The methyl ester was prepared in the usual way, the yield being 86% of the theoretical. Hydrolysis of this ester gave an acid which after repeated recrystallization melted at 106°.

Identification of a By-Product.—The by-product obtained by extraction with ether while the reaction mixture was still alkaline appears on evaporation of the ether as a heavy brown oil which crystallizes on standing. Fourteen grams of this was obtained in the oxidation of 289 g. of α-allylnaphthalene. Recrystallized repeatedly from 30% alcohol it forms colorless prisms, m. p. 110°.

Anal. Subs., 0.2553 g.: H_2O, 0.1602 g.; CO_2, 0.7232 g.; H, 7.02; C, 77.25.

The simplest formula corresponding with this analysis is $C_{13}H_{14}O_2$ for which the calculated figures are H, 6.98, C, 77.20.

Anal. Calcd. for $C_{13}H_{14}O_2$: OH, 16.83. Found:[7] OH, 16.43, 16.44.

The by-product is therefore α-naphthylmethylethylene glycol, $C_{10}H_7CH_2CHOH-CH_2OH$.

Summary

1. α-Naphthylacetic acid has been prepared in satisfactory yield by the oxidation of α-allylnaphthalene with potassium permanganate in alkaline solution.

2. A by-product during the oxidation has been shown to be α-naphthylmethylethylene glycol.

(7) Verley and Bolsing method, *Ber.*, **34**, 3354 (1901).

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Some Naphthyl Derivatives of Barbituric Acid

BY DEWITT T. KEACH

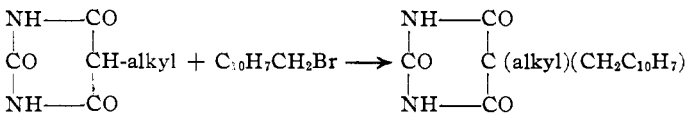
In the quarter of a century since Fischer and Dilthey and Fischer and von Mering found that certain of the 5,5-disubstituted derivatives of barbituric acid could be used therapeutically as sedatives and hypnotics a large number of compounds of this type have been prepared. In 1930 the number of such compounds which had been made and tested was given as nearly a hundred[1] and many have been added since that time, but so far as the writer is aware none of those prepared to date contain the naphthyl group. There are two types of such compounds, those in which the naphthyl group is attached directly to the 5-carbon atom and those in which one or more methylene groups intervene between the 5-carbon atom and the naphthyl group. A study of both types is of considerable interest because of the properties of some of those containing the phenyl group, the naphthyl group having in many compounds an effect similar to that produced by the phenyl group.

In the work reported in this paper six barbituric acids which contain

(1) Shonle, Keitch and Swanson, THIS JOURNAL, **52**, 2449 (1930).

the naphthyl group have been prepared, three of these being naphthylmethyl and three naphthylethyl derivatives. Work is now in progress on the type in which the attachment of the naphthyl group is directly to the 5-carbon atom.

In the preparation of the barbituric acids reported in this paper it was decided to introduce the naphthylmethyl and naphthylethyl groups according to the following



and it was found possible to accomplish this in the case of the naphthylmethyl derivatives. All attempts to substitute naphthylethyl in this manner, however, were unsuccessful and in these cases the corresponding malonic ester derivatives were made and condensed with urea in the usual way.

α-Naphthylmethyl bromide and α-naphthylethyl bromide used in alkylation were prepared from the corresponding alcohols. α-Naphthylcarbinol was made by the method of K. Ziegler[2] and the bromide made from this alcohol by the use of hydrobromic acid and sulfuric acid, a yield of 51% being secured. α-Naphthylmethylcarbinol was prepared by the Grignard method using ethylene oxide, the yield secured being 65%. This carbinol has previously been prepared by Grignard[3] by the use of ethylene chlorohydrin with a yield of 80%, but inasmuch as one mole of α-naphthyl bromide used in this method reverts to naphthalene this is equivalent to only a 40% yield compared to the method using ethylene oxide. The α-naphthylethyl bromide was prepared from the alcohol by treating the alcohol with phosphorus tribromide (using one and one-third moles of the bromide to one mole of the alcohol) in petroleum ether solution. A yield of 63% of the bromide was secured.

Both of the bromides mentioned above have been made previously by the bromination of α-methyl and α-ethylnaphthalene, respectively.[4]

Experimental

Barbituric Acids Containing the α-Naphthylmethyl Group.—One molecular proportion of the appropriate alkyl barbituric acid was dissolved in a mixture of alcohol and water by gentle heating in a flask fitted with a reflux condenser. An alcohol and water solution of one and one-half molecular proportions of α-naphthylmethyl bromide and two molecular proportions of crystallized sodium acetate was then added and the reaction mixture digested from one to three hours over a low flame. In the preparation of 5-ethyl-5-α-naphthylmethylbarbituric acid, precipitation occurred during the heating

(2) Ziegler, *Ber.*, **54**, 737–740 (1921).

