added aqueous potassium iodide to obtain 257.2 g. of iodomercurial. Refluxing the mercurial with 800 ml. of chloroform, 400 ml. of water, and 50 g. of iodine gave 57.6 g. of a black tarry oil contaminated with sulfonium salts for a 56% crude yield. The reaction time was 24 hr. Chromatography of 5.03 g. through alumina with pentane–ether mixture, eluted 3.11 g. of crystalline material, m.p. 51–77°. The original oily products were seeded with these crystals, and the resulting precipitate was subjected to repeated fractional crystallizations from large volumes of methanol–acetone solvents. Two fractions were obtained: prisms, m.p. 79.5–80.2°, and plates, m.p. 69.5–70.5°. When the samples were mixed, the melting point was 48–58°.

Anal. Calcd. for $C_8H_{14}I_2OS$: C, 23.32; H, 3.42. Found: (m.p. 80°) C, 23.55; H, 3.38. (m.p. 70°) C, 23.57; H, 3.38.

Methallyl Sulfone.—The procedure of Baker, Stevens, and Dort[8] was used. The product distilled at 105–107° (1.5 mm.), and weighed 5.73 g., 50.3% yield.

2,6-Dimethyl-2,6-bis(iodomethyl)-*p*-oxathiane 4,4-Dioxide (X).—To a solution of 0.06 mole of mercuric acetate in 60 ml. of water was added 0.0326 mole of methallyl sulfone. After 45 min. the mixture was made basic and filtered. Addition of 11 g. of potassium iodide precipitated the mercurial which weighed 28.7 g. when dried. The mercurial was refluxed in a mixture of 200 ml. of chloroform, 50 ml. of water and 15 g. of iodine for 22 hr. to yield 8.2 g. of solid material, m.p. 117–124°. Three grams of unchanged mercurial was also recovered. The solid product was recrystallized from alcohol to give pure X, m.p. 127–127.5°.

Anal. Calcd. for $C_8H_{14}I_2O_3S$: C, 21.64; H, 3.18. Found: C, 21.75; H, 3.20.

Chromatography of remaining noncrystalline product through silica gel with petroleum ether–acetone eluent gave additional X and some uncharacterized oil.

Oxidation of Sulfide IX to Sulfone X.—To 2.5 ml. of peracetic acid was added 0.13 g. of IX, m.p. 80°. After 12 hr., water was added and the resulting precipitate was recrystallized from acetone, m.p. 124.5–125.5°. Mixed melting point with authentic X was 125.5–127.5°. The infrared spectra were identical. Sulfide IX, m.p. 70°, did not react under these conditions.

Attempted Oxidation of Sulfone X to the Diacid.—A mixture of 1.43 g. of X and 20 ml. of concd. nitric acid was heated on a steam bath to dryness. Nitrogen oxides and iodine vapor were evolved. The resulting oils showed a positive halogen test (Beilstein) after repeated nitric acid treatments until only a tar remained.

Reaction of Sulfide IX with Sodium Sulfide.—The reaction conditions under which II was treated, gave only unchanged starting material when IX, m.p. 80°, was treated with sodium sulfide.

Reaction of Hydantoin with Acetals

HERBERT E. JOHNSON AND DONALD G. CROSBY

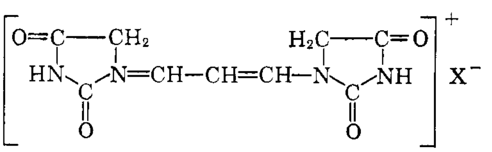
Research and Development Department, Union Carbide Chemicals Co., South Charleston 3, W. Va.

Received January 11, 1962

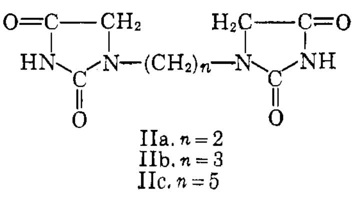
Under anhydrous conditions, hydantoin and 1,1,3,3-tetraethoxypropane react in the presence of mineral acid to give the corresponding salt of 1-(1′-hydantylidine)-3-(1″-hydantyl)propene-2. 1,1,2,2-Tetraethoxyethane and 1,1,5,5-tetramethoxypentane react similarly with hydantoin yielding, after hydrogenation, 1,2- and 1,5-di(1′-hydantyl)ethane and -pentane, respectively. Monoacetals and hydantoin gave the corresponding 1,1′-methylene dihydantoins.

