the column yielded a picrate which could be purified only with large losses to melt at 153–155°.

dl-s-**Butylamine.**—Three grams of α-methylallylamine and 0.2 g. of Adams catalyst in 20 cc. of ethanol absorbed 1125 cc. of hydrogen during ten minutes (calcd. for 1 mole, 1050 cc.). The catalyst was filtered off and picric acid was added to the filtrate. The solution was chilled in an ice–salt-bath, thereby yielding 6.0 g. of yellow picrate of m. p. 129–130°. After two recrystallizations from ethanol the substance was obtained as large, flat, pale yellow needles of m. p. 129–130.5°.

Anal. Calcd. for $C_{10}H_{24}N_7O_4$: C, 39.7; H, 4.7. Found: C, 39.7; H, 4.7.

The picrate of m. p. 130° we prepared from *dl-s*-butylamine (b. p. 62–64°), obtained from two different sources showed no depression in mixture melting point with our analyzed picrate. We believe, therefore, our picrate of m. p. 130.5° to be a pure substance and the m. p. of 139–140° quoted for the picrate of *dl-s*-butylamine by Heilbron[9] to be an error.

We also prepared a picrate of m. p. 147° from *n*-butylamine. This picrate mixed with the picrate of *dl-s*-butylamine of m. p. 130° melted at 111–122°.

α-**Methylallyl Isothiocyanate from** α-**Methylallylamine.**—α-Methylallylamine (22.0 g.) dissolved in ether was treated with 25 cc. of carbon disulfide. The precipitate which was filtered off weighed 27 g. and melted at 106°. Even on drying in a vacuum at room temperature the substance decomposed. Twenty-seven grams of freshly prepared dithiocarbamate derivative was dissolved in 500 cc. of water and the solution was treated with 20 g. of mercuric chloride in 500 cc. of water. The suspension was steam distilled and the distillate was extracted with ether. The ethereal solution when evaporated gave a residue weighing 3.5 g. (17%) which distilled from 158–173°. The substance then began to decompose and the distillation was stopped. The distillate weighing 2.0 g. was redistilled and the boiling range observed was 155–165°. The distillate treated with aqueous-alcoholic ammonia furnished a thiourea derivative of m. p. 105°, identical (m. p. and m. m. p.) with the thiourea derivative described by Charon. For analysis the substance crystallized from ethyl acetate as large glistening white hexagons of m. p. 106°.

Anal. Calcd. for $C_5H_{10}N_2S$: C, 46.1; H, 7.7. Found: C, 46.3; H, 7.6.

(9) Heilbron, "Dictionary of Organic Compounds," Vol. I, The Oxford University Press, 1934, p. 215.

Summary

α-Methylallylamine has been isolated and characterized. A convenient route to this compound from crotyl alcohol has been described.

CHICAGO, ILLINOIS RECEIVED JULY 11, 1941

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Pinacolonylbarbituric Acids

BY S. M. MCELVAIN AND ROBERT F. TAYLOR

The substituents in the 5-position of those barbituric acids that are effective hypnotics are generally two alkyl groups or a combination of an alkyl and an alkylene group and the variations of the chain length and branching of these groups account for many of the pharmacological characteristics of the members of this important group of drugs. The present paper is concerned with the preparation of some barbituric acids that have as one of the 5-substituents a different type of group, *viz.*, the pinacolonyl group.

These compounds were prepared by the following sequence of reactions

$$(CH_3)_3CCOCH_3 + O{=}C(COOC_2H_5)_2 \longrightarrow (CH_3)_3CCOCH_2\overset{OH}{\overset{|}{C}}(COOC_2H_5)_2 \xrightarrow{-H_2O}$$

I

$$(CH_3)_3CCOCH{=}C(COOC_2H_5)_2 \xrightarrow{H_2 + Ni}$$

II

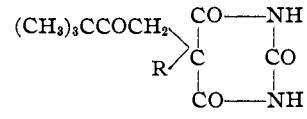
$$(CH_3)_3CCOCH_2CH(COOC_2H_5)_2 \xrightarrow[NaOC_2H_5]{RBr}$$

