[CONTRIBUTION FROM THE ABBOTT LABORATORIES, NORTH CHICAGO, ILL.]

Hypnotics Containing the 1-Ethylpropyl Group; Syntheses with Higher Esters of *p*-Toluenesulfonic Acid

BY D. L. TABERN AND E. H. VOLWILER

The isomerization of diethylcarbinol derivatives into the corresponding methylpropylcarbinol analogs has been known for many years.[1] Sherrill, Otto and Pickett, and Sherrill, Baldwin and Haas[2] have recently investigated the problem in considerable detail and evolved a method which they feel permits the synthesis of 3-bromopentane (diethylcarbinyl bromide) in a fair state of purity.

Prior to the publication of Sherrill's work, we had attempted to synthesize a series of barbituric acids containing these groups, and found that particularly in those instances where the other group attached to the 5 carbon atom was ethyl, the use of the bromide prepared from either alcohol led to the same barbituric acid melting at 128–130°,[3] which because of the greater stability of the 1-methylbutyl form of the carbinol, we concluded to be ethyl 1-methylbutylbarbituric acid.[4] Under the name "Nembutal" (Pentobarbital Sodium) this substance has found extensive application in medicine, particularly because its sedative and antispasmodic action is rapid of onset and of marked intensity, and in turn passes away with comparative rapidity.[5]

Shortly after the publication of our paper, Shonle, Kelch and Swanson[6] described both ethyl methyl-propyl-carbinyl and ethyl diethylcarbinyl barbituric acids, reporting melting points of 128.5–130 and 127–129°, respectively, as well as the allylmethylpropylcarbinyl and allyldiethylcarbinylbarbituric acids, the first melting at 86–88° and the second being "wax-like." The intermediate esters boiled at the same point and differed only by a small amount of refractive index. In their pharmacological data, they report identical minimum effective doses and minimum lethal doses for the ethyl substituted compounds, and very similar values for the allyl homologs. In view of considerable variations of efficiency and toxicity among the other amyl isomers, these values made it seem even more probable that isomerization had taken place during their syntheses.

There is also disagreement in other instances in this field. Boedecker[7] had reported that mono-(1-methyl-butyl)-barbituric acid melted at 162–163°, while Shonle found 164–166°. German Patent 293,163 reported 198° for mono-(1-ethylpropyl)-barbituric acid, and 162° for the ethyldiethylcarbinyl as contrasted to Shonle's values of 165–168 and 127–129°, respectively. Throughout this latter patent, it is emphasized that malonic and cyanoacetic esters are essentially equivalent and may be used interchangeably for synthetic purposes.

In our earlier work, we employed commercial diethylcarbinol.[8] This gave a dinitrobenzoate melting at 86–87° as contrasted with that from methylpropylcarbinol which melted at 59–60°. When this diethylcarbinol was converted to the bromide according to the method of Sherrill, a product having a refractive index of 1.4430 was secured; employing this material, isomerization seemed to take place during the prolonged refluxing with sodium ethylate necessary for the reaction with the sodium ethyl malonic ester. The same seemed to be true if condensation with unsubstituted malonic ester was carried out with vigorous boiling; if, on the other hand, it was allowed to proceed at room temperature, reasonably uniform mono-diethylcarbinylmalonic ester resulted. As added confirmation of this isomerization, methylpropylcarbinyl and diethylcarbinyl bromides (from Sharples alcohol) were condensed hot with sodium malonic ester, the esters hydrolyzed and converted through the acids and acid chlorides to the *p*-toluidides. Both melted at 76–78° and the mixed melting point showed no depression. Later, employing very pure diethylcarbinyl bromide made from synthetic alcohol by dry hydrogen bromide at

(1) Wagner and Saytzeff, *Ann.*, **179**, 313 (1875).

(2) Sherrill, Otto and Pickett, THIS JOURNAL, **51**, 3023 (1929); Sherrill, Baldwin and Haas, *ibid.*, **51**, 3034 (1929).

