ladium on charcoal. The reaction is completed in 1/2 h if alcohol is used as a solvent, and the pressure is 50 atm. The yield is quantitative. B. p. 120°—130°/11 mm Hg.

D. *Preparation of ethyl* neo*pentylcyanoacetate.* Ethyl trimethylethylidenecyanoacetate is hydrogenated as described above to ethyl *neo*pentylcyanoacetate. The yield is quantitative and the boiling point 110°—114°/8 mm Hg.

5. Alkylations of ethyl neo*pentylcyanoacetate.* A. *Preparation of ethyl ethyl*neo*pentylcyanoacetate.* 91.5 g of ethyl *neo*pentylcyanoacetate, 138 g of powdered anhydrous potassium carbonate, 275 ml of dry acetone and 94 g of ethyl iodide are refluxed with good stirring for 3 h. The resulting mixture is cooled, poured into ice-water, separated, extracted with benzene, dried and distilled under reduced pressure. In this way 100 g, 95 %, of ethyl ethyl*neo*pentylcyanoacetate is obtained. B. p. 116°—118°/7 mm Hg. This ester is recovered unchanged after refluxing with 120 ml of alcohol, and 50 ml of conc. sulphuric acid for 16 h.

B. *Preparation of ethyl allyl*neo*pentylcyanoacetate.* 41 g of ethyl *neo*pentylcyanoacetate 62 g of powdered anhydrous potassium carbonate, 125 g of dry acetone and 33 g of allylbromide are refluxed for 5 h. The mixture is then treated as above yielding 49.5 g, 99 %, of ethyl allyl*neo*pentylcyanoacetate boiling at 127°—128°/8 mm Hg.

The author is indebted to this colleagues and assistants at Pharmacia for good help with this project.

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5-*neo*Pentyl-5-Allylbarbituric Acid and Related Compounds

III. On the Preparation of *neo*Pentyl-substituted Barbituric Acids

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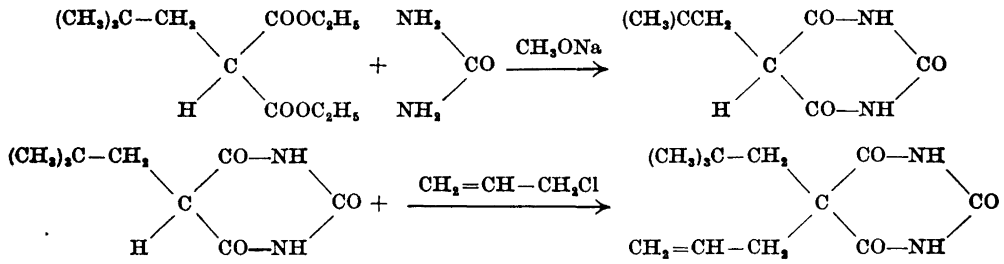
Since J. von Mering in 1903 discovered the hypnotic activity of a compound he erroneously considered to be 5,5-diethylbarbituric acid [1], 5,5-disubstituted barbituric acids have been extensively studied. In Chemical Abstract Decimal Index 1917—1926 the heading "barbituric acid" covers about 5 pages, in Decimal Index 1937—1945 8 pages and in Subject Index 1956 2 pages. This shows that the interest in substituted barbituric acids is ever increasing.

In spite of the enormous interest devoted to 5,5-disubstituted barbituric acids it appears that no barbituric acid containing a *neo*pentylsubstituent in the 5 position has been described. This is still more remarkable as many very useful hypnotics are barbituric acids with a side chain in the 5 position containing five carbon atoms usually in a branched-chain arrangement.

The introduction of a *neo*pentyl group in a molecule gives often a reactivity very different from that obtained with other aliphatic groups of the same size. This is clearly demonstrated by the well-known extremely low reactivity of *neo*pentyl halides compared with that of other alkyl halides and the tendency of *neo*pentyl compounds to undergo rearrangements instead of simple substitution reactions. Therefore, it is of interest to see if the properties of *neo*pentylsubstituted barbituric acids differs from those substituted with other alkyl groups. Consequently, a number of *neo*pentylsubstituted barbituric acids have been prepared by the methods indicated in paper No. 1 in this series [2].

The chemical properties of the *neo*pentyl-substituted barbituric acids resemble those of other alkyl barbituric acids in all respects. In some cases a slight steric effect of the *neo*pentyl group could be observed resulting in a comparatively low yield in certain syntheses, but this effect is by no means as marked as that produced by a *tert*-butyl group [3].

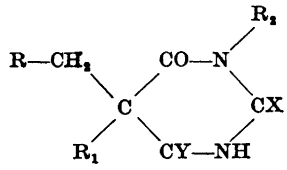


On the other hand the pharmacological properties are very interesting, especially those of 5-*neo*pentyl-5-allylbarbituric acid. This compound has the same depressive effect on the central nervous system as other barbiturates. In contrast to most barbiturates having only alkyl or alkenyl substituents in both 5 positions it has a distinct anticonvulsive effect. Therefore, in this respect it resembles 5-phenyl-5-ethylbarbituric acid. In contrast to this compound 5-*neo*pentyl-5-allylbarbituric acid has a moderate duration of effect just as most barbiturates substituted with branched chained alkyl groups.

