TABLE II

5-(2 OR 3-OXOALKYL)-2 THIOHYDANTOIN ISONICOTINOYLHYDRAZONES

R—C(=NNHCOC$_5$H$_4$N)—(CH$_2$)$_n$—CH—C(=O)—NH—C(=S)—NH

| Compound R | n | M.p., °C. (cor.) | Solvent | Yield, %[a] | Nitrogen, % Calcd. | Nitrogen, % Found | Sulfur, % Calcd. | Sulfur, % Found |
|---|---|---|---|---|---|---|---|---|
| *n*-Butyl | 2 | 237.5–238.6 | DMF–$H_2O$ | 77 | 20.16 | 19.99 | 9.23 | 9.35 |
| *n*-Amyl | 2 | 228.2–229.4 | DMF–$H_2O$ | 86 | 19.38 | 19.30 | 8.87 | 9.05 |
| *n*-Butyl | 1 | 199.1–202.2 | $CH_3OH$ | 52 | 21.01 | 20.64 | 9.62 | 9.38 |
| *n*-Amyl | 1 | 101[b] | $CH_3OH$ | 50 | 20.16 | 20.22 | 9.23 | 9.18 |
| *n*-Hexyl | 1 | 128–140[c] | $C_2H_5OH$–$H_2O$ | 35 | 19.38 | 19.28 | 8.87 | 8.65 |
| *n*-Heptyl | 1 | 196.8–197.5 | *i*-$C_3H_7OH$ | 61 | 18.65 | 18.51 | | |
| *n*-Octyl | 1 | 185–187 | $C_2H_5OH$ | 64 | 17.98 | 18.30 | 8.23 | 8.61 |

[a] The yields are based on weights of products of analytical purity. [b] These are uncor. m.p.'s. [c] The product melts in this range, solidifies and remelts at 180–185° (uncor.).

containing 3 ml. of triethylamine there was added dropwise with stirring 63 g. of 1-hepten-3-one while the temperature was kept at 10°. The whole was left overnight and concentrated *in vacuo*. The residue, which solidified on cooling, was slurried with pentane and dried; wt. 130 g. A sample was purified by crystallization from ether and then pentane, m.p. 66–68°.

*Anal.* Calcd. for $C_{16}H_{27}NO_6$: N, 4.25. Found: N, 4.58.

One hundred and ten grams of the ester was boiled under reflux for four hours with 650 ml. of concentrated hydrochloric acid. The solution was taken to dryness, leaving a residue which was dissolved in water. The filtered solution was neutralized with ammonia to precipitate 38.5 g. of the amino acid; yield 62%. After recrystallization from water the compound melted at 122–125°.

*Anal.* Calcd. for $C_9H_{17}NO_3$: N, 7.48. Found: N, 7.67.

**2-Amino-5-oxodecanoic Acid.**—The adduct from 1-octen-3-one and ethyl acetamidomalonate was obtained as described above in 63% yield, m.p. 60–61° after crystallization from pentane.

*Anal.* Calcd. for $C_{17}H_{29}NO_6$: N, 4.08. Found: N, 4.40.

The acid was obtained by hydrolysis of the ester as described above; yield, 57%. It melted at 132–135° after recrystallization from water.

*Anal.* Calcd. for $C_{10}H_{19}NO_3$: N, 6.96. Found: N, 6.97.

**5-(2 or 3-Oxoalkyl)-2-thiohydantoins.**—The thiohydantoins were prepared by the method described previously.[15] The compounds are listed in Table I.

**Isonicotinoylhydrazones of the 5-(Oxoalkyl)-2-thiohydantoins.**—An example of the method is given for the hydrazone of 5-(2-oxoheptyl)-2-thiohydantoin.

The ketone (10.65 g.) and 5.48 g. of isonicotinoyl hydrazide in 200 ml. of methanol was heated under reflux for 15 hours. The methanol was removed *in vacuo* and the residue was slurried with hexane whereupon it crystallized. After two crystallizations from methanol, once with the aid of charcoal, the product melted at 101°. The compounds so prepared are listed in Table II.

The 5-(3-oxoalkyl)-2-thiohydantoins formed hydrazones which separated from the reaction mixture directly. These were filtered and crystallized from aqueous dimethylformamide as indicated in Table II.