(3) Stanfield and Schierz [*ibid.*, **54**, 4356 (1932)] report identical melting points for the methylpropyl- and diethylcarbinyl derivatives of hexabromostearic acid (135.7–135.9 and 135.8–135.9°, respectively). Likewise, Soday and Boord [*ibid.*, **55**, 3926 (1933)] obtained 3-methyl-1-hexene, starting from either 2-pentyl or 3-pentyl bromide. Apparently, isomerization took place during the formation of the Grignard reagent.

(4) Volwiler and Tabern, *ibid.*, **52**, 1676 (1930).

(5) Fitch, Waters and Tatum, *Am. Jour. Surg.*, **9**, 112 (1930).

(6) Shonle, Kelch and Swanson, THIS JOURNAL, **52**, 2440 (1930).

(7) U. S. Patent 1,739,662 (1929); British Patent 244,122 (1925).

(8) Supplied through the courtesy of the Sharples Solvents Corporation.

−20 to −30° in an atmosphere of hydrogen (n^{20} 1.4440) no reaction was found to take place on twenty-four hours of refluxing in benzene. In alcohol sodium bromide separated, but little if any disubstituted malonic ester could be isolated. This is in harmony with Kailan and Raft,[9] who find that the rate of esterification of diethylcarbinol is only about one-tenth that of other amyl alcohols.

A satisfactory means of introducing the diethylcarbinyl group into monosubstituted malonic esters was ultimately found in the use of the diethylcarbinyl ester of *p*-toluenesulfonic acid; a little pyridine may be used as a catalyst.

The lower normal alkyl toluene sulfone esters have been found to result from the simple reaction of the alcohols alone, in the presence of potassium hydroxide in anhydrous ether, or with dry sodium carbonate at 115–125°.[9,10,11] None of these methods was found satisfactory with the secondary alcohols which we studied. Patterson and Frew[12] prepared menthyl *p*-toluenesulfonate from the acid chloride and menthol in the presence of pyridine. Ferns and Lapworth[13] confirmed these results in the preparation of the bornyl and phenyl esters, but found this method to fail completely with ethyl and benzyl alcohols, further reaction taking place with the formation of pyridium salts. Since the completion of these studies, Sekera and Marvel[14] have reported the formation of the toluenesulfonic esters of certain higher normal alcohols by this method.

In this work, we have found the reaction between pyridine, pure toluenesulfonyl chloride and secondary alcohols to proceed smoothly at 15–30°, giving the desired esters in nearly quantitative yields. Purification is difficult because the products are normally non-distillable liquids; analyses, however, confirmed their essential purity. The unpurified products were employed directly in all of the experiments to be described. Save for the use by Clemo and Tenniswood[15] of cyanoethyl *p*-toluene sulfonic ester for the preparation of the corresponding monocyanoethylmalonic ester, this reaction does not seem to have been applied to barbituric acid syntheses.

(9) Kailan and Raft, *Monatsh.*, **61**, 116 (1932).

(10) (a) Krafft and Roos, *Ber.*, **25**, 2225 (1892); (b) Hahn and Walther, *ibid.*, **54**, 1540 (1921); (c) Gilman and Beaber, THIS JOURNAL, **47**, 518 (1925).

(11) Slotta and Franke, *Ber.*, **63**, 678 (1930).

(12) Patterson and Frew, *J. Chem. Soc.*, **89**, 332 (1906).

(13) Ferns and Lapworth, *ibid.*, **101**, 273 (1912).

(14) Sekera and Marvel, THIS JOURNAL, **55**, 345 (1933).

(15) Clemo and Tenniswood, *J. Chem. Soc.*, **134**, 2550 (1931).

We find the reaction between the alkyltoluenesulfonic esters studied and sodium monoalkylmalonic esters in an anhydrous organic solvent to proceed rapidly at room temperature and almost violently at 80°, thus avoiding the prolonged boiling necessary when the secondary alkyl halides are employed. Yields with esters from normal alcohols are excellent; with secondary they are only moderate, but amply sufficient to repay the use of the method where there is any question of isomerization. In this work, diethyl, ethylisopropyl, ethyl-*n*-propyl, ethyl-1-methyl-butyl, ethyl-*n*-amyl and a number of other barbiturates were synthesized through the toluenesulfonic esters to test the general applicability of the method; the other derivatives to be described containing the 1-methylbutyl group were prepared employing the bromide.

