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THE IDENTIFICATION OF ALKYLBARBITURIC ACIDS

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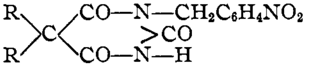
The use of *p*-nitrobenzyl bromide as a reagent for the identification of acids was proposed by Reid.[1] Nearly one hundred acids were tested of which about 90 gave solid esters melting at convenient temperatures. Although Reid had in mind the carboxylic and sulfonic acids, among other acids tested were saccharin, uric and cyanuric acids.[2] Of these the last two gave compounds which melted above 280° or not at all.

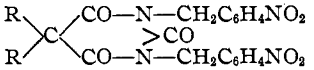
Barbituric acid and its derivatives, in which the acidic hydrogens are capable of replacement by sodium, offered a good chance to see if the reagent could find application here. Especially of interest was the possibility of directly substituting an organic radical in the place of the imide hydrogens, the success of which has, to our knowledge, been recorded in only one instance. Fabre[3] showed that veronal (5,5-diethylbarbituric acid) condenses with two molecules of xanthydrol in the presence of acetic acid to form an insoluble 1,3-disubstituted veronal. We have now succeeded in effecting a similar condensation with *p*-nitrobenzyl chloride in the presence of sodium carbonate (or equivalent base). Acids of the veronal type (both imide hydrogens present) readily give compounds containing one or two nitrobenzyl groups. These are easily soluble in alkali if only one imide hydrogen is replaced or insoluble when both hydrogens are substituted by nitrobenzyl groups.

The compounds formed may be represented by the following probable structural formulas: (A) for the mono-substituted derivative, and (B)



$$\begin{matrix}\mathrm{R}\\ \mathrm{R}\end{matrix}\!>\!\mathrm{C}\!<\!\begin{matrix}\mathrm{CO{-}N{-}CH_2C_6H_4NO_2}\\ >\mathrm{CO}\\ \mathrm{CO{-}N{-}H}\end{matrix}$$

(A)



$$\begin{matrix}\mathrm{R}\\ \mathrm{R}\end{matrix}\!>\!\mathrm{C}\!<\!\begin{matrix}\mathrm{CO{-}N{-}CH_2C_6H_4NO_2}\\ >\mathrm{CO}\\ \mathrm{CO{-}N{-}CH_2C_6H_4NO_2}\end{matrix}$$

(B)

for the di-substituted derivative (R = alkyl).

Procedure

The procedure is essentially as described in the previous papers. With compounds suspected of having 2 replaceable hydrogens, *i. e.*, those of the veronal type, about 0.5 g. (approx. 1 equivalent) is taken. To this, in a small round-bottomed flask, is added about 0.25 g. of sodium carbonate and 5 cc. of water. The mixture is warmed to dissolve the acid compound and 0.85 g. of *p*-nitrobenzyl chloride, or equivalent amount of bromide (hereafter designated as reagent), and 10 cc. of alcohol are added. These proportions also hold for compounds of the type where only one methylene hydrogen and one N-hydrogen are still replaceable, and are the proportions generally used for

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[1] Reid; Lyman and Reid; Lyons and Reid, THIS JOURNAL, **39**, 124, 701, 1727 (1917).

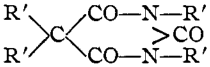
[2] Lyons and Reid, *ibid.*, **39**, 1749 (1917).

[3] Fabre, *J. pharm. chim.*, **26**, 241 (1922).

totally unknown substances. However, if the compound is suspected of having only 1 replaceable hydrogen the amounts of carbonate and reagent taken are only half of that given above and when there are 3 replaceable hydrogens the amounts of carbonate and reagent are increased by one-half. The mixture thus obtained is refluxed for about an hour. If the *p*-nitrobenzyl derivative precipitates during the course of the reaction, it is filtered hot on a Büchner funnel. If no precipitate forms, a small sample is cooled. If it still does not precipitate, hot water is added until a cloudiness persists. Cooling then usually gives the desired substance slightly contaminated with some unreacted reagent. The precipitate is washed with water, and more carefully with alcohol and ether and recrystallized as described below.

The various crops of crystals are designated as 1st 1st, 1st 2nd and 2nd 1st, meaning first crystallization first crop and first crystallization second crop, etc. The 2nds were in most instances discarded since high purity rather than quantitative yield was desired. All melting points recorded are uncorrected.

***p*-Nitrobenzyl Derivatives of Barbituric Acid.**—There are four replaceable hydrogens in barbituric acid, making it possible, at least theoretically, to prepare derivatives containing 1, 2, 3 or 4 nitrobenzyl groups. Using 4 equivalents of reagent to one of the acid gave a yellow substance which had no melting point; it charred and burned up. The substance is insoluble in alcohol and ether but is somewhat soluble in chloroform. It is also insoluble in alkali. It probably contains 4 *p*-nitrobenzyl groups and may be represented by the following structural formula



$R' = (—CH_2C_6H_4NO_2)$

Using less than 4 equivalents of reagent, a mixture of substances was obtained. Besides an insoluble substance having no melting point, a substance soluble in alkali which melted at about 265° was obtained from the mother liquor.