(15) M. Jackman, *et al.*, THIS JOURNAL, **70**, 2884 (1948).

RENSSELAER, N. Y.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

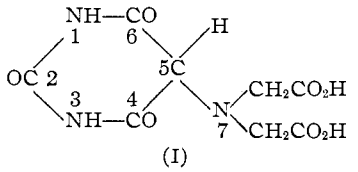
# Preparation of 1-Alkyluramil-7,7-diacetic Acids

BY ALVIN STEIN,[1] HARRY P. GREGOR AND PAUL E. SPOERRI

RECEIVED JULY 13, 1956

A series of 1-alkyluramil-7,7-diacetic acids, up to and including 1-octyluramildiacetic acid, has been prepared. The route to these compounds, starting from substituted malonic esters and ureas, is described.

The barbituryl derivative I of iminodiacetic acid, uramil-7,7-diacetic acid, was shown by Schwarzenbach[2] to form the most stable chelates




(I)

known with the alkali metals. Our interest in this phenomenon prompted the synthesis of a number of derivatives of I; this paper describes procedures involving condensation of substituted ureas with malonic acid or its derivatives to the corresponding barbituric acids, conversion of these to 5-aminobarbituric acids (uramils) and alkylation with chloroacetic acid to the final products.

**1-Alkylbarbituric Acids.**—Although an imposing number of 5,5-disubstituted barbituric acids (barbiturates) have been prepared, only a few N-alkyl derivatives unsubstituted on the methylene carbon have been investigated.[3–7] The majority of the latter compounds had been made by the Biltz and Wittek[8] technique of condensing malonic acid and an alkylurea with acetic anhydride in acetic acid.

(1) A portion of this work is abstracted from the Dissertation of Alvin Stein, submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry at the Polytechnic Institute of Brooklyn, June, 1956.

(2) G. Schwarzenbach, E. Kampitsch and R. Steiner, *Helv. Chim. Acta*, **29**, 364 (1946).

(3) E. Grimaux, *Ber.*, **12**, 378 (1879).

(4) A. Michael, *J. prakt. Chem.*, **2**, 35, 456 (1887).

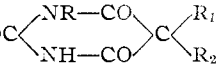
(5) H. Biltz and T. Hamburger, *Ber.*, **49**, 635 (1916).

(6) E. Mulder, *ibid.*, **12**, 465 (1879).

(7) J. R. Wood and A. E. Anderson, *J. Chem. Soc.*, **95**, 979 (1909).

(8) H. Biltz and H. Wittek, *Ber.*, **54B**, 1035 (1921).