The reaction of hydantoin with aldehydes to give 5-alkylidine derivatives is well known and provides useful intermediates for the preparation of certain α-amino acids.[1] Aromatic aldehydes invariably react with greater facility than aliphatic aldehydes containing α-hydrogens, due to the absence of complicating self-condensation reactions. Hydantoin and its derivatives with an open 1-position are also known to react with formaldehyde in strongly acidic aqueous media to produce 1,1′-methylene dihydantoins.[2] Higher aliphatic aldehydes have apparently not been found to undergo this condensation although their reaction with amides to give methylene diamides has been reported.[3] Thus, it seemed expedient to investigate the reaction of hydantoin with aliphatic aldehydes or appropriate derivatives under conditions which might lead to 5-substituted hydantoins and, hopefully, eliminate or minimize self-condensation. This communication describes the mineral acid-catalyzed reaction of hydantoin with various aliphatic acetals.

1,1,3,3-Tetraethoxypropane (TEP), in a variety of nonaqueous solvents, reacts smoothly with two equivalents of hydantoin in the presence of sulfuric acid to precipitate 1-(1′-hydantylidine)-3-(1″-hydantyl)propene-2 bisulfate (Ia) in 80–100% yield. A hydrochloride (Ib) was similarly formed when anhydrous hydrogen chloride was present in the reaction mixture, but its structure is not as well



Ia. X = HSO_4
Ib. X = Cl



IIa. $n = 2$
IIb. $n = 3$
IIc. $n = 5$

---

(1) E. Ware, *Chem. Rev.*, **46**, 403 (1950).

(2) R. Behrend and R. Niemeyer, *Ann.*, **365**, 38 (1909); J. F. Walker, U. S. Patents 2,417,999 and 2,418,000.

(3) For examples see Beilstein's *Handbuch der Organischen Chemie*, Vol. 2, pp. 179, 180 and Vol. 3, pp. 24–26.

established due to the existence of more than one equivalent of chloride in the molecule.

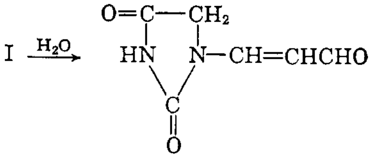
The structure of I was established by hydrogenation to 1,3-di(1′-hydantyl)propane (IIb) and subsequent hydrolysis to the corresponding amino acid IV. Both IIb and IV were found to be identical with authentic samples, conveniently prepared from 1,3-propanediamine as illustrated.

$$2\ HOCH_2CN + H_2NCH_2CH_2CH_2NH_2 \longrightarrow NCCH_2NHCH_2CH_2CH_2NHCH_2CN$$

$$\downarrow \text{(1) HCl; (2) LiOH}$$

$$IIb \xleftarrow{KCNO} \underset{IV}{HO_2CCH_2NHCH_2CH_2CH_2NHCH_2CO_2H}$$

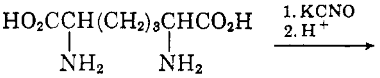
Reaction of I with water or dilute acid or base produced an aldehyde believed to be 3-(1′-hydantyl)acrolein (V). The infrared spectrum (λ_{CHO} 3.65, 6.03 μ; $\lambda_{C=C}$ 6.18 μ; λ_{CONH} 3.12, 5.63, 5.75 μ) of the product was consistent with this structure and an absorption at 278 mμ (ϵ 32,000) in the ultraviolet added further conformation. A 2,4-dinitrophenylhydrazone of V formed readily and hydrogenation of V proceeded smoothly with the absorption of two equivalents of hydrogen. The resultant alcohol, however, could not be crystallized.



V

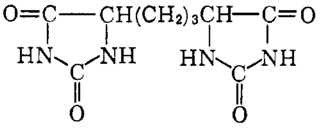
When hydantoin and 1,1,2,2-tetraethoxyethane[4] or 1,1,5,5-tetramethoxypentane[4] were allowed to react as in the preparation of I, no comparable material precipitated. However, when the reaction was conducted in the presence of palladium in a hydrogen atmosphere, the respective saturated materials (IIa, IIc) were obtained. Apparently, a steric factor becomes important when the hydantoin contains a substituent in the 5- position, since TEP fails to give an insoluble 5,5′-disubstituted derivative of I when allowed to react with 5-isopropylhydantoin. The extreme insolubility of I must contribute to its ready isolation for acetamide, benzamide, and *N*-methylacetamide, which might be expected to give products analogous to I, failed to precipitate any product when reacted with TEP under the conditions described for the preparation of Ia. No further characterization of the reaction products was attempted.