The 5-*neo*pentyl-5-allylbarbituric acid has in contrast to, *e.g.*, 5-phenyl-5-ethylbarbituric acid and 5-*iso*amyl-5-ethylbarbituric acid a normalizing effect on rats subjected to a psychical stress.

All these pharmacological results suggest that 5-*neo*pentyl-5-allylbarbituric acid has

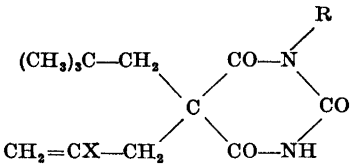
Table 1. Syntheses of barbituric acids



R	R_1	R_2	X	Y	Yield	M. p.	Equiv. wt. Found	Calc.
$(CH_3)_3C$	H	H	O	O	75	—	—	—
	H	H	O	NH	77	—	—	—
	H	H	NH	O	81	—	—	—
	H	H	NH	NH	77	—	—	—
	H	CH_3	O	O	66	144°	214	212.2
	H	C_2H_5	O	O	70	136°	226	226.3
	H	$(CH_3)_2CH$	O	O	57	102°	243	240.2
	CH_3	H	O	O	69	225.5—226.5°	211	212.2
	C_2H_5	H	O	O	62	194.5—195.5°	227	226.3
	C_2H_5	$CH_3CH_2CH_2$	O	O	28	137—139°	269	268.4
	$CH_2=CHCH_2$	H	O	O	56	156—157°	238	238.3
	$CH_2=CHCH_2$	H	O *	O	75	156—157°	238	238.3
	$CH_2=CHCH_2$	CH_3	O	O	53	135—136°	252	252.3
$C_2H_5C(CH_3)_2$	C_2H_5	H	O *	O	63	178.5—179.5°	241	240.2
	$CH_2=CH—CH_2$	H	O	O	36	139.5—140.5°	251	252.3
	$CH_2=CH—CH_2$	H	O *	O	49	139.5—141.5°	251	252.3
	$CH_2=CH—CH_2$	H	S	O	50	143—144.5°	266	268.3

* Guanidine is used instead of urea and the resulting iminobarbituric acid is hydrolyzed by refluxing for 8 h with 1 litre of 20 % hydrochloric acid.

Table 2. Preparation of



X	R	Yield	M. p.	Equiv. wt. Found	Calc.
Br	CH_3—	71	177 —180°	325	331.2
Br	C_2H_5—	68	144.8—145.0°	346	345.2
Br	$(CH_3)_2CH$—	55	177—178°	358	359.3
Br	$CH_3CH_2CH_2$—	64	152—153.5°	358	359.3
Br	$C_2H_5(CH_3)CH$—	51	165—166°	368	373.3
Cl	CH_3—	61	178—181°	289.5	286.8

properties that makes it useful as a sedative drug. Clinical investigations have confirmed this assumption [4].

For the syntheses of *neo*pentylsubstituted barbituric acids all the standard methods have been tried [5]. Most of them can be used with success, but the best method seems to be the condensation of the corresponding malonic ester with urea or guanidine. For the preparation of 5-*neo*pentyl-5-allylbarbituric acid the following reactions seem to be best *(cf.* p. 620).

The condensation of diethyl *neo*pentylallylmalonate with urea seems to give a somewhat low yield of the barbituric acid probably due to steric effects. The disubstituted cyanoacetic esters containing one *neo*pentyl group do not give the corresponding iminobarbituric acid probably due to the very low reactivity of the cyano group.

Experimental. Condensations to barbituric acids. 55 *g* of sodium are dissolved in 1 100 ml of anhydrous methanol in a 3-litre three-necked flask provided with a stirrer, a reflux condenser and a stopper, and 75.5 g of dried urea and 1 mole of the malonic ester are added. The mixture is refluxed for 6 h whereupon the methanol is distilled off as completely as possible by means of an oil-bath, the temperature of which should not exceed 100°. At the end of the distillation the pressure is reduced. The contents of the flask are dissolved in water and the solution extracted with benzene to remove water insoluble products, whereupon the water-layer is acidified with conc. hydrochloric acid while cooling and stirring. The barbituric acid is filtered off, washed with water and dried in a drying oven at 80° to constant weight. The products can usually be recrystallized from dilute methanol. The yields and melting points are given in Table 1.