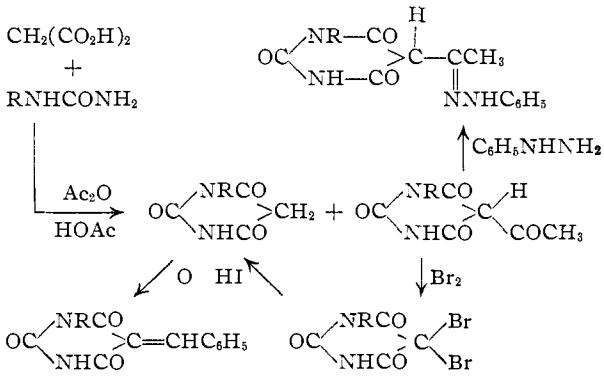
TABLE I

1-ALKYLBARBITURIC ACIDS, 5-BENZAL DERIVATIVES AND 1-ALKYLURAMILS 

| R | $R_1$ | $R_2$ | Yield, % | Composition | M.p.,[a] °C. | Analyses,[b] % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Nitrogen Calcd. | Nitrogen Found |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $C_4H_9$ | H | H | 65 | $C_8H_{12}N_2O_3$ | 109–110[c] | 52.16 | 52.03 | 6.57 | 6.65 | 15.21 | 15.08 |
| *i*-$C_3H_7$ | H | H | 68 | $C_7H_{10}N_2O_3$ | 108–109.5[d] | 49.40 | 49.35 | 5.92 | 5.99 | 16.47 | 16.41 |
| $C_8H_{17}$ | H | H | 83 | $C_{12}H_{20}N_2O_3$ | 131.5–132.5 | 59.98 | 60.09 | 8.39 | 8.52 | 11.66 | 11.72 |
| $C_{12}H_{25}$ | H | H | 93 | $C_{16}H_{28}N_2O_3$ | 124–125 | 64.83 | 64.88 | 9.52 | 9.44 | 9.45 | 9.38 |
| $CH_3$ | H | $NH_2$ | 60–75 | $C_5H_7N_3O_3$ | 253–256 d.[f] | 38.21 | 38.14 | 4.42 | 4.45 | 26.74 | 26.61 |
| $C_4H_9$ | H | $NH_2$ | 65–75 | $C_8H_{13}N_3O_3$ | 221 d. | 48.23 | 48.33 | 6.58 | 6.64 | 21.10 | 20.92 |
| $C_8H_{17}$ | H | $NH_2$ | 75 | $C_{12}H_{21}N_3O_3$ | 202 d. | 56.45 | 56.59 | 8.29 | 8.34 | 16.46 | 16.33 |
| *i*-$C_3H_7$ | .. | $CHC_6H_5$ | | $C_{14}H_{14}N_2O_3$ | 169–170 | | | | | 10.85 | 10.76 |
| $C_8H_{17}$ | .. | $CHC_6H_5$ | | $C_{19}H_{24}N_2O_3$ | 143–144.5 | | | | | 8.53 | 8.49 |
| $C_{12}H_{25}$ | .. | $CHC_6H_5$ | | $C_{23}H_{32}N_2O_3$ | 134.5–136 | | | | | 7.29 | 7.24 |
| $C_3H_7$ | H | H | 56 | $C_7H_{10}N_2O_3$ | 105–106[e] | | | | | | |
| $C_6H_{13}$ | H | H | 94 | $C_{10}H_{16}N_2O_3$ | 131–132 | | | | | 13.20 | 13.21 |
| $C_7H_{15}$ | H | H | 98 | $C_{11}H_{18}N_2O_3$ | 133.5–134 | | | | | 12.38 | 12.55 |
| $C_2H_5$ | H | $NH_2$ | 71 | $C_6H_9N_3O_3$ | 225 d.[g] | | | | | 24.55 | 24.57 |
| *i*-$C_3H_7$ | H | $NH_2$ | 77 | $C_7H_{11}N_3O_3$ | 222 d. | | | | | 22.69 | 22.70 |
| $C_3H_7$ | H | $NH_2$ | 64 | $C_7H_{11}N_3O_3$ | 217 d. | | | | | 22.69 | 22.83 |
| $C_6H_{13}$ | H | $NH_2$ | 45 | $C_{10}H_{17}N_3O_3$ | 216 d. | | | | | 18.49 | 18.31 |
| $C_7H_{15}$ | H | $NH_2$ | 54 | $C_{11}H_{19}N_3O_3$ | 205 d. | | | | | 17.42 | 17.58 |

[a] All melting points uncorrected. [b] Analyses by Dr. K. Ritter, Basel, Switzerland. [c] Reference 11, m.p. 136–140°. [d] If dried in air, m.p. 88.5–91°; if vacuum dried, m.p. 108–109.5°. [e] Reference 11, m.p. 104°. [f] Lit. 272°dec. [g] Lit. 230°dec.

Attempts, here, to repeat the Biltz and Wittek synthesis led to highly colored and impure products, contrary to the literature description. Examination of the reaction product from methylurea and malonic acid showed it to be a mixture of the desired 1-methylbarbituric acid with 5-acetyl-1-methylbarbituric acid. A similar contamination with acetyl compound was observed when other alkylureas were condensed with malonic acid using acetic anhydride in acetic acid. The 5-acetyl-1-alkylbarbituric acids, however, could be converted to 1-alkylbarbituric acids by a series of known reactions involving treating the acetyl compound with bromine and reducing the resulting dibromo compound with hydriodic acid.[5]



Condensation of malonic ester with ureas using sodium in dry alcohol proved to be a more reliable technique for preparing pure alkylbarbituric acids, and modifications, as required, of the procedure of Dickey and Gray[9] served to make this the method of choice for all the acids reported in Table I.

It is interesting to note the discrepancy in melting point between 1-butylbarbituric acid prepared here by the sodium in alcohol method (109–110°) with that made by other workers[10] using acetic anhydride as condensing agent (136–140°); contamination with acetyl by-product may explain the higher melting point and range of the latter compound.