That I and IIb were not 5-substituted hydantoins was also established by the nonidentity of IIb to the hydantoins of 2,6-diaminopimelic acid (VII). Of the two isomers of 2,6-diaminopimelic acid (VI), the meso isomer was readily available[5] and reaction of it with potassium cyanate produced the meso-hydantoin VII. Racemization of VI with base and subsequent reaction with potassium cyanate gave the racemic hydantoin VII



$$\underset{NH_2}{HO_2CCH}(CH_2)_3\underset{NH_2}{CHCO_2H} \xrightarrow{1.\ KCNO;\ 2.\ H^+}$$

VI



VII

Comparison of melting points and infrared spectra of IIb with the two isomers of VII proved that the materials were different.

The structure of I is of interest since there is apparently no record of the formation of this particular system. The related systems, VIII and IX, are known[6,7] and comparison of their infrared spectra with the one of I shows a favorable coincidence of the major absorbances. In particular, the absorbance at about 6.3 μ appears as a strong bond in all three and is undoubtedly due to the presence of the conjugated

$$[(CH_3)_2N{-}CH{=}CHCH{=}\overset{+}{N}(CH_3)_2]X^-$$

VIII

$$[(CH_3)_2N{-}CH{=}N{-}CH{=}\overset{+}{N}(CH_3)_2]X^-$$

IX

system. The ultraviolet spectrum of Ia could be obtained using sulfuric acid as a solvent and solutions in 90–100% acid were found to be reasonably stable as evidenced by the identity of the absorption over a period of several hours. A single absorbance was observed at 342 mμ (ϵ 69,000). Solutions in 5–20% acid produced a spectrum identical to the spectrum of the aldehyde V. The use of 75% sulfuric acid as a solvent resulted in a spectrum identical at first to those obtained in 90–100% acid. However, the spectrum changed with time resulting in a decrease at 342 mμ and a new absorption at 305 mμ. Thus, after two and four hours the absorption spectrum at 342 and 305 mμ was 50,000; 16,400 and 36,400; 21,700, respectively. An isomerization (*viz. cis* to *trans*) to a more stable form of I may be responsible for this change. The corresponding absorbances of VIII and IX occur at about 305 and 270 mμ, respectively.[7] The formation of I might also be related to the synthesis of pyrimidine salts by the acid-catalyzed condensation of TEP with urea-type compounds.[8]

The reaction probably proceeds by an initial protonation of an acetal oxygen followed by loss of ethanol to give the ion X. Attack of X on the

---

[4] Obtained from C. A. Noffsinger of this laboratory.

[5] Generously supplied by the Charles Pfizer Co.

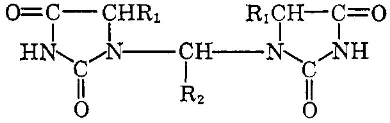
[6] W. T. Simpson, *J. Am. Chem. Soc.*, **71**, 754 (1949).

[7] H. Gold, *Angew. Chemie.*, **72**, 956 (1960).

[8] D. G. Crosby and R. V. Berthold, *J. Org. Chem.*, **25**, 1916 (1960).

TABLE I

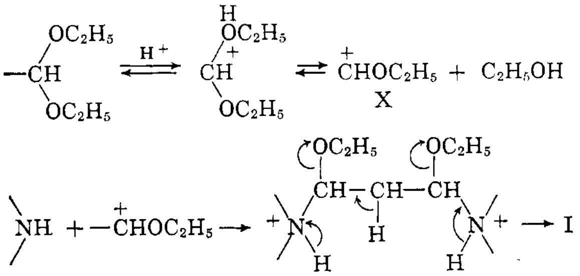
1,1'-METHYLENEDIHYDANTOINS



R_1	R_2	M.P.	Yield, %	Formula	Calcd. C	Calcd. H	Calcd. N	Found[c] C	Found[c] H	Found[c] N
H	H	292–305[a]	97	$C_7H_8N_4O_4$	39.62	3.80	26.41	39.82	3.91	26.71
H	CH_3	258–261	96	$C_8H_{10}N_4O_4$	42.48	4.48	24.77	42.49	4.22	25.02
H	CH_2Cl	204–206	70	$C_8H_9ClN_4O_4$	36.86	3.48	21.49	36.86	3.27	21.75
i-C_3H_7	H	225–230	60[b]	$C_{13}H_{20}N_4O_4$	52.69	6.80	18.91	52.36	6.81	18.58