(3) Grignard, *Compt. rend.*, **141**, 44 (1905).

(4) Schmidlin and Massini, *Ber.*, **42**, 2389 (1909); Mayer and Oppenheimer, **49**, 2138 (1916); Wislicenus and Elvert, **42**, 2822 (1909); Shoesmith and Rubli, *J. Chem. Soc.*, 3098 (1927); Von Berthelot and Bardy, *Ann.*, **166**, 136 (1873).

period; with the others the reaction product crystallized out on cooling the reaction mixture. After filtration a slight additional yield was obtained by evaporation and cooling of the filtrate. All three of the acids of this type are colorless. Physical and analytical data in connection with these new barbituric acids are given in Table I.

TABLE I

	Barbituric acid, naphthylmethyl	M. p., °C.	Analyses, N, % Calcd.	Found		Yield, %	Recryst. from	Crystal form
1	5,5-Ethyl-α-	247	9.46	9.37	9.32	59	90% alc.	Prisms
2	5,5-*n*-Butyl-α-	214	8.64	8.50	8.55	60	Benzene	Prisms
3	5,5-Allyl-α-	212	9.09	9.01	9.11	72	35% alc.	Needles

α-Naphthylethyl Substituted Malonic Esters.—The usual procedure of the malonic ester synthesis was followed in substituting the α-naphthylethyl group excepting that constant stirring was employed and during the addition of the α-naphthylethyl bromide the reaction mixture was heated on the steam-bath. Sodium bromide did not precipitate until nearly all of the α-naphthylethyl bromide had been added. The product, dried in the usual manner, was distilled under reduced pressure. The fraction boiling at 198–203° under a pressure of 4 mm. was viscous and light yellow in color. To convert this material into the desired disubstituted malonic esters the following procedure was employed: the calculated amount of sodium ethylate was prepared and to this, while being heated on the steam-bath, the α-naphthylethylmalonic ester was slowly added. The heating on the steam-bath was also continued during the addition of the appropriate alkyl bromide. The product in all cases was distilled under reduced pressure after drying in the usual manner. The esters thus produced were all yellow in color and very viscous. They were not analyzed, the method of formation together with the subsequent condensation with urea to form the disubstituted barbituric acids being considered sufficient evidence of their constitution. Physical data in connection with these new esters are given in Table II.

TABLE II

	Malonic ester	B. p., °C.	Pressure, mm.	Yield, %
1	α-Naphthylethyl	198–203	4	37
2	Ethyl-α-naphthylethyl	188–193	3–4	67
3	*n*-Butyl-α-naphthylethyl	202–206	3–4	81
4	Allyl-α-naphthylethyl	212–213	5–6	47

Barbituric Acids Containing the α-Naphthylethyl Group.—The barbituric acids were prepared as follows: one molecular equivalent of the ester, usually 12 g., was treated with one and one-half molecular equivalents of urea in a solution of two equivalents of sodium in absolute alcohol. The success of these condensations was found to depend to a great extent on the use of pure reagents. The reaction mixture was heated in an autoclave for five hours at 100–105°. The alcohol was then evaporated, the sodium salt dissolved in a small amount of cold water and acidified with concentrated hydrochloric acid. In all cases the ureide separated as a gummy mass and there was considerable loss of material in separating the barbituric acid from the oil (unchanged ester) by re-

TABLE III

	Barbituric acid	M. p., °C.	Analyses, N, % Calcd.	Found		Yield, %	Crystal form
1	5,5-Ethyl-α-naphthylethyl	178	9.03	8.89	8.89	8	Needles
2	5,5-*n*-Butyl-α-naphthylethyl	187	8.28	8.01	8.17	19	Plates
3	5,5-Allyl-α-naphthylethyl	169	8.66	8.41	8.55	33	Plates
4	5-α-Naphthylethyl	196–198	9.93	9.87	..	..	Plates

crystallization from 70% alcohol. The yields were calculated on the basis of the amount secured after two recrystallizations. All three of the ureides are colorless. Physical and analytical data in connection with these new barbituric acids are given in Table III.

Comparative studies of the barbituric acid derivatives with two well-known barbituric acids, barbital and amytal, were made on white rats. For this purpose 2% solutions of the sodium salts of the several compounds were injected intraperitoneally into the test animals, which were starved for twenty-four hours previous to the injections. For each dose three to five animals were used.

The amount of each compound which caused the following symptoms was noted: (a) ataxia, (b) hypnosis, or light sleep, M.H.D., (c) anesthesia, *i. e.*, failure to respond to any external stimuli, M.A.D. and (d) death, M.L.D. These data are given in Table IV.