The 1-alkylbarbituric acids melt considerably lower than barbituric acid itself and are much more soluble in water or alcohol; alkylation of the nitrogen atom apparently diminishes the extent of inter-molecular hydrogen bonding. Alkylation of barbituric acids occurs readily only with reactive halides; thus, neither barbituric acid, 1-methylbarbituric acid nor 5,5-diethylbarbituric acid reacted with chloroacetic acid, while 3 equivalents of the very reactive *p*-nitrobenzylbromide reacted with 1-methylbarbituric acid to yield an alkali-insoluble product.

**1-Alkyluramils.**—The alkyluramils reported in Table I were made by modifications of the elegant method of Davidson and Epstein,[11] who treated an aqueous solution of barbituric acid with sodium nitrite and, without isolating the intermediate 5-nitroso compound, effected reduction to uramil with ammoniacal sodium hydrosulfite.

The 5-amino function was also introduced directly by using appropriately substituted malonic esters. Acetamidomalonic ester was condensed with 1-butyl- or 1-octylurea to the corresponding 7-acetyluramils, which were then hydrolyzed with acid to the uramils (attempted alkaline hydrolysis led to extensive decomposition); acetyl chloride, in turn, converted these uramils to their 7-acetyl derivatives, identical to the above compounds.

Ethyl phthalimidomalonate[12] reacted with urea

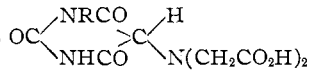
(9) J. B. Dickey and A. R. Gray, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 60.

(10) G. Bruckmann and S. D. Isaacs, THIS JOURNAL, **51**, 316 (1929).

(11) D. Davidson and E. Epstein, *J. Org. Chem.*, **1**, 305 (1936).

(12) T. B. Johnson and N. A. Shepard, THIS JOURNAL, **35**, 994 (1913).

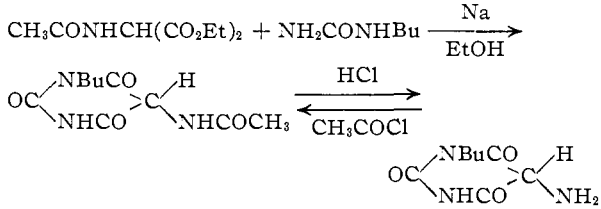
TABLE II

1-ALKYLURAMIL-7,7-DIACETIC ACIDS 

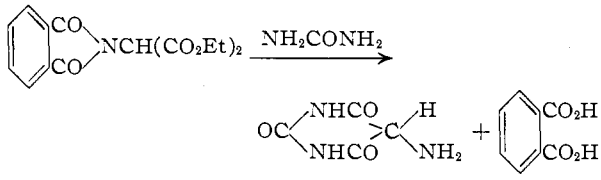
| R | Composition | M.p., °C. | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found | Neut. equiv. Calcd. | Neut. equiv. Found |
|---|---|---|---|---|---|---|---|---|---|---|
| $CH_3$ | $C_9H_{11}N_3O_7 \cdot H_2O$ | 176 d. | 37.10 | 37.20 | 4.50 | 4.64 | 14.40 | 14.42 | 145.6 | 142.5 |
| $C_2H_5$ | $C_{10}H_{13}N_3O_7$ | 202 d. | 41.80 | 41.94 | 4.56 | 4.53 | 14.63 | 14.46 | 143.6 | 145.2 |
| $C_4H_9$ | $C_{12}H_{17}N_3O_7 \cdot H_2O$ | 109.5–110.5 | 43.19 | 43.24 | 5.93 | 5.75 | 12.45 | 12.61 | 166.7 | 167.3 |
| $C_8H_{17}$ | $C_{16}H_{25}N_3O_7$ | > 80 d. | 51.74 | 51.55 | 6.79 | 6.95 | 11.32 | 11.32 | 185.5 | 182.3 |
| $C_6H_{13}$ | $C_{14}H_{21}N_3O_7$ | >114 d. | | | | | 12.24 | 12.34 | | |

to give a product which hydrolyzed during the reaction to phthalic acid and uramil in low yields.