[a] Reported,[2] 283–295. [b] Crude yield probably contains a mixture of isomers. [c] Satisfactory analytical results were difficult to obtain apparently due to combustion difficulties.

more nucleophilic 1-nitrogen of the hydantoin and repetition of the process yields the intermediate XI. Loss of two molecules of ethanol thereby produces I.



XI

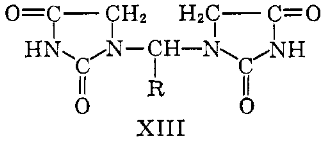
The possibility that I is the bis-quaternized salt XII seems unlikely since tetraethoxyethane and/or tetramethoxypentane do not give similar products and the formation of the aldehyde V is not as readily rationalized. Hydrogenolysis or hydrogenation of

$$^{+}N{=}CHCH_2CH{=}N^{+}$$

XII

the two- and five-carbon intermediates corresponding to XI and XII does, however, provide a logical source of IIa and IIc.

To determine the course of the reaction with monoacetals, the reaction of hydantoin and 5-isopropylhydantoin with various acetals was investigated. In all cases where a product precipitated, it was found to be the methylene dihydantoin derivative XIII. The structure of these materials is based on the analogous acid catalyzed reaction of carbamates and simple amides with acetals which produces methylene diamides[3] and the identity of the reaction product of hydantoin and formal with the product obtained from hydantoin and formaldehyde.[2]



XIII

The formation of XIII, like I, seems to be sterically dependent. Thus, 5-isopropylhydantoin and formal produced the corresponding XII only with difficulty, while acetal gave none of the homologous material. Acetal and chloroacetaldehyde dimethylacetal reacted satisfactorily with hydantoin, but reaction with the acetals of butyraldehyde and benzaldehyde did not cause any product to precipitate. It is likely that in those cases where XIII fails to precipitate, the reaction has terminated at the alkoxymethylamide stage.

Experimental[9]

1-(1'-Hydantylidine)-3-(1''-hydantyl)propene-2 Bisulfate (Ia).—A mixture of 100 g. (1.0 mole) of recrystallized hydantoin and 1 l. of acetic acid was prepared and 150 g. of concd. sulfuric acid added while keeping the temperature of the mixture at about 20°. A 110-g. (0.5 mole) quantity of TEP was then added over a 10-min. period while maintaining the temperature at about 20°. The mixture soon became clear, followed by the precipitation of yellow solids. After 2 hr. the product was recovered, washed well with acetic acid followed by ether and dried. A total of 138 g. (82%) of Ia was obtained as a light yellow crystalline solid, m.p. 159–160° dec. Higher yields can be obtained by employing a slight excess of hydantoin in the reaction mixture. Since the product cannot be recrystallized without extensive decomposition a sample was dried *in vacuo* at 40° and analyzed without further purification.

Anal. Calcd. for $C_9H_9N_4O_4 \cdot HSO_4$: C, 32.34; H, 3.16; N, 16.76. equiv. wt., 167. Found: C, 32.10; H, 3.12; N, 16.26; equiv. wt., 173.

In a manner similar to the preparation of the bisulfate Ia the hydrochloride Ib was prepared. In this case the acetic acid was saturated with dry hydrogen chloride at 20° before the addition of the TEP. A 119-g. yield of light yellow product, m.p., 181–190° dec., was obtained.

1,3-Di(1'-hydantyl)propane (IIb). A. By Hydrogenation of Ib.—A mixture of 45 g. (0.133 mole) of the bisulfate Ib, 5 g. of 10% palladium-on-carbon, and 150 ml. of absolute ethanol was shaken under 42–24 p.s.i. of hydrogen until absorption ceased. The catalyst and precipitated product were removed by filtration and added to 100 ml. of water containing 8 g. of sodium hydroxide. The catalyst was then removed and the dissolved product recovered by acidification of the filtrate. After drying, 15 g. (49%) of off-white crystalline solids was obtained, m.p. 248–256°. Several crystallizations from water yielded an analytical sample as

---

[9] Melting points are corrected. Infrared spectra were recorded by a Perkin-Elmer Model 21 spectrophotometer and ultraviolet spectra by a Cary Model 14 spectrophotometer.

colorless needles, m.p. 266–268° (274–278° if inserted at 260°). A mixed melting point with an authentic sample (see below) was undepressed and the infrared spectra of two were found to be identical.

