. Kleiderer and H. A. Shonle, *J. Am. Chem. Soc.*, 56, 1772 (1934).

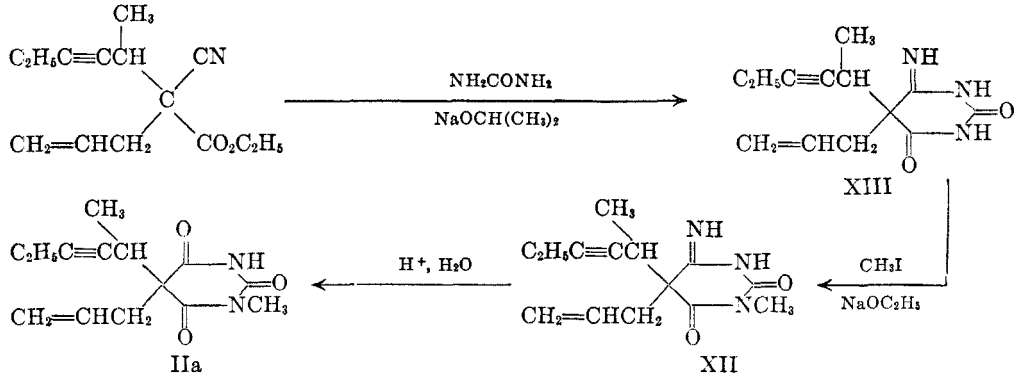
CHART 2

SYNTHESIS OF β-ISOMERS

(A) *Synthesis of β-Enantiomorphs*



(B) *Synthesis of β-dl-Acid* (IIa)



[a] R is $C_2H_5C{\equiv}CCH(CH_3)$.

A striking difference in potency is seen between the β-*l*-acid (XIa) and the α-*l*-acid (Va), in which the configuration of the (1-methyl-2-pentynyl) side chains is identical and that at the 5-carbon of the rings differ. This change in configuration at the 5-carbon results in a five-fold increase in potency of the β-*l*-form. Although the β-*l*-form is the most potent, its depressant action is accompanied by stimulating action making it less suitable for use as an anesthetic. Even though the α-*l*-form is more potent than the α-*dl*-form, the difference in potency is not sufficient to make the resolution commercially feasible. The α-*dl*-barbituric acid has had extensive clinical use as an anesthetic.[5]

EXPERIMENTAL

The physical properties of the barbituric acid derivatives (with the exception of the starting materials) are listed in Tables II and III. All of the melting points were taken by the capillary method, and temperatures are uncorrected.

3-Hexyne-2-ol[6] was prepared by the reaction of ethylacetylenemagnesium bromide with acetaldehyde in 72% yield, b.p. 78–80° at 60 mm., n_D^{25} 1.4445.

Anal. Calcd. for $C_6H_{10}O$: C, 73.42; H, 10.27. Found: C, 73.15; H, 10.33.

2-Bromo-3-hexyne. An ether solution of 3-hexyne-2-ol containing a catalytic amount of pyridine was treated with phosphorus tribromide. The bromide was obtained in 70% yield, b.p. 74–76° at 50 mm., n_D^{25} 1.4853–1.4858.

Anal. Calcd. for C_6H_9Br: C, 44.72; H, 5.63. Found: C, 44.97; H, 5.78.

Ethyl(1-methyl-2-pentynyl)cyanoacetate. An ethanol solution of the sodium derivative of ethyl cyanoacetate was treated with 2-bromo-3-hexyne. The yield was 35%, b.p. 104–107° at 5 mm., n_D^{25} 1.4483–1.4495.

Anal. Calcd. for $C_{11}H_{15}NO_2$: N, 7.25. Found: N, 7.06.

Ethyl allyl(1-methyl-2-pentynyl)cyanoacetate. An ethanol solution of the sodium derivative of ethyl(1-methyl-2-pentynyl)cyanoacetate was treated with allyl bromide. The

(5) V. K. Stoelting, *Current Researches Anesthesia & Analgesia*, **36**, 49 (1957).

(6) 3-Hexyne-2-ol is listed with the "Special Acetylenic Chemicals" in the Farchan Laboratories price list A-4, April 1952.