All of the new barbituric acid derivatives produced a condition of ataxia. The two *n*-butyl derivatives failed to produce either hypnosis or anesthesia. Allyl-α-naphthylethylbarbituric acid while producing no hypnotic action at low doses did produce anesthesia at sub-lethal doses. None of those producing either a state of hypnosis or anesthesia were comparable in effect to either barbital or amytal. It is of interest to note that ethyl-α-naphthylmethylbarbituric acid produced convulsions as does ethylbenzylbarbituric acid.

TABLE IV

Barbituric acid	Symptoms No. of animals	Symptoms of ataxia, mg./kg.	M.H.D., mg./kg.	M.A.D., mg./kg.	M.L.D., mg./kg.	Therapeutic index, $\frac{\text{M.L.D.}}{\text{M.A.D.}}$
Barbital	36	100	200	320	480	1.50
Amytal	27	40	60	90	200	2.22
Ethyl-α-naphthylmethyl	37	200	400	500	1000	2.00
N-butyl-α-naphthylmethyl	33	200	None	None	1000	None
Allyl-α-naphthylmethyl	18	200	400	500	600	1.20
Ethyl-α-naphthylethyl	20	300	400	600	600	1.00
N-butyl-α-naphthylethyl	26	700	None	None	1000	None
Allyl-α-naphthylethyl	21	200	None	500	600	1.20

I am indebted to Edward E. Swanson and H. A. Shonle of the Lilly Research Laboratories, Eli Lilly & Co., for the pharmacological work published in this paper.

Summary

1. α-Naphthylethyl substituted derivatives of diethyl malonate have been prepared by the normal malonic ester synthesis.

2. α-Naphthylmethyl and α-naphthylethyl derivatives of barbituric acid have been prepared, the α-naphthylmethyl by the action of α-naphthylethyl bromide with the monosubstituted barbituric acid in the presence of sodium acetate; the α-naphthylethyl by the usual condensation of the substituted malonic ester with urea in sodium ethylate solution.

3. None of the barbituric acids prepared possesses desirable physiological properties comparable in effect to barbital or amytal.

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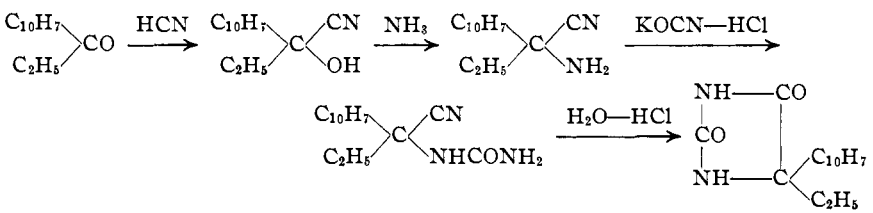
Synthesis of 5,5-α-Naphthylethylhydantoin

BY DEWITT T. KEACH

Phenylethylhydantoin (nirvanol) has been used considerably as an hypnotic, and it is probable that other hydantoins having an aryl group in the 5 position would possess similar properties. Because of this fact and the relationship of the hydantoins to the barbituric acids, the writer, in the course of work on the determination of the physiological effect of the naphthyl group introduced into the barbituric acid molecule, decided to attempt the synthesis of 5,5-α-naphthylethylhydantoin.

The method followed was essentially that used by Read[1] in his work on 5,5-phenylethylhydantoin, *i. e.*, α-naphthyl ethyl ketone reacting with anhydrous hydrocyanic acid produced the corresponding cyanohydrin and this with ammonia gave a disubstituted aminoacetonitrile. This aminoacetonitrile was dissolved in hydrochloric acid, treated with alkali cyanate, and upon boiling the solution the hydantoin precipitated. This is shown by



α-Naphthyl ethyl ketone was made by the method of E. Caille,[2] a method which avoids the difficulties connected with a separation of α- and β-naphthyl ethyl ketone.

Experimental Part

α-Naphthylethylaminoacetonitrile.—Eighty grams of α-naphthyl ethyl ketone was added to 16 g. of anhydrous hydrocyanic acid in a small amount of absolute alcohol and excess dry ammonia run in during constant stirring. The mixture was then stirred at room temperature for forty-eight hours. The very dark red reaction mixture was then poured into dilute hydrochloric acid and extracted twice with ether, made strongly alkaline with concentrated ammonia solution and again extracted twice with ether. Upon evaporation of this ether extract 23 g. of the aminoacetonitrile and 40 g. of unchanged

(1) Read, THIS JOURNAL, **44**, 1748 (1922).
(2) Caille, *Compt. rend.*, **153**, 393 (1911).