III

$$(CH_3)_3CCOCH_2CR(COOC_2H_5)_2 \xrightarrow{\text{urea}}$$

IV

V



After a study of a wide variety of conditions it was found that pinacolone and oxomalonic ester reacted at 160° in eight hours to produce an 83% yield of the diethyl pinacolonyltartronate (I). This ester was surprisingly resistant to dehydration. Treatment with phosphorus pentoxide at 68°, or with iodine at 225°, left it practically unchanged. At higher temperatures the pentoxide produced some of the unsaturated ester II, but its formation was accompanied by considerable decomposition and charring. However, conversion of the ester I to the corresponding bromide with either phosphorus tribromide or anhydrous hydrogen bromide in benzene and the distillation of this bromide produced hydrogen bromide and the unsaturated ester II in 74–78%

yields. In addition to these acidic reagents it was found possible to dehydrate the tartronic ester (I) with certain basic reagents. Such reagents as sodium ethoxide and sodium or potassium *t*-butoxide in solution in the corresponding alcohols reacted with the ester (I) to give deep-red solutions from which, after acidification, varying yields (depending upon the reaction time) of the unsaturated ester could be isolated. The best results were obtained with potassium *t*-butoxide in *t*-butyl alcohol which, after forty-five minutes at room temperature, produced a 52% yield of the unsaturated ester (II). Sodium triphenylmethyl in ether solution also reacts quite rapidly with the ester (I); however, the reaction products were mainly a tar and triphenylmethane with only a small amount of the ester (II). The mechanism proposed by Hauser and Breslow[1] for dehydration with basic reagents seems to be a satisfactory explanation for the dehydration of I with potassium *t*-butoxide.

Diethyl pinacolonylidenemalonate II is a yellow liquid that reacts readily with bromine in carbon tetrachloride and dilute potassium permanganate. Alkaline reagents cause it to polymerize with the production of a red coloration similar to that produced by the action of these reagents on the tartronic ester (I). If the traces of bromide remaining from its preparation are removed by refluxing this unsaturated ester with Raney nickel, it absorbs hydrogen extremely rapidly. In fact, with an active Raney nickel catalyst it was found that the hydrogenation of the ester was practically complete at room temperature before the steel hydrogenation bomb was disconnected from the hydrogen storage tank. The hydrogenation mixture generally was heated to 100° for thirty minutes to ensure completed hydrogenation. Even under these mild conditions a small amount (5–10%) of ethyl pinacolonylacetate, $(CH_3)_3CCOCH_2CH_2COOC_2H_5$, resulting from the hydrogenolysis of the malonic ester (III), was always formed.

The disubstituted malonic esters (IV), in which R is ethyl, allyl and isoamyl, were prepared readily from III in yields of 78–90% of the theoretical. From these esters and urea the corresponding barbituric acids (V) were formed. The acids in which R is ethyl and allyl were prepared in an ethyl alcohol solution with sodium ethoxide as the condensing agent and the yields in both cases amounted to about 40% of the theoretical. In the case of the isoamyl derivative the barbituric acid was prepared in an isopropyl alcohol solution with sodium isopropoxide as the condensing agent. In this solvent, which is much less efficient for alcoholysis of the malonic ester than is ethyl alcohol, the yield of the barbiturate amounted to 73%.

A very peculiar solubility behavior of each of the sodium salts of these barbituric acids should be noted. When the aqueous solution of the residue that remained after the removal of the alcohol from the reaction mixture in which the barbituric acid was prepared, was extracted with ether, about one-third of the sodium barbiturate passed from the water to the ether layer. This ether-soluble sodium compound was soluble in ethyl acetate and could be recrystallized from an ethyl acetate–ligroin mixture. It was converted by dilute acid into the same barbituric acid that was precipitated when the aqueous alkaline solution of the reaction mixture was acidified.