1,3,5,5-Tetra-*p*-nitrobenzylbarbituric Acid.—0.82 g. of barbituric acid dihydrate (1 equivalent) was dissolved in 5 cc. of water containing 0.8 g. of sodium hydroxide (does not dissolve in sodium carbonate solution unless large volume is used). To this were added 10 cc. of alcohol and 3.4 g. (4 equivalents) of reagent. The mixture was refluxed for one hour. It was cooled and the insoluble lemon yellow precipitate was filtered, washed with water, alcohol and ether. The weight was 2 g. It charred when heated. From the mother liquor, on concentration, only some reagent was obtained.

Below are given in tabular form all data relating to the preparation of the *p*-nitrobenzyl derivatives of barbituric acid and 15 of its alkyl derivatives, and the analyses of several such compounds.

TABLE Ia

EXPERIMENTAL DATA

	"Barbituric acid"	Acid taken, g.	Reagent (R), g.	Na_2CO_3, g.	1st 1st, g.	Final m. p., °C.
1	"Barbituric"	0.82	3.4	0.8	2.0	. . .
2	"Barbituric"	.92	1.7	.53	0.5	264
3	"Veronal"	.92	1.7	.53	2.0	192
4	"Veronal"	.92	0.86	.27	0.6[a]	192[a]
5	"Ipral"	.49	0.86	.27	0.8	160
6	"Dial"	1.04	1.71	.53	2.0	190[b]
7	"Neonal"	0.53	0.86	.27	0.7	146
8	"Amytal"	1.1	1.7	.53	.6	138
9	"Butalone"	0.56	0.86	.27	.8	169

TABLE Ia (*Concluded*)

	"Barbituric acid"	Acid taken, g.	Reagent (R), g.	Na_2CO_3, g.	1st 1st, g.	Final m. p., °C.
10	"Luminal"	.58	.86	.27	.6	182
11	5-Ethyl-5-*n*-amyl-	.55	.86	.27	.7	131
12	1-Methyl-5-hexyl-	.47	.68	.2	.2	139
13	5-*Iso*propyl-	.56	1.7	.53	.35	187
14	5-*n*-Butyl-	.3	0.83	.27	.5	180[c]
15	5-Ethyl-1,3-diphenyl-	1.5	1.06	.2	1.0	218
16	N-Methyl-"Veronal"	1.0	0.86	.27	1.5	104
17	N-Ethyl-"Veronal"	1.06	.86	.27	1.5	69[d]
18	N-Phenyl-"Veronal"	0.65	.43	.14	0.5	133

[a] 0.3 g., 148°C. Obtained from the mother liquor, after filtering off the di-(R′) derivative, by adding hydrochloric acid and concentrating.

[b] Distinguished from the di-(R′) derivative of veronal by its being acted upon by bromine in chloroform.

[c] Use of 3 equivalents of R′ gave an identical compound.

[d] Reaction mixture crystallized with difficulty.

TABLE Ib

EXPERIMENTAL DATA

	Crystallized from	Resultant product, R′ = *p*-nitrobenzyl Formula	 Name, -Barbituric acid
1	...	$C_4O_3N_2R'_4$	1,3,5,5-Tetra-(R′)-
2	H_2O	$C_4H_{4-x}O_3N_2R'_x$	......
3	$CHCl_3$-C_2H_5OH[a]	$C_8H_{10}O_3N_2R'_2$	1,3-Di-(R′)-5,5-diethyl-
4	H_2O	$C_8H_{11}O_3N_2R'$	1-(R′)-5,5-diethyl-
5	$CHCl_3$-C_2H_5OH[a]	$C_9H_{12}O_3N_2R'_2$	1,3-Di-(R′)-5-ethyl-5-*iso*propyl-
6	$CHCl_3$-C_2H_5OH[a]	$C_{10}H_{11}O_3N_2R'_2$	1,3-Di-(R′)-5,5-diallyl-
7	$CHCl_3$-C_2H_5OH[a]	$C_{10}H_{10}O_3N_2R'_2$	1,3-Di-(R′)-5-ethyl-5-butyl-
8	$CHCl_3$-C_2H_5OH[a]	$C_{11}H_{16}O_3N_2R'_2$	1,3-Di-(R′)-5-*iso*-amyl-5-ethyl-
9	$CHCl_3$-C_2H_5OH[a]	$C_{12}H_{10}O_3N_2R'_2$	1,3-Di-(R′)-5-ethyl-5-phenyl-
10	$CHCl_3$-C_2H_5OH[a]	$C_{11}H_{14}O_3N_2R'_2$	1,3-Di-(R′)-5-ethyl-5-butyl-
11	$CHCl_3$-C_2H_5OH[a]	$C_{11}H_{16}O_3N_2R'_2$	1,3-Di-(R′)-5-ethyl-5-*n*-amyl-
12	$CHCl_3$-C_2H_5OH[a]	$C_{11}H_{16}O_3N_2R'_2$	3,5-Di-(R′)-1-methyl-5-hexyl-
13	$CHCl_3$-C_2H_5OH[a]	$C_7H_7O_3N_2R'_3$	1,3,5-Tri-(R′)-5-*iso*propyl-
14	$CHCl_3$-C_2H_5OH[a]	$C_8H_9O_3N_2R'_3$	1,3,5-Tri-(R′)-5-*n*-butyl-
15	$CHCl_3$-C_2H_5OH[a]	$C_{18}H_{15}O_3N_2R'$	5-(R′)-5-ethyl-1,3-diphenyl-
16	C_2H_5OH	$C_9H_{13}O_3N_2R'$	1-(R′)-3-methyl-5,5-diethyl-
17	C_2H_5OH	$C_{10}H_{15}O_3N_2R'$	1-(R′)-3,5,5-triethyl-
18	C_2H_5OH	$C_{14}H_{15}O_3N_2R'$	1-(R′)-3-phenyl-5,5-diethyl-

