magnesium sulfate. After removal of the ether by distillation the residual oil was distilled twice *in vacuo*.

N,N-Diethylethanesulfenamide: yield 31%, b.p. 61°, (38 mm.) $n^{26}D$ 1.4500. *Anal.* Calcd. for $C_6H_{15}NS$: C, 54.08; H, 11.35; N, 10.51; S, 24.06. Found: C, 54.66; H, 11.32; N, 9.95; S, 23.74.

N,N-Dipropylpropanesulfenamide: yield 30%, b.p. 74° (5 mm.), $n^{25}D$ 1.4533. *Anal.* Calcd. for $C_9H_{21}NS$: C, 61.65; H, 12.07; S, 18.29. Found: C, 61.77; H, 11.71; S, 18.04.

N,N-Di-*n*-butylpropanesulfenamide: yield 70%, b.p. 56–57° (0.32 mm.), $n^{27.5}D$ 1.4543. *Anal.* Calcd. for $C_{11}H_{25}NS$: C, 64.96; H, 12.39; S, 15.76. Found: C, 64.45; H, 12.38; S, 15.98.

N,N-Di-*n*-butyltrimethylmethanesulfenamide: yield 77%, b.p. 60–62° (0.67 mm.), $n^{28}D$ 1.4539–1.4542. *Anal.* Calcd. for $C_{12}H_{27}NS$: C, 66.29; H, 12.52; S, 14.75. Found: C, 66.68; H, 12.78; S, 14.92.

N,N-Di-*n*-butylhexanesulfenamide: yield 68%, b.p. 74–76° (0.001 mm.), $n^{28}D$ 1.4570–1.4574. *Anal.* Calcd. for $C_{14}H_{31}NS$: C, 68.50; H, 12.73; S, 13.07. Found: C, 68.78; H, 12.75; S, 13.40.

Hydrolysis of N,N-Diethylethanesulfenamide. (a) With Potassium Hydroxide in Methanol.—Ten grams of N,N-diethylethanesulfenamide (0.75 mole) was dissolved in 150 ml. of 1 *N* KOH in methanol. The solution was refluxed for 3 hr., at which time the absorption spectrum of a sample had stabilized with an ultraviolet absorption plateau in the region of 240–255 mμ. The solution was then distilled at atmospheric pressure. Fractions boiling at 65–67.5° were collected. They gave positive nitroprusside tests for disulfides,[13] became cloudy when diluted with water and had ultraviolet spectra maxima at 249 mμ. The combined fractions were diluted with water, acidified with dilute HCl and extracted with ether. The ether extract was dried and the ether was removed by distillation. The residue, 1.4 g., appeared to be diethyl disulfide, $n^{29}D$ 1.4991.[14] The aqueous layer was concentrated to a solid residue, yield 7 g. (0.064 mole), m.p. 220–222°, mixed m.p. with authentic diethylammonium chloride 222–224°.

(b) With Dilute Hydrochloric Acid.—Eighteen grams of N,N-diethylethanesulfenamide (0.135 mole) was added to 135 ml. of cold 2.5 *N* HCl and shaken. After an hour the mixture was extracted with ether. The ether extract was distilled. A fraction, b.p. 42–43° (11 mm.), redistilled, 44–46° (15 mm.), $n^{27}D$ 1.4991, yield about 2.8 g. (0.023 mole), which must have been diethyl disulfide was obtained.

Anal. Calcd. for $C_4H_{10}S_2$: C, 39.30; H, 8.24. Found: C, 39.52; H, 8.03.

Another fraction, b.p. 122–124° (11 mm.), redistilled, 72–74° (1 mm.), $n^{27}D$ 1.4976, yield about 3.22 g. (0.021 mole), which must have been the product described by Fichter and Braun as diethyl disulfoxide was obtained.

Anal. Calcd. for $C_4H_{10}S_2O_2$: C, 31.15; H, 6.53; S, 41.57. Found: C, 31.39; H, 6.71; S, 41.82.