Pharmacological Data. The pinacolonylbarbituric acids (V) are being studied pharmacologically by Mr. E. E. Swanson of the Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana, who has kindly furnished a preliminary report that is summarized in Table I. Corresponding data for amytal (Sodium Isoamyl Ethyl Barbiturate, Lilly) are included for comparison. The values were determined intraperitoneally in white rats. It may be seen from this table that these pinacolonylbarbituric acids have higher minimum anesthetic doses (M. A. D.), much longer durations of anesthesia, higher minimum lethal doses (M. L. D.) and consequently lower therapeutic indices than does amytal.

Table I

Pharmacological Data for Pinacolonylbarbituric Acids, $(CH_3)_3CCOCH_2CRCONHCONHCO$

Compound	M. A. D., mg./kg.	Duration of anesthesia, min.	M. L. D., mg./kg.	Therapeutic index, M. L. D./ M. A. D.
R is ethyl	225	780	365	1.62
R is allyl	250	900	400	1.60
R is *i*-amyl	400	560	600	1.50
Amytal	90	200	200	2.22

Experimental

Diethyl Pinacolonyltartronate (I).—A mixture of 37.5 g. (0.375 mole) of pinacolone and 37.5 g. (0.215 mole) of oxomalonic ester[2] was sealed in a glass tube and heated for

(1) Hauser and Breslow, This Journal, **62**, 3344 (1940).

(2) "Organic Syntheses" Coll. Vol. I, 1932, p. 261.

TABLE II

SUBSTITUTED PINACOLONYLMALONIC ESTERS, $(CH_3)_3CCOCH_2CR(COOC_2H_5)_2$

R is	Formula	B. p., °C. (1 mm.)	Yield, %	d^{25}_4	$n^{25}D$	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Ethyl	$C_{15}H_{26}O_5$	106–107	78	1.0112	1.4395	62.9	9.2	62.8	9.4
Allyl	$C_{16}H_{26}O_5$	107–108	90	1.0111	1.4445	64.4	8.8	64.0	8.9
Isoamyl	$C_{18}H_{32}O_5$	114–115	78	0.9792	1.4415	65.8	9.8	65.7	10.0

seven hours at 160° in an electric furnace. Four such tubes were cooled and opened and the yellow liquid distilled at atmospheric pressure to remove excess pinacolone.

The residue was distilled under diminished pressure. After some unchanged oxomalonic ester (20 g.) had come over, 170 g. (83% on basis of unrecovered oxomalonic ester) of diethyl pinacolonyltartronate, b. p. 111–112° (1 mm.); $n^{25}D$ 1.4420; d^{25}_4, 1.0759 was obtained.

Anal. Calcd. for $C_{13}H_{22}O_6$: C, 56.9; H, 8.1. Found: C, 56.9; H, 8.1.

Variations of temperatures (25 to 225°) and reaction times (four to forty hr.) caused no improvement of the yields. Catalysts such as piperidine acetate, aniline hydrobromide and acetamide in glacial acetic acid were likewise without beneficial effect.

Diethyl Pinacolonylidenemalonate (II). Phosphorus Tribromide Method.—A solution of 20 g. of diethyl pinacolonyltartronate and 15 g. of phosphorus tribromide in 50 ml. of xylene was heated under reflux until bubbles of vapor began to rise through the liquid. After the first vigorous reaction slowed down, refluxing was continued until a noticeable darkening of the solution occurred (about ten minutes).

The solution was cooled and 30 ml. of absolute alcohol was added through the condenser while the flask was rotated to ensure mixing. After the resulting alcoholic solution had been refluxed for one hour, the excess alcohol was distilled off.

The remaining liquid was washed twice with 25 ml. of water and the washings were extracted once with 20 ml. of ether. The solvents were distilled and 14.6 g. (78%) of the diethyl pinacolonylidenemalonate, b. p. 105–106° (1 mm.); $n^{25}D$ 1.4445; d^{25}_4 1.0378, was obtained.

Anal. Calcd. for $C_{13}H_{20}O_5$: C, 60.9; H, 7.9. Found: C, 60.5; H, 8.1.

