and III absorb strongly at 10.3 mμ while I does not. Absorption at this wave length is indicative of a *trans*-substituted double bond.[5] Absorption at 13.15 mμ, which is characteristic of the *cis*-substituted double bond,[5] is present in the spectra of I and II but absent in that of III.

I was isomerized to a mixture of II and III on treatment with acid. The action of sunlight on I produced only III. The action of light or acid on III yielded only high molecular weight material.[6,7] There was no evidence of light-catalyzed isomerization of III.

EXPERIMENTAL[8]

1,5-Diphenylpentadiyne-3-one. A solution of 1,5-diphenylpentadiyne-3-ol (5.0 g.) in 50 ml. of acetone was added to a suspension of manganese dioxide (50.0 g.) in 450 ml. of petroleum ether (b.p. 30–60°), stirred vigorously for 3 hr., filtered, and the solvent removed on a steam bath leaving a light red oil which solidified in an ice bath. The solid was recrystallized from petroleum ether (b.p. 30–60°) as light yellow needles; 3.5 g. (70%), m.p. 64°.

cis-cis-1,5-Diphenylpentadiene-3-one. (*I*). To a solution of 1,5-diphenylpentadiyne-3-one (2.0 g.) in 50 ml. of methanol was added 0.5 g. of Lindlar catalyst. The suspension was stirred in an atmosphere of hydrogen until the calculated amount (2 moles) had been taken up, the catalyst removed by filtration and the solvent removed *in vacuo*. The resulting oil (2 g.) was washed with petroleum ether (b.p. 30–60°) and distilled to give 1.2 g. (60%) of light yellow oil, b.p. 130°/0.02 mm.

Anal. Calcd. for $C_{17}H_{14}O$: C, 87.15; H, 6.03. Found: C, 87.06; H, 6.31.

Attempts to prepare the 2,4-dinitrophenylhydrazone of *cis-cis*-1,5-diphenylpentadiene-3-one, in all cases but one, resulted in the derivative of the *trans-trans* isomer melting at 181°. Under less vigorous conditions, a derivative was prepared which melted at 92°. On acid hydrolysis this material gave *trans-trans*-1,5-diphenylpentadiene-3-one.

1,5-Diphenylpent-1-en-4-yn-3-ol. Ethylmagnesium bromide was prepared by adding 100 ml. of ethyl bromide to 20.5 g. of magnesium turnings in 250 ml. of dry ether. Phenylacetylene (80 ml.) was added slowly and the solution stirred for 1 hr. after addition was complete. The solution was cooled to 0° and 21.5 g. of cinnamaldehyde was added dropwise over a period of 30 min. The reaction mixture was poured over 100 g. of ice and 25 g. of ammonium chloride, the ether layer washed with water, dried over calcium chloride, and the solvent removed on a steam bath. The residue solidified in an ice bath and was recrystallized from petroleum ether (b.p. 30–60°) as white needles; 23 g. (60%), m.p. 68°.

1,5-Diphenylpent-1-en-4-yn-3-one. Kiliani's reagent[3] was added dropwise to a solution of 1,5-diphenylpent-1-en-4-yn-3-ol (2.0 g.) in 50 ml. of acetone until the yellow color persisted. The solution was diluted with water and extracted with ether. The ether layer was washed several times with water, dried over anhydrous sodium sulfate, and the ether removed on a steam bath. The residue solidified in an ice bath and was recrystallized from petroleum ether (b.p. 30–60°) as light yellow needles; 1.8 g. (90%), m.p. 69°.

cis-trans-1,5-Diphenylpentadiene-3-one (II). To a solution of 2.0 g. of 1,5-diphenylpent-1-en-4-yn-3-one in 50 ml. of methanol was added 0.5 g. of Lindlar catalyst. The suspension was stirred in an atmosphere of hydrogen until the calculated amount (1 mole) had been taken up, the catalyst removed by filtration, and the solvent removed *in vacuo*. The residue solidified in an ice bath and was recrystallized from ethanol as light yellow needles; 1.0 g. (50%), m.p. 60°. The 2,4-dinitrophenylhydrazone was prepared in the usual manner and melted at 159°.