Anal. Calcd. for $C_9H_{12}N_4O_4$: C, 44.99; H, 5.04; N, 23.33. Found: C, 45.21; H, 4.95; N, 23.63.

B. From IV and Potassium Cyanate.—A mixture of 5.2 g. (0.0167 mole) of the lithium chloride complex of IV (see below), 4.5 g. (0.056 mole) of potassium cyanate, and 30 ml. of water was boiled for 5 min. After cooling to room temperature, the solution was acidified and again boiled for 5 min. Upon cooling, the product precipitated and was collected to give 3.2 g. (80%) of authentic IIb as colorless needles, m.p. 265–268° and undepressed when mixed with IIb obtained from Ib.

***N,N′*-Dicarboxymethyl-1,3-propanediamine (IV). A. By Hydrolysis of the Hydantoin IIb.**—A mixture of 56 g. (0.23 mole) of the hydantoin IIb, 400 ml. of water, and 84 g. of lithium hydroxide was refluxed for 6 hr. The precipitated lithium carbonate was removed and the filtrate adjusted to about pH 6 with concd. hydrochloric acid and acetic acid. Five volumes of ethanol were added and the precipitated product collected after the mixture had stood overnight. Purification of the obtained 28 g. of product was effected by dissolving in 150 ml. of water containing 10 g. of lithium chloride, decolorizing with carbon, and diluting with 5 vol. of ethanol. Colorless needles were obtained, the infrared spectrum of which was found to be identical in detail to the lithium chloride complex of IV obtained *via* synthesis from 1,3-propanediamine.

B. Synthesis from 1,3-Propanediamine.—To 43 g. (0.525 mole) of 70% aqueous glycolonitrile was added 19 g. (0.256 mole) of 1,3-propanediamine in portions, while maintaining the temperature at about 35°. The mixture was then warmed to 60–70° for 30 min., cooled to 20° and added to 300 ml. of concd. hydrochloric acid at 25°. After stirring the reaction mixture for 1 hr. at 25° it was refluxed for 2.5 hr. The clear solution was then evaporated to dryness under reduced pressure, added to 200 ml. of water, neutralized with concd. lithium hydroxide to about pH 6–7 and diluted with 800 ml. of ethanol. The precipitate was collected to give 60 g. (76%) of product, m.p. 260–265° dec., which is apparently complexed with two moles of lithium chloride and two moles of water. A 10-g. sample was purified by dissolving it in 100 ml. of water containing 10 g. of lithium chloride and diluting with 800 ml. of ethanol. Five grams of very light tan needles was obtained, m.p. 261–265° dec.

Anal. Calcd. for $C_7H_{14}N_2O_4 \cdot 2H_2O \cdot 2LiCl$: C, 27.03; H, 5.83; N, 9.01; Cl, 22.81; ash, 35.3 (as sulfate). Found: C, 27.23; H, 5.54; N, 9.28; Cl, 22.29; ash, 34.0 (as sulfate).

The pure acid IV was obtained as colorless micro crystals, m.p. 220–226° dec., by repeated decantations and crystallizations from water–methanol.

Anal. Calcd. for $C_7H_{14}N_2O_4$: C, 44.20; H, 7.42; N, 14.73. Found: C, 43.95; H, 7.51; N, 14.59.

3-(1′-Hydantyl)acrolein (V).—Forty-five grams (0.133 mole) of bisulfate Ia was added at 50° with stirring to 200 ml. of water containing 10 ml. of concd. hydrochloric acid. The mixture was held at 50° for 15 min., cooled to 5° and the precipitated product collected. A total of 15 g. (75%) of light yellow solids was obtained, m.p. 181–198°. Several crystallizations from water afforded an analytical sample as pale yellow needles, m.p. 222–224°; $\lambda_{\max}^{C_2H_5OH}$ 278 mμ, ϵ 32,000.