Potassium *t*-Butoxide Method.—To a solution of 3.9 g. (0.1 g. atom) of potassium in 100 ml. of absolute *t*-butyl alcohol was added 27.4 g. (0.1 mole) of diethyl pinacolonyltartronate. After the solution had stood at room temperature with occasional shaking for forty-five minutes, hydrogen chloride dissolved in ether was added until the color of the solution changed from red to yellow.

The ether layer was washed with water, dried and distilled. A yield of 12.2 g. (52%) of the pinacolonylidenemalonic ester was obtained and 2.9 g. (10%) of tartronic ester was recovered.

Hydrogen Bromide Method.—A solution of 15 g. (0.055 mole) of tartronic ester in 50 ml. of benzene was chilled in an ice–salt-bath and saturated with dry hydrogen bromide. The solution was stoppered tightly and allowed to stand for three days at room temperature. Benzene and water were distilled off at atmospheric pressure. When the residue was heated, hydrogen bromide was evolved and 9.6 g. (74% of theoretical on the basis of unrecovered ester) of the unsaturated ester was obtained; after this material had distilled 1.1 g. of the unchanged tartronic ester was recovered.

Diethyl Pinacolonylmalonate.—The last traces of bromide were removed from the pinacolonylidenemalonic ester by refluxing at 0.1 mm. with 5 g. of Raney nickel; then 71 g. was hydrogenated using 5 g. of Raney nickel in a steel reaction vessel of 270-ml. capacity. Although hydrogenation was practically complete in five minutes at room temperature and approximately 100 atmospheres of pressure, the reaction was heated to 100° for an additional thirty minutes. No more than 5% of the total amount of hydrogen absorbed was taken up at this higher temperature. Distillation gave 4.4 g. (9%) of ethyl pinacolonylacetate, b. p. 104–105° (11 mm.); $n^{25}D$ 1.4298; d^{25}_4 0.9627, and 63.5 g. (88%) of diethyl pinacolonylmalonate, b. p. 106–107° (1 mm.); $n^{25}D$ 1.4360; d^{25}_4 1.0207.

Anal. Calcd. for diethyl pinacolonylmalonate, $C_{13}H_{22}O_5$: C, 60.44; H, 8.59. Found: C, 60.12; H, 8.59.

Anal. Calcd. for ethyl pinacolonylacetate, $C_{10}H_{18}O_3$: C, 64.57; H, 9.74. Found: C, 64.71; H, 9.80.

Substituted Pinacolonylmalonic Esters.—To a solution of 0.1 g. atom of sodium in 50 ml. of absolute alcohol was added 0.1 mole of diethyl pinacolonylmalonate and 0.11 mole of the alkyl bromide, and the resulting solution was refluxed until neutral. The alcohol was then removed by distillation and the ester residue treated with water to dissolve the inorganic salt. After separation of the water layer the ester layer was dried and distilled. The properties of the esters that were prepared are summarized in Table II.

Pinacolonylbarbituric Acids.—The barbituric acids were prepared by the standard procedure,[3] using sodium ethoxide in ethyl alcohol for the ethyl- and allyl-substituted malonic esters and sodium isopropoxide in isopropyl alcohol for the isoamyl compound. The melting points, yields and analyses of these barbituric acids are summarized in Table III. It is apparent that the use of isopropyl alcohol as the condensing medium greatly improves the yield of the barbituric acid. About one-third of the yield of the barbituric acid in each case appeared as the sodium salt along with the unchanged malonic ester in the ether extract of the aqueous alkaline solution of the reaction residue that remained after the evaporation of the alcohol in which the reaction was run. This ether soluble salt could be recrystallized from an ethyl acetate–ligroin (b. p. 60–68°) mixture using an ice–salt-bath; if, however, a dry-ice-bath was used the salt came out of this solvent in a crystalline form that did not redissolve when the solvent was warmed. The ether soluble salt upon acidification yielded the same barbituric acid as was obtained from the acidification of the aqueous alkaline extract of the reaction mixture.

(3) Fischer and Dilthey, *Ann.*, **335**, 335 (1904).