Diethylcarbinyl *p*-toluenesulfonate, like the bromide, does undergo isomerization, but somewhat less readily. On reaction with pyridine at 100–125°, diethylcarbinyl and methylpropylcarbinyl toluenesulfonates yield one and the same pyridinium compound, melting at 118–120°. With other similar esters the reaction proceeded normally (the *n*-amyl analog melts at 128–130°).

On attempted hydrolysis of diethylcarbinyl toluenesulfonic ester by boiling aqueous potassium hydroxide there resulted a mixture of amylene (identified by its boiling range of 30–40° and by conversion to a dibromide boiling 177–180°, see Sherrill, *loc. cit.*), and of alcohols boiling at 110–116°. The dinitrobenzoate of the mixed alcohols melted at about 70°, indicating a large percentage of methylpropylcarbinol.

A much more satisfactory method from the standpoint of yields was found in the use of cyanoacetic esters. Here the reaction between diethylcarbinyl bromide and sodio-cyanoacetic ester proceeds so readily at 50–60° that there seems to be little tendency to isomerize. The second alkyl group can then be introduced in excellent yield, even though the first group introduced is a secondary radical. Condensation with urea or a substituted urea gave the imino barbiturate, which was then hydrolyzed by 15–20% sulfuric acid to the barbituric acid, which was purified by solution in potassium hydroxide or ammonium hydroxide and precipitation by carbon dioxide followed by crystallization from dilute alcohol to constant melting point. In those cases where both modes of synthesis were em-

ployed, the barbiturates were found to have identical properties.

The various barbiturates were prepared either by condensing the substituted malonic esters with urea by known procedures, or in the case of those containing the allyl group, by the method used by Volwiler.[16]

It is to be noted that in each case there is an unmistakable difference in melting point between the 1-methylbutyl and the 1-ethylpropyl barbiturates. Again, especially in the lower members, pharmacologic tests show a definite and fairly uniform variation in hypnotic efficiency.

Ethyl (1-methylbutyl) and ethyl (1-ethylpropyl) malonic esters were hydrolyzed to the malonic acids, these converted to the acetic acids, then to the acid chlorides by thionyl chloride and finally to the amides and acetyl ureas. Again, melting points and properties were distinctly different. The amides were also prepared from the cyano esters by hydrolysis to the cyano acids, elimination of carbon dioxide, followed by controlled hydrolysis of the nitriles; and ethyl (1-ethylpropyl) acetyl urea was made by heating the barbiturate in alkaline solution at 110° in a sealed tube. In marked contrast to the results reported by Tabern and Shelberg for other barbiturates,[17] the ethyldiethylcarbinylbarbituric acid is extremely stable under these conditions, only a small portion undergoing hydrolysis during several days at 110°. When heated to 150° for several days, the amide seemed to be the principal product of the reaction.

Experimental

Diethylcarbinyl Bromide.—This was prepared according to the method of Sherrill, employing even greater precautions. Synthetic diethyl carbinol (b. p. 114–117°) was cooled to −20 to −25° and with rapid mechanical agitation dry hydrogen bromide was passed in. Saturation occurred in about one hour. The viscous mixture was transferred to a pressure bottle fitted at the top with a large rubber balloon. It was then rapidly warmed to 55–60°, when separation into two layers took place. When the reaction seemed at an end the contents of the bottle were returned to the flask, rapidly cooled to −20° and resaturated with hydrogen bromide. The heating to 60° was repeated once or twice. Purification consisted of washing with water, ice cold sulfuric acid and water, followed by fractionation. The portion boiling at 118.5–119.5° was collected; refr. index 1.4440 at 20°. The dinitrobenzoate melted at 98–100°.