The above described hydrochloric acid solution from a previous hydrolysis of N,N-diethylethanesulfenamide (2.66 g., 0.02 mole), after extraction with ether, was evaporated *in vacuo*. The residue, m.p. 220–222°, weighed 2.2 g. (0.02 mole); recrystallized from methanol–ether, m.p. 224–225°; mixed m.p. with authentic diethylamine hydrochloride, 223–225°.

(13) E. Walker, *Biochem. J.*, **19**, 1082 (1925).

(14) R. Nasini, *Ber.*, **15**, 2882 (1882), reports $n^{20}D$ 1.50633.

RAHWAY, NEW JERSEY

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH LABORATORY]

Some 5-(Oxoalkyl)-2-thiohydantoins and Their Derivatives

BY S. ARCHER, MARY JACKMAN UNSER AND E. FROELICH

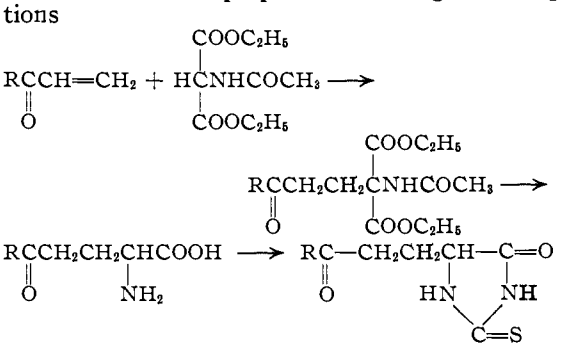
RECEIVED AUGUST 20, 1956

A number of 5-(2-oxoalkyl)-2-thiohydantoins were prepared by condensing the appropriate 1-chloro-2-alkanones with ethyl acetamidomalonate and hydrolyzing the intermediate esters to the amino acids and finally converting these to the thiohydantoins. The requisite amino acids for the preparation of the 5-(3-oxoalkyl)-2-thiohydantoins were obtained by hydrolysis of the adducts of alkyl vinyl ketones and ethyl acetamidomalonate. The thiohydantoins and the isonicotinoylhydrazones derived therefrom were examined for tuberculostatic activity.

In a previous communication[1] it was reported that a few members of a series of 5-(alkyl)-2-thiohydantoins showed appreciable antituberculosis activity when administered to mice infected with *M. tuberculosis* H37Rv. The maximally effective drug in this group was 5-(*n*-heptyl)-2-thiohydantoin; higher and lower homologs as well as isomers thereof showed decreased activity.

In a further study of this problem it appeared to us that there was a similarity between the alkyl naphthoquinones of Fieser[2] which possess antimalarial activity and our compounds in the sense that both series were characterized by the presence of lipophilic chains coupled to nuclei containing polar groups. Since it had been shown in the antimalarial work that oxygenation of the side-chain of certain active members increased therapeutic effectiveness it was decided to prepare a series of 5-(2 and 3-oxoalkyl)-2-thiohydantoins for examination as antituberculosis agents.

Two members of the 5-(3-oxoalkyl)-2-thiohydantoin class were prepared according to the equations



The alkyl vinyl ketones, prepared as previously described,[3] condensed readily with ethyl acetamidomalonate in the expected manner[4] to furnish crystalline adducts which were hydrolyzed to the amino acids which were, in turn, converted to the desired thiohydantoins.

(1) E. Froelich, *et al.*, THIS JOURNAL, **76**, 3099 (1956).

(2) L. F. Fieser, *et al.*, *ibid.*, **70**, 3151 (1948).

(3) S. Archer, W. B. Dickinson and M. J. Unser, *J. Org. Chem.*, in press.

(4) O. A. Moe and D. J. Warner, THIS JOURNAL, **70**, 2763 (1948).