Anal. Calcd. for $C_{23}H_{18}N_4O_4$: N, 13.52. Found: N, 13.53.

Isomerization studies. cis-cis-1,5-Diphenylpentadiene-3-one (2.0 g.) was exposed to normal room light for 24 hr. *trans-trans*-1,5-Diphenylpentadiene-3-one (2.0 g.) was obtained as the only product. The *cis-cis* isomer showed no change in a month's time in the absence of light. *cis-trans*-1,5-Diphenylpentadiene-3-one remained unchanged after several days exposure to normal room light.

Concentrated hydrochloric acid (1 ml.) was added to a solution of *cis-cis*-1,5-diphenylpentadiene-3-one (0.5 g.) in 25 ml. of methanol and the solution heated on a steam bath for 5 min. The solution was diluted with water and extracted with ether. The ether layer was washed with dilute sodium bicarbonate then with water. The ether layer was dried over calcium chloride and the ether removed on a steam bath. The residue was recrystallized from petroleum ether (b.p. 30–60°) yielding approximately equal amounts of the *cis-trans* and the *trans-trans* isomers.

Department of Chemistry and Geology
Clemson College
Clemson, S. C.

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16-Hydroxylated Steroids. XXII.[1] The Preparation of the 16-Methyl Ether of Triamcinolone[2]

Milton Heller, Stephen M. Stolar, and Seymour Bernstein

Received August 7, 1961

The isolation of 2-methoxy-estrogens[3] as metabolites of known estrogens has encouraged us to study the influence of ether functions on biologically active steroids. In the corticoid field, 9α-methoxy and ethoxy groups,[4] 6β and 6α-methoxy groups,[5] and a 16β-methoxy grouping[6] have been introduced

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into the molecule. The 21-methyl ether derivatives[7] of active corticoids have also been synthesized.

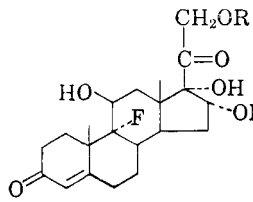
In view of the importance of 16α-substituents[4b,8] on the corticoid molecule, it was thought desirable to prepare the 16α-methoxy derivatives of such compounds. The only related compounds which have been described are 16α-methoxyprogesterone[9] and 16α-methoxydeoxycorticosterone.[10]

Treatment of 21-acetoxy-9α-fluoro-11β,16α,17α-trihydroxypregn-1,4-diene-3,20-dione (triamcinolone 21-acetate) (Ia)[11] with fluoroboric acid and diazomethane[12] afforded a product which was assigned the structure, 21-acetoxy-9α-fluoro-11β,-17α-dihydroxy - 16α - methoxypregn - 1,4 - diene-3,20-dione (Ib), plus an isomeric compound II. Saponification of Ib gave 9α-fluoro-11β,17α,21-trihydroxy-16α-methoxypregn-1,4-diene-3,20-dione (Ic). The formulation Ib was inferred from the known relative reactivity of secondary *vs.* tertiary hydroxyl groups toward diazomethane under these conditions,[12a,b] and the expected steric inhibition of reactivity of the 11β-hydroxyl group. Further confirmation of this structure was achieved by oxidation of Ib to yield 21-acetoxy-9α-fluoro-17α - hydroxy - 16α - methoxypregn - 1,4 - diene-3,11,20-trione (III). The hypsochromic effect on the ultraviolet absorption spectra when comparing Ib with respect to III (4 mμ) was in accordance with previous reports[13] on the change of the C11 moiety from a hydroxyl to a carbonyl grouping. Finally, sodium bismuthate oxidation[14] of the triol Ic furnished 9α-fluoro-11β-hydroxy-16α-methoxy-androst-1,4-diene-3,17-dione (IV). The latter structure was supported by infrared analysis which showed an absorption band at 1748 cm.$^{-1}$ characteristic of a strained five-membered ring carbonyl function and by the maintenance of the methoxyl grouping. These oxidation experiments indicated that the methylated hydroxyl group was at C16.