TABLE II

PHYSICAL PROPERTIES OF THE α-ISOMERS

Compound No.	Compound	M.P.	$[\alpha]^t_D$[a]	t	Empirical Formula	Nitrogen, % Calcd.	Nitrogen, % Found
III	α-*d*-Imino B.A.[b]–*d*-RSO_3H[c] salt	215–217	+30.0	25	$C_{24}H_{35}N_3O_6S$	8.51	8.30
VI	α-*l*-Imino B.A.–*l*-RSO_3H salt	210–213	−28.2	25	$C_{24}H_{35}N_3O_6S$	8.51	8.61
IV	α-*d*-Imino B.A.	96–100	+113.5	25	$C_{14}H_{19}N_3O_2$	16.08	16.31
IVa	α-*l*-Imino B.A.	96–99	−113.6	30	$C_{14}H_{19}N_3O_2$	16.08	15.91
I	α-*dl*-Imino B.A.	92–94			$C_{14}H_{19}N_3O_2$	16.08	15.80
VII	α-*d*-Imino B.A. HCl	214–216	+9.2	27	$C_{14}H_{20}ClN_3O_2$	14.11	13.88
VIIa	α-*l*-Imino B.A. HCl	218	−8.2	28	$C_{14}H_{20}ClN_3O_2$	14.11	13.24
	α-*dl*-Imino B.A. HCl	203			$C_{14}H_{20}ClN_3O_2$	14.11	13.84
V	α-*d*-B.A.	104–106.5	+40.6	31	$C_{14}H_{18}N_2O_3$	10.68	10.48
Va	α-*l*-B.A.	104–107	−40.0	28	$C_{14}H_{18}N_2O_3$	10.68	10.44
II	α-*dl*-B.A.	96			$C_{14}H_{18}N_2O_3$	10.68	10.83

[a] Concn. 5% in ethanol. [b] B.A. is 5-allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid. [c] 10-Camphorsulfonic acid.

TABLE III

PHYSICAL PROPERTIES OF THE β-ISOMERS

Compound No.	Compound	M.P.	$[\alpha]^t_D$[a]	t	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
IXa	*d*-1-CH_3-5-R[b]-B.A.–brucine salt	135–150	−50.4[c,d]	32	$C_{34}H_{40}N_4O_7$	9.08	8.86
IX	*l*-1-CH_3-5-R-B.A.–brucine salt	103–110	−60.7[c]	29	$C_{34}H_{40}N_4O_7$	9.08	9.68
Xa	*d*-1-CH_3-5-R-B.A.	112–116	+5.0	30	$C_{11}H_{14}N_2O_3$	12.61	12.90
X	*l*-1-CH_3-5-R-B.A.	114–118	−5.2	28	$C_{11}H_{14}N_2O_3$	12.61	12.36
VIII	*dl*-1-CH_3-5-R-B.A.	89–92			$C_{11}H_{14}N_2O_3$	12.61	12.88
XII	β-*dl*-imino B.A.[e]	142–143			$C_{14}H_{19}N_3O_2$	16.08	15.88
XI	β-*d*-B.A.	66–70	+55.8	31	$C_{14}H_{18}N_2O_3$	10.68	10.45
XIa	β-*l*-B.A.	68–70	−56.3	28	$C_{14}H_{18}N_2O_3$	10.68	10.72
IIa	β-*dl*-B.A.	65–66			$C_{14}H_{18}N_2O_3$	10.68	10.68
XIII	5-Allyl-4-NH=5-R-B.A.	233			$C_{13}H_{17}N_3O_2$	16.99	16.96

[a] Concn. 5% in ethanol. [b] R is $C_2H_5C{\equiv}CCH(CH_3)$—. [c] $[\alpha]_D$ concn. 5% in chloroform. [d] $[\alpha]^{32}_D$ −26.6° concn. 5% in ethanol. [e] B.A. is 5-allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid.

yield of ester was 92%, b.p. 105–115° at 1 mm., n^{25}_D 1.4582–1.4592.

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.80; H, 8.42; N, 6.21.

Synthesis of α-isomers. α-dl-5-Allyl-6-imino-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (I). Ethyl allyl(1-methyl-2-pentynyl)cyanoacetate was condensed with methylurea by refluxing in a solution of two molecular equivalents of sodium in ethanol for 4 hr. Most of the ethanol was distilled under vacuum, and the residue was dissolved in water. The aqueous solution was extracted with ether and acidified with acetic acid. The oil which separated crystallized on standing and was filtered. The α-*dl*-iminobarbituric acid (I) was recrystallized three times from dilute ethanol.