The preparation of the 5-(2-oxoalkyl)-2-thiohydantoins was considerably more difficult. The procedure was essentially the same as that used in the 3-oxoalkyl series except that ethyl acetamidomalonate was condensed with 1-chloro-2-alkanones prepared by a slight modification of the method described by Cason and Prout and Cason.[5]

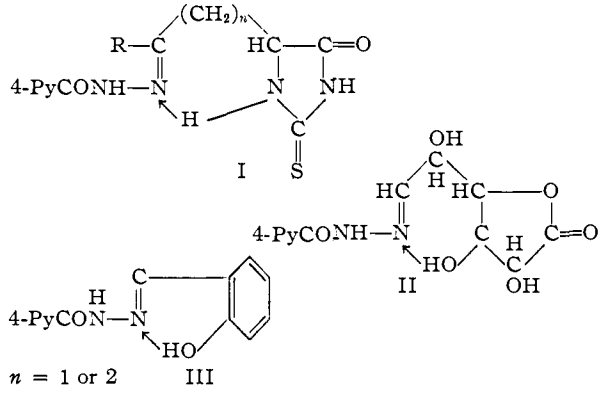
The condensation of phenacyl bromide with ethyl sodioacetamidomalonate in 70% yield was reported by Wiss and Fuchs.[6] When applied in our work this method failed to give the required amino acids in yields higher than 20%. Accordingly, we turned our attention to the use of other salts. Ethyl acetamidomalonate was converted to the lithio salt with the aid of butyllithium in ether. Condensation with 1-chloro-2-octanone followed by hydrolysis afforded 2-amino-4-oxodecanoic acid in 40% over-all yield. However, in other runs the yield varied considerably and this result was ascribed to the presence of variable amounts of unconverted butyl bromide in the reaction mixture. This halide could compete for the lithio salt thereby interfering with the 1-chloro-2-alkanone condensation. Since bromobenzene would be a harmless contaminant we used phenyllithium in the exchange reaction and were able then to obtain fair and consistent yields of the oxoamino acids. Conversion to the thiohydantoins proceeded uneventfully.

Several carbonyl derivatives of the oxoalkylthiohydantoins were prepared. Of greatest chemotherapeutic interest were the isonicotinoylhydrazones. This group of substances was readily obtained by interaction of the carbonyl-containing thiohydantoin and isoniazid.

Chemotherapeutic Results.—The 5-(oxoalkyl)-2-thiohydantoins and their derivatives were tested for their antituberculous effect in mice infected with a human strain of *M. tuberculosis*. None of the 5-(3-oxoalkyl)-2-thiohydantoins were active. On the other hand, 5-(2-oxoöctyl)-2-thiohydantoin and 5-(2-oxononyl)-2-thiohydantoin did exhibit significant tuberculostatic action but neither was as effective as 5-heptyl-2-thiohydantoin.

The isonicotinoylhydrazones of both the 2- and 3-oxoalkylthiohydantoins were effective antituberculous compounds, but at doses which suggested that the biological action was due solely to the isoniazid portion of the molecule. We were quite surprised to find that these highly active hydrazones were relatively non-toxic, *i.e.*, the oral LD_{50} for many of these compounds was greater than 2000 mg./kg., in marked contrast to the high toxicity of isoniazid itself (LD_{50} *ca.* 150 mg./kg.). With certain exceptions the antituberculous activity of isonicotinoylhydrazones of aldehydes and ketones parallels the acute toxicity.[7]

Inspection of the models of the hydrazones of the 2-oxoalkyl- and 3-oxoalkylthiohydantoins reveals that hydrogen bonding is possible as shown in formula I.



It is suggested that bonding of this type is in some way responsible for the low order of toxicity observed in mice. In the exceptions alluded to above the aldehyde moieties of the molecules are sugars in which bonding similar to (six- instead of seven-membered ring) that shown in formula II is possible.

Two bonded hydrazones which have been considered sufficiently non-toxic to warrant clinical trial are the isonicotinoylhydrazones of galacturonolactone (II)[8] and salicylaldehyde (III).[9] Of the large number of hydrazones examined by Sah[10] the majority of the active compounds were those in which hydrogen bonding was possible.