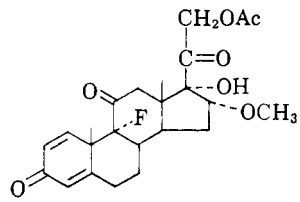
The compound II of unknown structure isolated in the diazomethane treatment of triamcinolone 21-acetate (Ia) was saponified with sodium carbonate in methanol to give a new compound V, which contained a saturated ketone (1729 cm.$^{-1}$) according to its infrared spectrum. Surprisingly, the latter compound was inert to re-acetylation. In fact, elemental and methoxy analyses suggested that the previous acetylated hydroxyl group may have been transformed into a methyl ether function. Neither II nor V was reactive to Blue Tetrazolium reagent. Also the acetate II is more polar than the 16α-methoxy acetate Ib in the partition chromatography system used to separate these compounds.

Similarly, as described above, 21-acetoxy-9α-fluoro - 11β,16α,17α - trihydroxypregn - 4 - ene-3,20-dione (Id)[11] was converted into the 16α-methoxy analog Ie, which in turn saponified to give 9α-fluoro-11β,17α,21-trihydroxy-16α-methoxypregn-4-ene-3,20-dione (If).

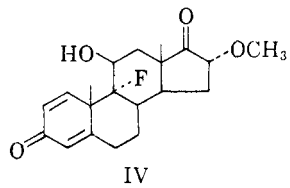
Bioassays.[15] In a 48 hr. thymus involution assay (intact immature female rat; hydrocortisone = 1)



I



III



IV

Ia. Δ[1]; R = Ac; R′ = H
b. Δ[1]; R = Ac; R′ = CH_3
c. Δ[1]; R = H; R′ = CH_3
d. R = Ac; R′ = H
e. R = Ac; R′ = CH_3
f. R = H; R′ = CH_3

the 16-methyl ether (Ic) of triamcinolone possessed an activity of 2. Its 11-carbonyl analog (III) was approximately equal to hydrocortisone in activity. The Δ[4]-16-methyl ether (If) was active but less than hydrocortisone.

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(15) The assays were carried out by the Metabolic Chemotherapy Department of these laboratories.

In an electrolyte assay (adrenalectomized rats; deoxycorticosterone as the standard) the above compounds at a 16 γ dose level did not produce sodium retention.

EXPERIMENTAL

Melting points. All melting points are uncorrected.

Absorption spectra. The ultraviolet spectra were determined in methanol, the infrared spectra were determined in a potassium bromide disk.

Petroleum ether. The fraction used had a b.p. 60–70°.

21-Acetoxy-9α-fluoro-11β,17α-dihydroxy-16α-methoxypregn-1,4-diene-3,20-dione (Ib) *and compound* II. To a solution of 2.6 g. of triamcinolone 21-acetate (Ia) in 2.5 liters of methylene chloride was added 2.6 ml. of fluoroboric acid solution (prepared by evaporating 50% fluoroboric acid under reduced pressure until all water was removed and diluting 0.133 ml. of the flask residue with 25 ml. of a 3:1 mixture of ether–methylene chloride). To this solution was added 50 ml. of a solution of diazomethane in methylene chloride (prepared from 35 g. of methylisonitrosourea and diluted to 200 ml. with methylene chloride) and the reaction mixture was allowed to stand at room temperature for 1 hr. Fluoroboric acid solution was added in sufficient quantity to discharge the yellow color. The above addition and procedure was repeated three more times so that all the diazomethane solution was added and the total reaction time was 4.5 hr. A few drops of acetic acid were added in order to discharge the diazomethane. The reaction mixture was filtered so as to remove the polymethylene formed, and the filtrate was washed with aqueous sodium bicarbonate and water until neutral. Evaporation gave 2.2 g. of an oil which was chromatographed on Florisil.[16] Elution with petroleum ether–15% acetone gave an impure solid (130 mg.) which was then partition chromatographed on Celite[17] using the system heptane–methylene chloride–ethylene glycol (50:50:10). Evaporation of the second holdback volume gave 95 mg., m.p. 245–251°. Four crystallizations from acetone–petroleum ether yielded 55 mg. of Ib, m.p. 249–252°; λ_{max} 239 mμ (ε 14,700); ν_{max} 3510, 3370, 1763, 1740, 1670, 1630, and 1618 cm.$^{-1}$; $[\alpha]_D^{25}$ +57.5° (chloroform).