Diethylcarbinyl *p*-Toluenesulfonate.—380 grams of freshly distilled *p*-toluenesulfonyl chloride was dissolved in 1000 cc. of dry benzene and 192 g. of diethylcarbinol and 200 cc. of pyridine added. The flask was placed in cold water (10–15°) where it was allowed to stand overnight, and finally left at room temperature for two days. The pyridine hydrochloride (200–210 g.) was filtered off and washed with benzene. The benzene filtrates were washed with cold dilute hydrochloric acid to remove excess pyridine, then with water, dried over sodium sulfate and the solvent removed *in vacuo* at 60°. On standing the residue solidified and after washing with petroleum ether it melted at 32–35°. This is interesting since all other isomeric toluenesulfonates are liquids. The toluenesulfonic ester decomposes on attempted distillation and so was used directly. Ether or other non-polar solvent may be employed in place of the benzene.

Ethyl 1-Ethylpropylmalonic Ester through 1-Ethylpropyl *p*-Toluenesulfonate.—190 grams of monoethylmalonic ethyl ester was converted to the sodium derivative by 23 g. of sodium; 240 g. of diethylcarbinyl *p*-toluenesulfonate dissolved in benzene was added slowly. A very vigorous reaction took place at once with the separation of sodium *p*-toluenesulfonate. In contrast to excellent yields secured by a similar technique with ethyl *n*-propyl, isopropyl and *n*-amyl toluenesulfonates but in agreement with those secured with methylpropylcarbinyl, the yields of disubstituted ester were always poor. Purified by fractionation and condensed with urea as usual, the resultant barbituric acid melted at 158.5–159.5°.

Ethyl (1-Ethylpropyl)-cyanoacetic Ester and the Barbituric Acid.—113 grams of cyanoacetic ester was added to a solution of 23 g. of sodium in absolute alcohol. On the slow addition of 160 g. of pure synthetic diethylcarbinyl bromide at about 50–60°, separation of sodium bromide took place. The next morning the mixture was refluxed briefly and the alcohol distilled.

The 1-ethylpropylcyanoacetic ester was treated with sodium ethylate and ethyl bromide in alcohol, and after being kept at 60° overnight it gave an excellent yield of ethyl 1-ethylpropylcyanoacetic ester boiling at 145–150° at 35–37 mm.

This was condensed with urea by sodium ethylate at 100–110° for three hours and the imino barbiturate precipitated by acid. It was redissolved in potash and precipitated by acetic acid. Without complete drying, about 25 g. was dissolved in 100 cc. of water plus 10 cc. of concd. sulfuric acid and refluxed for ten hours or longer. On cooling the barbituric acid solidified and was filtered off. A trace of unhydrolyzed material was removed by dissolving in ammonia, filtering and precipitating by carbon dioxide. Final purification was effected by recrystallization from dilute alcohol, m. p. 158.5–159.5°.

Other alkyl analogs were prepared in essentially the same manner. Occasionally in the higher members, a considerable amount of material insoluble in mineral acid was formed during the condensation; it was not studied further.

***n*-Propyl (1-Ethylpropyl)-barbituric Acid.**—Normal propyl (1-ethylpropyl)-cyanoacetic ester was prepared as in the case of the ethyl analog. This was condensed with urea and the imino barbiturate hydrolyzed by 20% sulfuric acid for ten hours as in the case of the ethyl analog, m. p. 130–133°.

Allyl (1-Ethylpropyl)-barbituric Acid.—Thirty-three grams of mono-(1-ethylpropyl)-barbituric acid (prepared

(16) Volwiler, THIS JOURNAL, **47**, 2236 (1925).
(17) Tabern and Shelberg, *ibid.*, **55**, 328 (1933).

either from the malonic or the cyanoacetic ester) was dissolved in one equivalent of potash (9.6 g.), to which had been added about 0.5 g. of copper sulfate; 20–21 g. of allyl bromide was added and the mixture shaken continuously for ten hours. By this time the allyl (1-ethylpropyl)-barbiturate had separated as a beautifully crystalline mass. Purification was carried out by repeated solution in ammonia and precipitation followed by crystallization from chloroform, m. p. 129–130°.

Methyl (1-Ethylpropyl)-barbituric Acid.—This compound, prepared through the cyanoacetic ester, melted at 204–206°.