To decide whether this effect could be due to steric factors the toxicity and antituberculous activity of the isonicotinoylhydrazones of salicylaldehyde[11] and *o*-methoxybenzaldehyde[10] were determined. Both hydrazones were fully protective at doses of 3 mg./kg./day. The oral LD_{50} of the salicylidene derivative was greater than 2000 mg./kg. wherein the value for the corresponding methyl ether was 375 mg./kg.

Acknowledgment.—We wish to thank Dr. C. F. Koelsch for valuable suggestions and Miss Alice Fruehan for carrying out some preliminary experiments.

Experimental[12]

1-Chloro-2-octanone.—A Grignard reagent was prepared in 1 liter of dry ether from 48.8 g. of magnesium turnings and 330.2 g. of *n*-hexyl bromide. The reagent was diluted with an equal volume of dry ether just prior to the addition of 196 g. of cadmium chloride (dried at 100°). The conversion to the dialkylcadmium was completed by allowing the stirred suspension to reflux for about one hour. The condenser was set for downward distillation and the ether

(5) (a) J. Cason and F. S. Prout, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 601; (b) J. Cason, THIS JOURNAL, **68**, 2078 (1946); *cf.* J. F. Bunnett and D. S. Tarbell, *ibid.*, **67**, 1944 (1945).

(6) O. Wiss and H. Fuchs, *Helv. Chim. Acta*, **35**, 407 (1952).

(7) J. Bernstein, *et al.*, *Am. Rev. Tuberculosis*, **65**, 357 (1952); **67**, 354 (1953).

(8) G. Brouet, B. N. Halpern, J. Marche and J. Mallett, *Presse Med.*, **61**, 863 (1953); P. Demoen, *et al.*, *Arch. Int. Pharm.*, **98**, 427 (1954).

(9) S. Katz, G. F. McCormick, P. B. Storey, A. deLeon, M. J. Romansky and E. E. Marshall, Trans. 13th Conference on Chemotherapy of Tuberculosis, Feb., 1954, p. 374; E. M. Bavin, D. J. Prain, M. Selter and D. E. Seymour, *J. Pharm. London*, **4**, 844 (1952); M. M. Nagley, *Lancet*, **267**, 337 (1954); E. M. Bavin, E. Kay and D. E. Seymour, *ibid.*, **267**, 337 (1954); V. C. Barry and M. L. Conalty, *ibid.*, **367**, 495 (1954).

(10) P. P. T. Sah and S. A. Peoples, *J. Am. Pharm. Assoc.*, **43**, 513 (1954).

(11) M. N. Shchukina, *et al.*, *Doklady Akad. Nauk S.S.S.R.*, **84**, 981 (1952); *C. A.*, **46**, 10431 (1952).

(12) Analyses were carried out under the supervision of Mr. K. D. Fleischer of this Laboratory. Melting points are uncorrected unless otherwise specified.

TABLE I

5-(2 OR 3-OXOALKYL)-2-THIOHYDANTOINS, R—C—C(=O)—NH—C(S)—NH

R	M.p., °C. (cor.)	Solvent	Yield, %[a]	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
3-Oxo octyl	106–107.7	i-C_3H_7OH–H_2O	63	11.56	11.34	13.23	12.88
3-Oxo heptyl	114.1–115.6	C_6H_6–C_5H_{12}	64	12.27	12.28	14.04	13.98
2-Oxo heptyl	98.2–101.2	C_2H_5OH–H_2O	52	12.27	12.15	14.04	13.77
2-Oxo octyl	100.6–101.5	C_2H_5OH	40	11.53	11.53	13.49	13.49
2-Oxo nonyl[b]	110.2–111.8	C_2H_5OH	61	10.93	10.94	12.51	12.61
2-Oxo decyl	110.7–112.7	C_2H_5OH	58	10.36	10.35	11.86	12.05