The hydrochloride of I was prepared in ether and recrystallized from acetone.

α-dl-5-Allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (II). A mixture of 38 g. (0.15 mole) of the α-*dl*-imino base (I), 20 ml. of concd. hydrochloric acid, and 380 ml. of water was refluxed with stirring for 1 hr. The α-*dl*-barbituric acid (II) separated as an oil that crystallized on cooling. It was filtered and recrystallized twice from dilute ethanol.

Reaction of α-dl-5-allyl-6-imino-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid with d-10-camphorsulfonic acid. A solution of 50 g. (0.19 mole) of I in 100 ml. of acetone was added to a solution of 45 g. (0.19 mole) of *d*-10-camphorsulfonic acid in 300 ml. of acetone. The less soluble α-*d*-imino base-*d*-10-camphorsulfonic acid salt (III) was filtered and recrystallized twice from ethanol.

α-d-5-Allyl-6-imino-5-(1-methyl-2-pentynyl)barbituric acid (IV). A suspension of 21 g. of III in water was neutralized with a solution of sodium bicarbonate and the oil which formed crystallized. The solid was recrystallized twice from ethanol.

The hydrochloride (VII) of IV was prepared in ether and recrystallized from isopropanol.

α-d-5-Allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (V). The α-*d*-imino base (IV) was hydrolyzed in the same manner as the α-*dl*-imino base (I). Recrystallization from dilute ethanol gave pure V.

α-l-5-Allyl-6-imino-5-(1-methyl-2-pentynyl)barbituric acid (IVa). *Method 1.* An acetone solution of the α-*dl*-imino base (I) was treated with half a molecular equivalent of *d*-10-camphorsulfonic acid. The less soluble salt III which formed was filtered. The filtrate containing the impure α-*l*-imino base (IVa) was concentrated under vacuum to an oily residue. The hydrochloride (VIIa) of IVa was prepared and recrystallized twice from isopropanol.

Method 2. The impure α-*l*-imino base (IVa), as obtained above from the filtrate of the salt III, was purified by treating it with half a molecular equivalent of *dl*-10-camphorsulfonic acid in acetone solution. The α-*l*-imino base-*l*-10-camphorsulfonic acid salt (VI) precipitated and was filtered and recrystallized three times from ethanol.

The α-*l*-imino salt obtained by either method 1 or 2 was neutralized with sodium bicarbonate solution and the base IVa recrystallized twice from dilute ethanol.

α-*l*-5-Allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (Va). *Method 1.* Evaporation to dryness on the steam bath of the acetone filtrate containing the more soluble α-*l*-imino base-*d*-10-camphorsulfonic acid (IIIa) resulted in hydrolysis of the imino group giving the α-*l*-barbituric acid

(Va). The latter was recrystallized once from petroleum ether (b.p. 35–60°), once from methanol, and once from ethanol.

Method 2. The *α-l*-imino base (IVa), obtained by method 1 or 2 above, was hydrolyzed to Va as described for the *α-dl*-barbituric acid (II).

Synthesis of β-isomers. Diethyl(1-methyl-2-pentynyl)malonate. The sodium derivative of diethyl malonate was alkylated with 2-bromo-3-hexyne in alcohol solution. The ester was obtained in 77% yield, b.p. 123° at 7 mm., n_D^{25} 1.4418–1.4423.

Anal. Calcd. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.79; H, 8.47.

dl-1-Methyl-5-(1-methyl-2-pentynyl)barbituric acid (VIII). Diethyl(1-methyl-2-pentynyl)malonate was condensed with methylurea by refluxing in ethanol solution containing 2 equivalents of sodium ethylate for 0.5 hr. The alcohol was distilled under vacuum, and the residue was dissolved in water and acidified with hydrochloric acid. The oil which separated crystallized on standing, and was filtered and the solid recrystallized twice from dilute ethanol.

Reaction of dl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (VIII) *with brucine.* A solution of VIII in absolute ethanol was added to a hot solution of an equimolecular amount of brucine in ethanol. After standing overnight, the less soluble *l*-barbituric acid-brucine salt (IX) was filtered and recrystallized twice from absolute ethanol.