Allylations of 5-neopentylbarbituric acid. The method given above for the preparation of 5-*neo*pentylbarbituric acid is followed until the methanol has been distilled off. 500 ml of water is now added and the pH of the resulting solution adjusted to about 8 by careful addition of conc. hydrochloric acid (about 128 ml). At this point a slight precipitation may be present which is filtered off. 120 g of allyl bromide is added and the mixture is stirred at 40° in a 2-litre flask fitted with a stirrer, a reflux condensor, and a thermometer. After about 2 h the mixture becomes acidic (pH about 3). The barbituric acid is now filtered off, washed with water and dried. The resulting 5-*neo*pentyl-5-allylbarbituric acid is practically pure, m. p. 154—157°, but may be purified by recrystallisation from dilute methanol. The yield is 63 %, m. p. 156°.

In the method given above the allyl bromide can be replaced by an equivalent amount of allyl chloride together with a solution containing 2 g of cupric sulphate. The yield is the same as above but the product must be dissolved in a dilute sodium hydroxide solution and precipitated with hydrochloric acid in order to obtain a pure product. By rigorous exclusion of all traces of water in the condensation step yields of up to 85 % may be obtained by this method in large scale runs.

Preparation of 5-β-bromoallyl-5-neopentylbarbituric acids. 1 Mole of 1-ethyl-5-*neo*pentylbarbituric acid is dissolved in a solution of 40 g of sodium hydroxide in 1 200 ml of water. 10 g of crystallized cupric sulphate dissolved in a small quantity of water is added, and then 390 ml of 2,3-dibromopropene. The mixture is

stirred at 40° in a 3-litre three-necked flask for 20 h.

The resulting mixture is distilled under reduced pressure (about 60 mm Hg) to remove the excess of 2,3-dibromopropene. About 240 ml are thus recovered. The residue in the flask is filtered and washed with a small quantity of petroleum ether.

The product is dissolved in an ice-cold solution of 65 g of sodium hydroxide in 2 500 ml of water. An insoluble residue of about 10 g is filtered off. The solution is treated with discolouration carbon and then 10 g of ethylenediaminetetraacetic acid are added to remove cupric ions. The filtered solution is carefully added to 150 ml of concentrated hydrochloric acid. The product is filtered off, washed with water and recrystallized from methanol. The yield is 235 g (68 %) of a pure white product with a melting point of 144.8°—145.0°.

In exactly the same way the compounds in Table 2 are prepared.

The author is indebted to his colleagues and assistants at Pharmacia for good help with this project.

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On the Relation between the Reaction Velocity and Dielectric Constant of the Medium

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According to Laidler and Eyring [1], the effect of the dielectric constant of the solvent on the rate of a bimolecular reaction between two dipole molecules A and B,

$$A + B \rightarrow M^* \rightarrow \text{Products},$$

can be expressed by the equation

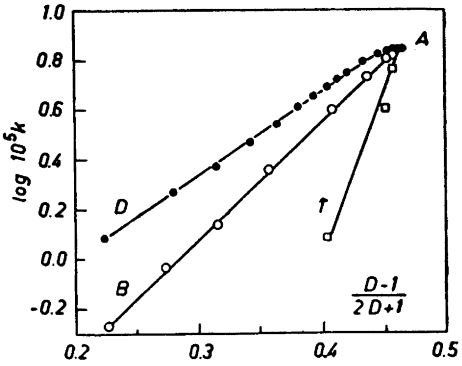

Fig. 1. Plot of log k for the reaction $(C_2H_5)_3N + C_2H_5I \rightarrow (C_2H_5)_4NI$ against $(D-1)/(2D+1)$ at 25°. A = acetone, B = benzene, D = dioxan, T = tetrahydrofuran.

where k and k_0 are the rate constants in a medium of dielectric constant D and in a medium of dielectric constant unity, respectively. The μ's and r's are the dipole moments and radii of the reactants and transition state, respectively. If the non-electrostatic term $\Sigma\Phi/kT$ is small enough to be neglected, and if μ^2_*/r^3_* is independent of the medium, the plot of log k against $(D-1)/(2D+1)$ should be a straight line for the same reaction carried out in different media. Linear plots were obtained for the reactions between pyridine and benzyl bromide and between triethylamine and benzyl bromide in benzene-ethanol mixtures, but not in benzene-nitrobenzene mixtures [1]. In cases where solvation phenomena play an important role, examination over larger areas of solvent mixtures has in general shown departure from linearity.

In Fig. 1 the eqn. (1) has been tested upon the results of some recent investigations concerning quaternary ammonium salt formation, *viz.* the reaction between triethylamine and ethyl iodide in acetone-benzene, acetone-dioxan, and acetone-tetrahydrofuran mixtures. The rate constants for 25° were calculated by the Arrhenius equation from the data of Tommila and Kauranen [2]. The dielectric constants of acetone-benzene mixtures were taken

$$\ln k = \ln k_0 - \frac{1}{kT}\,\frac{D-1}{2D+1}\left(\frac{\mu_A^2}{r_A^3} + \frac{\mu_B^2}{r_B^3} - \frac{\mu_*^2}{r_*^3}\right) + \frac{\Sigma\Phi}{kT} \qquad (1)$$