Anal. Calcd. for $C_6H_6N_2O_3$: C, 46.76; H, 3.92; N, 18.18. Found: C, 46.76; H, 3.77; N, 18.24.

The 2,4-dinitrophenylhydrazone was prepared in the usual manner and was obtained as flat red-orange needles, m.p. 244–246°, after two crystallizations from nitrobenzene.

Anal. Calcd. for $C_{12}H_{10}N_6O_6$: C, 43.12; H, 3.02; N, 25.14. Found: C, 43.39; N, 3.04; N, 25.01.

***meso*-1,3-Di(5′-hydantyl)propane (VII).**—A slurry of 5.2 g. (0.025 mole) of *meso*-2,6-diaminopimelic acid hydrate (VI),[5] 4.5 g. (0.055 mole) of potassium cyanate, and 30 ml. of water was treated as described above for the preparation of IIb from IV to give 2.6 g. of colorless solids, m.p. 216–220°. Several crystallizations from water raised the m.p. to 220–224°.

Anal. Calcd. for $C_9H_{12}N_4O_4$: C, 44.99; H, 5.04: N, 23.33. Found: C, 44.78; H, 5.18; N, 23.32.

Racemic 1,3-Di(5′-hydantyl)propane (VIIb).—Ten grams of *meso*-VI, 10 g. of lithium hydroxide, and 100 ml. of water were refluxed for 5 hr., cooled to 25°, neutralized to pH 6–7 with concd. hydrochloric acid, and diluted with 5 vol. of ethanol. The precipitate was collected to give 9.5 g. of colorless racemic 2,6-diaminopimelic acid. Treatment of 5.2 g. of this material with potassium cyanate as described above afforded 3.45 g. (57%) of crude racemic VII, m.p. 210–225°. Crystallization from water afforded pure racemic VII as colorless micro crystals, m.p. 234–237°.[10]

Anal. Calcd. for $C_9H_{12}N_4O_2$: C, 44.99; H, 5.04; N, 23.33. Found: C, 44.91; H, 5.07; N, 23.46.

1,2-Di(1′-hydantyl)ethane (IIa).—To a mixture of 33 g. (0.33 mole) of hydantoin, 250 ml. of acetic acid, and 50 g. (0.51 mole) of sulfuric acid was added 26 g. (0.125 mole) of 1,1,2,2-tetraethoxyethane[4] with stirring at 10°. After stirring for 2 hr. at 25° a clear solution resulted which was then hydrogenated over 2 g. of 10% palladium on carbon under 40–25 p.s.i. of hydrogen. The reaction mixture was processed as described for the preparation of IIb from Ia to give 8 g. (29%) of colorless crystals, m.p. 270–300° dec. An analytical sample, m.p. 297–309° dec. was obtained after several crystallizations from water.

Anal. Calcd. for $C_8H_{10}N_4O_4$: C, 42.42; H, 4.45; N, 24.87. Found. C, 42.39; H, 4.21; N, 24.68.

1,5-Di(1′-hydantyl)pentane (IIc).—In the manner described for IIb, 33 g. (0.33 mole) of hydantoin, and 31 g. (0.125 mole) of 1,1,5,5-tetramethoxypentane[4] reacted to give 6 g. (18%) of pure IIc as colorless crystals, m.p. 189–190°, from water.

Anal. Calcd. for $C_{11}H_{16}N_4O_4$: C, 49.29; H, 6.01; N, 20.89. Found: C, 49.29; H, 6.05; N, 21.11.

1,1-Di(1′-hydantyl)-2-chloroethane (XIII. R = CH_2Cl).—The following represents a general procedure for the reaction of monoacetals with hydantoin. A mixture of 50 g. (0.5 mole of hydantoin, 40 g. (0.26 mole) of chloroacetaldehyde diethyl acetal, 150 ml. of acetic acid, and 20 g. of concd. sulfuric acid was heated with stirring for 5 hr. at 50°. At this time the reaction mixture was cooled to 20° and the precipitated material collected. The filter cake was dried to give 45 g. (70%) of the desired product as colorless crystals, m.p. 205–207°. Analytical data are recorded in Table I.

Acknowledgment.—The authors are grateful to F. G. Bollinger and C. R. McClure for capable assistance and to Q. Quick and his associates for microanalyses and spectral data.

---

(10) French Patent 1,255,546 reports a 1,3-di(5′-hydantyl)propane of m.p. 232–236°.