TABLE III

PINACOLONYLBARBITURIC ACIDS, $(CH_3)_3COCH_2C(R)CONHCONHCO$

R is	Formula	M. p., °C.[a]	Yield, %	N Analyses, % Calcd.	Found
Ethyl	$C_{12}H_{18}O_4N_2$	204–205	42	11.0	11.1
Allyl	$C_{13}H_{18}O_4N_2$	190–191	40	10.5	10.5
Isoamyl	$C_{15}H_{24}O_4N_2$	209–210	73	9.5	9.4

[a] These melting points were determined on material that had been dried at 100° and under 15 mm. pressure.

Summary

The preparation of three pinacolonylbarbituric acids, $(CH_3)_3CCOCH_2CRCONHCONHCO$, in which R is ethyl, allyl and isoamyl, is described. These acids are prepared from the corresponding malonic esters which are obtained from a series of reactions that start with pinacolone and oxomalonic ester.

Each of these new barbituric acids has a higher minimum anesthetic dose, a much longer duration of action and a higher minimum lethal dose than does amytal, the 5-ethyl-5-isoamylbarbituric acid.

MADISON, WISCONSIN RECEIVED JUNE 24, 1941

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, No. 249]

The Rates of Reaction of Diacetone Glucose, Diacetone Galactose and Diacetone Sorbose with Triphenylchloromethane in Pyridine Solution[1]

BY R. C. HOCKETT, H. G. FLETCHER, JR., AND J. B. AMES

Triphenylchloromethane has found many uses in the investigation of carbohydrates because its property of only partially etherifying most polyalcohols, when restricted quantities of agent are applied in pyridine solution, has added a number of compounds to the list of partially substituted sugars which are necessary for synthesis of saccharides and correlation of properties with structure.[2]

A widespread erroneous impression that the etherification is confined entirely to primary hydroxyl groups has been shown groundless by the preparation of trityl ethers from such compounds as α-methyl-L-fucopyranoside which contains only secondary groups[3] as well as by preparation of ditrityl ethers from several glycosides[4] which contain only one primary group. Despite these reports, the use of trityl chloride[5a] as an agent for detecting primary alcohol structures continues to be reported.[5b]

The frequency with which partially tritylated sugar derivatives are encountered is probably due to two factors: the relatively low activity of trityl chloride as compared with many acylating agents and the relatively great crystallizing tendencies of trityl ethers. Even if acetyl chloride shows the same degree of "preference" for the primary hydroxyl group that is shown by trityl chloride (and it may), the fact has remained obscured by the poor crystallizing properties of monoacetates in the sugar group.

This "preference" of trityl chloride for the primary hydroxyl group is most simply interpreted by the hypothesis that such groups generally react to break the hydrogen–oxygen bond more rapidly than do most secondary or tertiary alcohols. The hypothesis is merely extended here to the reaction with triphenylchloromethane from the well-known cases of hydrogen displacement by sodium and rates of esterification by oxygen acids. If "selectivity" is regarded as the ratio between two reaction velocities, it will be recognized that only under favorable conditions can a reaction be depended upon to show which type of group is present. Either the reaction velocities must be very widely separated so that the mere presence or absence of reaction under given conditions may be depended upon to give the correct answer, or else definite knowledge must be had concerning the actual reaction rates of various types of hy-

(1) A preliminary study with diacetone glucose and diacetone galactose was carried out by Mr. J. B. Ames as a thesis for the degree of Bachelor of Science. The measurements were refined and extended to the sorbose derivative by Mr. H. G. Fletcher, Jr., as a thesis for the same degree. A paper covering this work was read at the Boston Meeting of the American Chemical Society in September, 1939.

(2) Helferich, *Z. angew. Chem.*, **41**, 871 (1928).

(3) Hockett and Hudson, THIS JOURNAL, **56**, 945 (1934); *cf.* Verkade, *Rec. trav. chim.*, **57**, 824 (1938).

(4) Jackson, Hockett and Hudson, THIS JOURNAL, **56**, 947 (1934).

(5) (a) This convenient abbreviation for triphenylchloromethane has become widely accepted; (b) von Vargha, *Ber.*, **68**, 18 (1935); Zemplén, Gerecs and Illés, *ibid.*, **71B**, 590 (1938).