[a] Yield based on the weight of recrystallized final products having the indicated analyses. [b] The oxime, prepared in the usual way, melted at 135.8–137.2° (cor.) after two crystallizations from ethanol. *Anal.* Calcd. for $C_{12}H_{21}O_2S$: N, 15.48; S, 11.81. Found: N, 15.55; S, 12.00. The thiosemicarbazone prepared in boiling methanol melted at 175–177° (cor.) after two crystallizations from absolute ethanol. *Anal.* Calcd. for $C_{13}H_{23}N_5OS_2$: N, 21.26; S, 19.46. Found: N, 21.12; S, 19.80.

was removed on the steam-bath while 1 liter of dry benzene was added slowly. When all the ether was removed (head temp. 78°) the whole was cooled to 5° and then a solution of 226 g. of chloroacetyl chloride in 400 ml. of benzene was added at such a rate that the internal temperature did not exceed 45°. The reaction mixture was stirred an additional 3.5 hours. The contents of the flask were carefully poured into a mixture of ice and dilute sulfuric acid. The layers were separated and the aqueous phase was washed with benzene. The combined organic layers were washed with water, dilute sodium bicarbonate, water and finally with saturated salt solution. The dried benzene solution was concentrated and then distilled to give 155 g. (48%) of the desired 1-chloro-2-octanone, b.p. 57–62° (1.0 mm.). On redistillation the ketone boiled at 58–59° (0.2 mm.), n^{25} 1.4439.

Anal. Calcd. for $C_8H_{15}ClO$: Cl, 21.80. Found: Cl, 21.37.

The same method was used for the preparation of the following ketones:

1-Chloro-2-hexanone.[13]—This compound was obtained in 35% yield, b.p. 64–67° (6.0 mm.), n^{25} 1.4356.

Anal. Calcd. for $C_6H_{11}ClO$: Cl, 26.34. Found: Cl, 26.05.

1-Chloro-2-heptanone.[14]—This substance, b.p. 79–82° (8.0 mm.), n^{25} 1.4402, was obtained in 46% yield.

Anal. Calcd. for $C_7H_{13}ClO$: Cl, 23.86. Found: Cl, 24.36.

1-Chloro-2-nonanone.—The procedure described above afforded the substance in 48% yield, b.p. 69–71° (0.3 mm.), n^{25} 1.4448.

Anal. Calcd. for $C_9H_{17}ClO$: Cl, 20.07. Found: Cl, 19.90.

1-Chloro-2-decanone.—The chloroketone, b.p. 78–80° (0.2 mm.), n^{25} 1.4477, was obtained in 34% yield.

Anal. Calcd. for $C_{10}H_{19}ClO$: Cl, 18.57. Found: Cl, 18.50.

1-Chloro-2-undecanone.—This ketone, obtained in 17% yield, boiled at 84–86° (0.1 mm.) and melted at 38–39°.

Anal. Calcd. for $C_{11}H_{21}ClO$: Cl, 17.32. Found: Cl, 17.40.

2-Amino-4-oxodecanoic Acid. A. Sodium Ethoxide Method.—A solution of 21.8 g. of sodium in 664 ml. of ethanol was treated with 206 g. of ethyl acetamidomalonate. The clear solution was evaporated to dryness, first at the water-pump suitably protected from moisture and then at 100° at <0.5 mm. The cake was broken up by vigorously shaking the flask. The powdered sodio derivative was covered with dry benzene and then a solution of 155 g. of 1-chloro-2-octanone in 1325 ml. of benzene was added with stirring. The resulting mixture was refluxed for eight hours, cooled and filtered. The residue from the evaporated filtrate was boiled under reflux for four hours with 2800 ml. of 6 *N* hydrochloric acid. During the last half-hour Darco was added to the solution. The filtered reaction mixture was taken to dryness and the residue was dissolved in a minimum quantity of water. Ammonia was added until the solution was faintly alkaline. On cooling 25.5 g. (13.2%) of the amino acid separated. After recrystallization from water the acid melted at 174–176°.

Anal. Calcd. for $C_{10}H_{19}NO_3$: N, 6.96. Found: N, 7.12.