[a] Dissolved in chloroform and precipitated by the addition of alcohol.

Analyses of several derivatives were performed by Mr. Edward G. Jones, using the Forster modification of the Kjeldahl method.

Anal. 1,3-Di-*p*-nitrobenzyl-5,5-diethylbarbituric acid. Subs., 0.2302, 0.2455: 20.66, 21.52 cc. of 0.1 *N* acid. Calcd. for $C_{22}H_{22}O_7N_4$: N, 12.34. Found: N, 12.20, 12.27.

Anal. 1-*p*-Nitrobenzyl-3-phenyl-5,5-diethylbarbituric acid. Subs., 0.2120: 16.02 cc. of 0.1 *N* acid. Calcd. for $C_{21}H_{21}O_5N_3$: N, 10.63. Found: N, 10.56.

Anal. 3,5-Di-*p*-nitrobenzyl-1-methyl-5-hexylbarbituric acid. Subs., 0.1618: 13.10 cc. of 0.1 *N* acid. Calcd. for $C_{25}H_{28}O_7N_4$: N, 11.30. Found: N, 11.39.

Summary

p-Nitrobenzyl chloride is a useful reagent for the identification of alkyl barbituric acids. It reacts with these acids, in the presence of sodium carbonate, to form crystalline substitution products with definite melting points. It reacts not only with the imide hydrogens but also with the methylene hydrogens to give completely substituted derivatives.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORIES OF CORNELL COLLEGE AND THE UNIVERSITY OF IOWA]

FACTORS INVOLVED IN THE PREPARATION OF MERCURY DI-ISOBUTYL BY THE REACTION OF FRANKLAND AND DUPPA

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In connection with an investigation involving the preparation of the sodium alkyls, it became necessary to make a large quantity of mercury di-*iso*butyl.[1] The mercury dialkyls have been known since the time of Frankland and Duppa,[2] who prepared mercury dimethyl and mercury diethyl by the action of dilute sodium amalgam on the alkyl iodide in the presence of ethyl acetate. The preparation of mercury di-*iso*butyl by this reaction has been studied in some detail and the results are given in this paper.

Other dialkyls prepared by the same reaction include the di-*iso*butyl,[3] the di-octyl,[4] the di-*n*-butyl,[5] and the dipropyl and di-*iso*propyl derivatives.[6] More recently, Marvel and Gould[7] have prepared the methyl, ethyl, *n*-propyl, *iso*propyl and *n*-butyl mercury di-alkyls through the use of the Grignard reagent with the mercuric halide, and Marvel and Calvery[8] the di-*sec.*-butyl, di-*sec.*-octyl, di-*tert.*-butyl and di-*tert.*-amyl derivatives.

Discussion of Experimental Work

In developing the best conditions for the preparation of mercury di-*iso*butyl by the Frankland and Duppa reaction, a number of variables

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[1] It is needless to add that mercury di-*iso*butyl is extremely poisonous. The compound is volatile and ill effects are not noticed at the time. Symptoms of poisoning include severe headaches, disorder of the digestive tract and a sensitivity both toward the odor and taste of the compound in the atmosphere of the laboratory. Continued exposure to the action of the mercury alkyls may result in a degeneration of the central nervous system and brain.

[2] Frankland and Duppa, *J. Chem. Soc.*, **16**, 415 (1863); *Ann.*, **130**, 104 (1864).

[3] Cahours, *Compt. rend.*, **76**, 133 (1873).

[4] Eichler, *Ber.*, **12**, 1880 (1879).

[5] Tiffeneau, *Bull. soc. pharmacol.*, **28**, 65 (1921).

[6] Goret, *ibid.*, **29**, 197 (1922).

[7] Marvel and Gould, THIS JOURNAL, **44**, 153 (1922).

[8] Marvel and Calvery, *ibid.*, **45**, 820 (1923).