The 1-alkyluramils crystallize from reducing solutions as white solids but on washing with water and standing in air become pink to red rapidly. They are amphoteric, dissolving in alkali (insoluble in bicarbonate) to form deep purple solutions or in



acid to light yellow solutions. The parent compound, uramil, decomposes at a considerably higher temperature and is much more insoluble than the 1-alkylated derivatives, effects which are probably attributable to diminished inter-molecular hydrogen bonding. The 7-acetyl derivatives, in contrast, do not turn red in air, melt at lower temperatures without decomposition and are stronger acids (decompose bicarbonates) and weaker bases (insoluble in mineral acids).



**1-Alkyluramil-7,7-diacetic Acids.**—Alkylation of iminodiacetic acid or methyl iminodiacetate with 5-bromobarbituric acid was attempted without success. However, 1-alkyluramils reacted with chloroacetic acid in warm alkaline solution, the characteristic deep purple color of uramils in alkaline solution disappearing as the alkylation of the 5-amino group with chloroacetic acid progressed. That the imino hydrogen atoms were not alkylated by chloroacetic acid was shown by treating 7-acetyl-1-butyluramil with chloroacetic acid under identical conditions, only starting materials being recovered at the end. The uramil-7,7-diacetic acids (Table II), precipitated by acidification of the reaction mixture with hydrochloric acid, were extensively contaminated with inorganic salts. In some cases, as many as eight recrystallizations from hot water failed to remove all salts, and each recrystallization was accompanied by great losses of product. Pure compounds finally were prepared by passing hot aqueous solutions of the impure acids through a cation exchange column (8% cross-linked sulfonic acid type) and concentrating the eluates in vacuum to precipitation. The acids assumed pink colorations on standing in air, alkaline solutions reddening more rapidly.

Titration of 0.002 *M* solutions of these acids with potassium hydroxide in 0.1 *M* potassium nitrate and in the presence of 0.02 *M* lithium chloride resulted in a marked lowering of the neutralization curve above *p*H 6 because of chelation with the substituted acids giving the same results within experimental error as the parent compound. The titer of aqueous solutions kept in glass containers changed remarkably on standing, presumably because of chelate formation with the alkaline earth metals present in the glass.

Alkaline decomposition[2] gave nitrilotriacetic acid, in harmony with structure (I) depicting two carboxymethyl groups on the exo-nitrogen atom.

## Experimental

**1-Alkylbarbituric Acids (Table I). A. Reaction of Malonic Acid and 1-Methylurea with Acetic Anhydride.**—To a flask protected from moisture there were added 5 g. (0.068 mole) of 1-methylurea, 8 g. (0.079 mole) of dry malonic acid and 15 ml. of glacial acetic acid. Solution was effected by warming to 60–70°, and 25 ml. (0.265 mole) of acetic anhydride was added from the separatory funnel over a 30-minute period, with frequent shaking. The temperature was raised to 90° in 3 hr. and kept at 90° for 3 more hr. The initially colorless solution became yellow, then orange and finally deep red in color. The solution was concentrated in vacuum to a sirup, 35 ml. of ethanol was added, and the mixture was warmed until solution occurred. On cooling with ice-water, 6.6 g. of bright yellow solid came down. After several recrystallizations from ethanol, the material still melted over a wide range. Eighty ml. of water was added to the yellow solid, the mixture was warmed several minutes, and the insoluble material was separated by filtration. The residue consisted of 2 g. of 5-acetyl-1-methylbarbituric acid melting at 190–197°, the melting point rising to 205–208° dec. after recrystallization from ethanol (lit.[3] 207° dec.); this compound yielded a phenylhydrazone melting at 219–220° dec. (lit.[3] 222° dec.). The aqueous filtrate was concentrated in vacuum until precipitation began and was then cooled in ice to give 2.8 g. of pale yellow 1-methylbarbituric acid which melted at 125–129° after recrystallization from alcohol (lit.[3] 132°.)

Modifications of the procedure, as follows, afforded pure 1-methylbarbituric acid with no 5-acetyl derivative. A solution of malonic acid (40 g., 0.395 mole) and methylurea (25 g., 0.340 mole) in 90 ml. of acetic acid at 60–70° was treated with 65 ml. (0.687 mole) of acetic anhydride in 1.3 hr., and the temperature was raised rapidly to 90° and kept at 90° for 3 hr. Proceeding then, as above, gave 24 g. (50%) of white 1-methylbarbituric acid, m.p. 130–131.5°, neut. equiv. 143.1 (calcd. 142.1). A solution of this compound in aqueous carbonate, when refluxed with an alcoholic solution of excess *p*-nitrobenzyl bromide, gave, on cooling and recrystallizing from acetone, an alkali-insoluble derivative, m.p. 298–300°.