Alkali Salts.—The sodium salts in general were made by solution of molecular equivalents of the barbituric acids and of sodium in absolute alcohol followed by concentration or by evaporation to dryness. They are white or nearly white solids, very soluble in water and fairly stable on exposure to air.

In the tables are reported the chemical and pharmacological properties of the series of alkyl diethylcarbinylbarbituric acids and the corresponding methylpropylcarbinyl analogs. Most of the latter are also new.

TABLE I

Barbituric acid	Cyanoacetic esters B. p., °C.	Mm.	Refr. index at 20°	Malonic esters B. p., °C.	Mm.	M. p. of barb. acids, °C.	Nitrogen, % Calcd.	Found
Ethyl (1-methyl-butyl)	140–150	40	1.4330	155–160	45	128–129	...	...
Ethyl (1-ethyl-propyl)	150–155	40	1.4360	155–160	45	158.5–159.5	12.3	12.32
Methyl (1-methyl-butyl)	.....	..	....	140–144	45	180–182	12.9	12.8
Methyl (1-ethyl-propyl)	145–150	30	1.4340	.....	..	204–206	12.9	12.8
n-Propyl (1-methyl-butyl)	.....	..	....	165–170	40	85–88	11.6	11.3
n-Propyl (1-ethyl-propyl)	155–165	34	1.4420	165–170	40	130–133	11.6	11.45
Allyl (1-methyl-butyl)	.....	..	....	.....	..	98–100	11.8	11.6
n-Butyl (1-methyl-butyl)	.....	..	.....	170–180	40	110–111	11.03	10.7
n-Butyl (1-ethyl-propyl)	170–180	35	1.4430	170–180	40	126–127	11.03	11.02

TABLE II

Barbituric acid	Rabbits intraperitoneally M. E. D. mg. per kg.	M. L. D. mg. per kg.
Ethyl (1-methyl-butyl)	20	55
Ethyl (1-ethyl-propyl)	25	75
Methyl (1-methyl-butyl)	50	170
Methyl (1-ethyl-propyl)	140	330
n-Propyl (1-methyl-butyl)	30	190
n-Propyl (1-ethyl-propyl)	40	70
Allyl (1-methyl-butyl)	15	50
Allyl (1-ethyl-propyl)	20	60
n-Butyl (1-methyl-butyl)	35	90
n-Butyl (1-ethyl-propyl)	45	110

Pharmacologic Evaluation

These compounds were evaluated pharmacologically by intravenous injection into rabbits and by intraperitoneal injection into rabbits and rats.[18] One hundred and fifty animals were used. Only the results by the rabbit intraperitoneal method are reported. However, the results obtained by the other two methods were parallel to the above; a further pharmacologic study is now in progress.

In the first stage by the intraperitoneal method, the rabbit lies down, has no ability to move the trunk or limbs, but maintains the head in proper position. In stage two, the animal lies down in complete relaxation but responds to pain stimuli produced by pinching the base of the ear, the tail or the leg with a sharp skin forceps. In stage three, there is no response to pinching Our M. E. D. was taken at stage two. All compounds were injected in the form of the sodium salts. The animals were deprived of food for eighteen hours before use.

Examination of the data obtained reveals that the 1-methylbutyl compounds are more efficient than the corresponding 1-ethylpropyl compounds, and that the higher members of the series show no apparent advantage over the lower ones.

Conclusions

Two methods have been described which permit the preparation of barbituric acids containing the diethylcarbinyl group without appreciable isomerization. The method employing the requisite cyanoacetic esters has the advantage of giving larger yields.

A series of homologous alkyl methylpropylcarbinyl and diethylcarbinyl barbituric acids has been synthesized. In the case of each pair, there are definite differences in melting points and hypnotic efficiencies.

NORTH CHICAGO, ILL. RECEIVED DECEMBER 29, 1933

(18) These determinations were carried out by Mr. H. C. Spruth and Miss C. Seeber of the Department of Pharmacology of the Abbott Laboratories, to whom we wish to express our sincere thanks.