B. Butyllithium Method.—A solution of butyllithium prepared from 8.6 g. of lithium and 68.0 g. of butyl bromide in ether was treated with a solution of 90 g. of ethyl acetamidomalonate in 750 ml. of benzene at 10°. The ether was removed on the steam-bath and then a solution of 67.2 g. of 1-chloro-2-octanone in 600 ml. of benzene was added. The mixture was refluxed for 16 hours and then filtered. The filtrate on concentration *in vacuo* left a residue which was refluxed for four hours with 1 liter of 6 *N* hydrochloric acid. A small oil layer was removed and the warm aqueous layer was cooled in ice whereupon the amino acid hydrochloride crystallized. The salt was collected, dissolved in water and the solution was made faintly basic with ammonia to precipitate 32.8 g. (40%) of the amino acid, m.p. 173–174°.

2-Amino-4-oxononanoic Acid. Phenyllithium Procedure.—Phenyllithium was prepared in 800 ml. of ether from 15.8 g. of lithium and 169 g. of bromobenzene. The murky solution was treated with 233 g. of ethyl acetamidomalonate in 1600 ml. of benzene. The ether was removed as described above and the lithio salt was then condensed with 127.5 g. of 1-chloro-2-heptanone in 215 ml. of benzene. The residue which remained after removal of the solvents was hydrolyzed by boiling with 1600 ml. of 6 *N* hydrochloric acid for four hours. The amino acid hydrochloride separated on cooling and was converted to the free amino acid as described above; wt. 67.5 g. (42%), m.p. 173–176° after recrystallization from water. When the sodium ethoxide method was used the best yield was 14%.

Anal. Calcd. for $C_9H_{17}NO_3$: N, 7.48. Found: N, 7.50.

2-Amino-4-oxoöctanoic Acid.—This acid was prepared in 30% yield by the phenyllithium method. The hydrochloride was isolated by chilling the hydrolysis solution. The liberated amino acid melted at 167–170° after recrystallization from water.

Anal. Calcd. for $C_8H_{15}NO_3$: C, 55.47; H, 8.70; N, 8.09. Found: C, 55.33; H, 8.40; N, 8.13.

2-Amino-4-oxoundecanoic Acid.—Seventy two grams (42%) of the amino acid was obtained from 141 g. of 1-chloro-2-nonanone by the phenyllithium procedure. It melted at 190–191° after recrystallization from water.

Anal. Calcd. for $C_{11}H_{21}NO_3$: N, 6.51. Found: N, 6.48.

2-Amino-4-oxododecanoic Acid.—This amino acid was obtained in 24% yield by the phenyllithium method. It melted at 182–183° after recrystallization from aqueous acetic acid.

Anal. Calcd. for $C_{12}H_{13}NO_3$: N, 6.11. Found: N, 6.03.

2-Amino-4-oxotridecanoic Acid.—This was obtained in 20% yield by the butyllithium procedure. It melted at 165–167° after crystallization from aqueous acetic acid.

Anal. Calcd. for $C_{13}H_{25}NO_3$: N, 5.76. Found: N, 5.86.

2-Amino-5-oxononanoic Acid.—To a stirred soluion of 120 g. of ethyl acetamidomalonate in 445 ml. of absolute ether

(13) Bunnett and Tarbell (ref. 5b) report b.p. 67–71° (14 mm.), n^{24} 1.4360.

(14) Bunnett and Tarbell (ref. 5b) report b.p. 80–82.5° (12 mm.), n^{20} 1.4371.

TABLE II

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

$R-C(=NNHCOC_5H_4N)-(CH_2)_n-\underset{\text{5}}{CH}-C(=O)-NH-C(=S)-NH$

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.

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

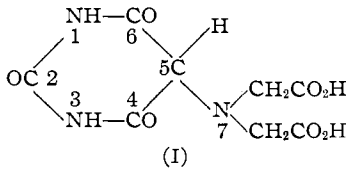
Preparation of 1-Alkyluramil-7,7-diacetic Acids

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).

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