*Anal.* Calcd. for $C_{26}H_{21}N_5O_9$: N, 12.80. Found: N, 12.91.

B. **Condensation of Malonic Ester and 1-Butylurea Using Sodium Ethylate.**—To 75 ml. of dry ethanol in a flask holding a reflux condenser protected with a drying tube there was added 3.0 g. (0.15 mole) of clean metallic sodium.

After the sodium had dissolved completely, there were added 19 ml. (20 g., 0.125 mole) of ethyl malonate and 14.5 g. (0.125 mole) of butylurea, and the solution was heated 7.5 hr. in an oil-bath at 120–130°. After 3 hr., a slightly frothy precipitate formed. Solution was effected by adding 13 ml. of concentrated hydrochloric acid plus 50 ml. of hot water and the cloudy solution was filtered. The filtrate was concentrated in vacuum until precipitation began, and the precipitate was filtered off and washed with water. Recrystallization from 450 ml. of boiling water plus some decolorizing carbon afforded 15 g. (65%) of pearly white flakes, m.p. 109–110° (lit.[10] 136–140°). The melting point was unchanged after recrystallization from alcohol.

Refluxing a methanolic solution with benzaldehyde yielded, on cooling, 55% of the 5-benzal derivative of 1-butylbarbituric acid, m.p. 153–154.5° (lit.[10] 154°).

**1-Alkyluramils.**—The following examples illustrate the methods employed for the synthesis of the alkyluramils.

**A. 1-Butyluramil. 1.**—To 9.2 g. (0.05 mole) of 1-butylbarbituric acid dissolved in 500 ml. of hot water there was added 3.8 g. (0.055 mole) of sodium nitrite and the resulting deep purple solution heated to boiling. A previously prepared solution of 30 g. of sodium hydrosulfite in 200 ml. of water and 50 ml. of concentrated ammonia was added, causing immediate decolorization. The solution was boiled vigorously for 35 minutes and then cooled in ice, yielding a white precipitate. The solid (6–6.5 g., 65–75% yield) was separated by suction filtration, washed well with water and dried in a vacuum oven during which time it became light pink. It was insoluble in cold water, cold methanol, hot ethanol and most organic solvents. Recrystallization of 2 g. of the compound from 130 ml. of boiling water plus 0.6 g. of sodium bisulfite afforded 1.5 g. of yellowish solid which slowly reddened in air, m.p. 216–221° dec. (placed in bath at 180° with heating rate of 6°/min.).

**2.**—Metallic sodium (0.53 g., 0.023 mole) was dissolved in 15 ml. of dry alcohol in a flask holding a reflux condenser protected from moisture with a calcium chloride tube. Butylurea (2.3 g., 0.02 mole) and acetamidomalonic ester (4.3 g., 0.02 mole) were added, and the flask heated 7 hr. in an oil-bath at 110°; precipitation occurred after 4 hr. The mixture was cooled in ice and 25 ml. of water was added, forming a yellow solution. Addition of 4 ml. of concentrated hydrochloric acid to the cooled solution produced a precipitate of pink-white 7-acetyl-1-butyluramil (2.4 g., 50%) which was separated by filtration, m.p. 186–188°. The solid was soluble in methanol, in cold 5% bicarbonate or dilute hydroxide with no coloration.

*Anal.* Calcd. for $C_{10}H_{15}N_3O_4$: N, 17.42. Found: N, 17.50.

No depression in melting point was observed when this material was mixed with the compound prepared by the following method: A mixture of 0.2 g. (0.001 mole) of 1-butyluramil, 0.1 g. (0.0012 mole) of sodium bicarbonate and 0.4 ml. of acetyl chloride was heated 0.75 hr. on a hot water-bath. The mix was cooled in ice, filtered, washed with cold water and dried to yield 0.15 g. (63%) of white solid, m.p. 186.0–187.0°.