The filtrates from the less soluble salt (IX) were combined and concentrated, and the precipitate that formed was filtered and recrystallized once from methanol and once from ethanol giving the more soluble *d*-barbituric acid-brucine salt (IXa).

l-1-Methyl-5-(1-methyl-2-pentynyl)barbituric acid (X). A suspension of IX in water was acidified with hydrochloric acid. The precipitate which formed was filtered and recrystallized twice from dilute ethanol.

β-d-5-Allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (XI). A mixture of an aqueous solution of the sodium salt of X and an equimolecular amount of allyl bromide was stirred for 17 hr. at 40–50°. The oily product was separated from the mixture by ether extraction. The ether solution was extracted once with sodium bicarbonate solution and then with dilute sodium hydroxide solution. The solution of the sodium salt was acidified with acetic acid, and the oil which separated crystallized on standing. The *β-d*-barbituric acid (XI) was filtered and recrystallized three times from dilute ethanol.

Filtrates from the recrystallization of XI were allowed to evaporate and the precipitate that was obtained was recrystallized twice from dilute ethanol, m.p. 104–105°. It was shown to be *α-d*-acid (V) when a sample mixed with authentic *α-d*-stereoisomer (V) showed no depression, m.p. 104–106°; a sample mixed with the *α-l*-stereoisomer (Va) showed a depression, m.p. 88–90°.

d-1-Methyl-5-(1-methyl-2-pentynyl)barbituric acid (Xa). The *d*-acid was obtained from the more soluble brucine salt and was purified in a manner similar to that used for the *l*-acid (X).

β-l-5-Allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (XIa). The *d*-acid (Xa) was allylated in the same manner as the *l*-acid (X). The product was recrystallized twice from dilute ethanol.

Filtrates from the recrystallization of XIa gave some of the *α-l*-acid (Va), which was identified by mixed melting point with authentic Va.

Alternate synthesis of β-dl-5-allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (IIa). *5-Allyl-4-imino-5-(1-methyl-2-pentynyl)barbituric acid* (XIII). To a solution of 23 g. (1 mole) of sodium in 460 ml. of isopropyl alcohol was added 45 g. (0.75 mole) of urea. The solution was cooled to 50° and 117 g. (0.5 mole) of ethyl allyl(1-methyl-2-pentynyl)-cyanoacetate was added. The solution was warmed at 60° for 4 hr. and then allowed to stand 92 hr. at room temperature. The isopropyl alcohol was distilled under vacuum, the residue was dissolved in water and the solution made neutral (*p*H 7.0–7.5) with dilute hydrochloric acid. The precipitate which formed was filtered and recrystallized twice from dilute ethanol.

β-dl-5-Allyl-4-imino-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (XII). To a solution of 0.56 g. (0.024 mole) of sodium in 20 ml. of ethanol were added 6 g. (0.024 mole) of XIII and 3.8 g. (0.024 mole) of methyl iodide. The solution was allowed to reflux for 3 hr. The ethanol was distilled under vacuum and the residue was treated with water, giving an oily mixture. The mixture was neutralized with acetic acid and ether extracted three times. The ether solution of Ia was dried with anhydrous sodium sulfate and treated with hydrogen chloride in ether. The hydrochloride oiled out, but soon crystallized. It was filtered, dissolved in water, and neutralized with sodium bicarbonate solution. The *β-dl*-iminobarbituric acid (XII) was recrystallized twice from dilute ethanol.

β-dl-5-Allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (IIa). The hydrolysis of XII was carried out in a manner similar to that used for the *α-dl*-imino base (I). The *β-dl*-barbituric acid (IIa) was recrystallized twice from dilute methanol and once from dilute ethanol, m.p. 47–48°. The acid IIa was polymorphous for, on recrystallization from petroleum ether (b.p. 35–60°), it melted at 65–66°.

Acknowledgment. We are indebted to Dr. N. R. Easton for suggesting the *d*-10-camphorsulfonic acid resolution of the imino derivative, and for many other valuable suggestions in this work. The pharmacological results were kindly furnished by Messrs. W. R. Gibson and W. C. Woods of the Lilly Pharmacological Division. Several of the intermediates used in the resolutions were supplied by C. F. Christie of the Lilly Organic Development Department. We wish to thank Miss Gloria Beckmann, Messrs. H. L. Hunter, G. M. Maciak, and R. M. Hughes for the microchemical analyses.

INDIANAPOLIS, IND.