To 0.5 g. (0.002 mole) of 7-acetyl-1-butyluramil dissolved in 5 ml. of methanol there was added 3 ml. of concentrated hydrochloric acid and the solution refluxed 10 minutes. Cooling in ice yielded no precipitate. The yellow solution became deep purple on alkalinization with 10% sodium hydroxide, and reacidification with 10% hydrochloric acid caused precipitation of 0.2 g. (49%) of pink solid which behaved similarly to 1-butyluramil prepared by other methods, m.p. 218° dec.

**B. 1-Octyluramil. 1.**—To 0.6 g. (0.002 mole) of powdered 1-octylbarbituric acid suspended in 75 ml. of boiling water there were added 0.3 g. (0.004 mole) of sodium nitrite, and the dark red mixture was boiled 15 minutes. Addition of a solution of 3 g. of sodium hydrosulfite in 30 ml. of water and 3 ml. of ammonia caused immediate decolorization to a light orange mixture. After 0.5 hr. of further stirring and heating, the cloudy white mix was cooled in ice and filtered. There was obtained 0.4 g. (80%) of light pink solid which, after purification in the usual way, melted at 202° dec.

**2.**—To a cooled solution of 1.5 g. (0.0062 mole) of octylbarbituric acid in 3 ml. of 5 *N* sodium hydroxide and 10 ml. of water there were added 0.5 g. (0.0065 mole) of sodium nitrite with good stirring. Upon dropwise addition of 10% hydrochloric acid the purple color of the violurate began to form and became progressively more intense. Each drop of acid caused localized precipitation which was dissolved by rapid stirring. Toward the end, the precipitate formed in larger quantities and dissolved more slowly. Finally, dark red solid (1-octylvioluric acid) precipitated, m.p. 160–162° dec.

Treatment of this solid in the customary way with 6 g. of sodium hydrosulfite in 50 ml. of water and 5 ml. of ammonia gave 1.6 g. (100%) of white solid which turned pink on drying, m.p. 203° dec.

**1-Alkyluramil-7,7-diacetic Acids.**—The following preparation of 1-methyluramil-7,7-diacetic acid indicates the method used for synthesizing homologs of uramil-7,7-diacetic acid. To the purple slurry resulting from treating 2.0 g. (0.013 mole) of 1-methyluramil with 5 ml. of approximately 5 *N* sodium hydroxide, there was added a solution of 3.7 g. (0.039 mole) of chloroacetic acid which had been neutralized with 6 ml. of 5 *N* sodium hydroxide to thymolphthalein. The mixture was heated in a boiling water-bath for 35 minutes, during which time 3.5 ml. of 5 *N* alkali was added in small portions so as to maintain the dichromatic alkaline color of the thymolphthalein. As the reaction progressed, the initially opaque purple mixture became decolorized and formed a faintly yellow solution (the blue-green color of the indicator being evident above *p*H 10). The solution was filtered from traces of insoluble matter, was cooled 0.5 hr. in an ice-bath and was acidified with 5 ml. of concentrated hydrochloric acid. Continued cooling in ice and scratching of the walls of the flask caused precipitation of 2.6 g. of light yellow solid. The solid left an extensive alkaline ash on burning and could not be separated from inorganic salts by eight recrystallizations from small amounts of hot water; each recrystallization was accompanied by considerable loss of material.

Commercial Nalcite HCR (sulfonic acid type ion-exchange resin), conditioned in the usual fashion with dilute alkali and acid, was added to a cylindrical tube to form a column measuring approximately 4 × 4 × 4 cm. The column was treated with 20 times its volume of 2 *N* hydrochloric acid, followed by washings with distilled water until the eluate gave no test for chloride ion with silver nitrate. The crude reaction product was dissolved in 50 ml. of warm water, a little decolorizing carbon was added, the solution was filtered onto the resin column and the liquid was passed through at a flow rate of 3 times the volume of resin per hour, the column finally being washed with 30 ml. of warm water. The colorless effluent liquid was then concentrated to dryness in vacuum, yielding 1.7 g. of pinkish-white solid which left no ash on burning in a crucible. The solid was recrystallized from a small amount of water and was dried in a vacuum oven at 30° for 24 hr. The compound reddened when heated in a melting point bath and decomposed *circa* 176°, the decomposition point varying greatly with the rate of heating and temperature of introduction of the sample into the bath.

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