Anal. Calcd. for $C_{24}H_{31}O_7F$ (450.49): C, 63.98; H, 6.94; F, 4.22; CH_3,[18] 3.34. Found: C, 64.11; H, 7.30; F, 4.63; CH_3, 4.50.

In another run with 200 mg. of triamcinolone 21-acetate (Ia), there was isolated before chromatography 20 mg. of an isomeric compound II on direct crystallization from acetone–petroleum ether. In another run with 7 g. of starting material Ia, the partition chromatogram showed a peak between the first and second holdback volumes. Work-up of this fraction and subsequent recrystallizations from methylene chloride–ether gave compound II melting at 265–266°; λ_{max} 239 mμ (ε 16,000); ν_{max} 3380, 1725, 1660, 1618, and 1605 cm.$^{-1}$; $[\alpha]_D^{25}$ +46° (pyridine). The infrared spectrum was identical to that of the sample isolated above.

Anal. Found: C, 64.11; 63.67; H, 6.84; 7.26; F, 4.05; CH_3, 4.38.

9α-Fluoro-11β,17α,21-trihydroxy-16α-methoxypregn-1,4-diene-3,20-dione (Ic). To a solution of 220 mg. of 21-acetoxy-9α-fluoro-11β,17α-dihydroxy-16α-methoxypregn-1,4-diene-3,20-dione (Ib) in 25 ml. of methanol kept under nitrogen, was added 0.7 ml. of 10% aqueous potassium carbonate. The reaction mixture was allowed to stand for 20 min. at room temperature, at which time it was neutralized with acetic acid and concentrated until solid had formed. Water was added and the crystals were filtered off and washed well with water to give 140 mg. of Ic; m.p. 245–248°. Several crystallizations from acetone–petroleum ether raised the melt to 252–254°; λ_{max} 238 mμ (ε 16,300); ν_{max} 3420, 1710, 1665, 1635, and 1615 cm.$^{-1}$; $[\alpha]_D^{25}$ +46° (methanol).

Anal. Calcd. for $C_{22}H_{29}O_6F$ (408.45): C, 64.69; H, 7.16; F, 4.65; CH_3, 3.68. Found: C, 64.30; H, 7.41; F, 4.96; CH_3, 4.61.

21-Acetoxy-9α-fluoro-17α-hydroxy-16α-methoxypregn-1,4-diene-3,11,20-trione (III). To a mixture of 0.9 g. of chromic acid in 10 ml. of pyridine was added a solution of 1 g. of 21-acetoxy-9α-fluoro-11β,17α-dihydroxy-16α-methoxypregn-1,4-diene-3,20-dione (Ib) in 40 ml. of pyridine. The reaction was allowed to stand for 18 hr. at room temperature, methanol was added, and the mixture was evaporated. The residue was taken up in water and extracted with ethyl acetate. The extract was washed with water, dried, and evaporated to afford an oil which on treatment with acetone–petroleum ether gave 0.53 g. of crystals, m.p. 198–203°. Two crystallizations from the same solvent pair gave 0.41 g. of III, m.p. 202–205°, λ_{max} 235 mμ (ε 16,800); ν_{max} 3450, 1750 (shoulder), 1728, 1670, 1640 and 1618 cm.$^{-1}$; $[\alpha]_D^{30}$ +112° (chloroform).

Anal. Calcd. for $C_{24}H_{29}O_7F$ (448.47): C, 64.27; H, 6.52; F, 4.24; CH_3, 3.35. Found: C, 64.09; H, 6.74; F, 4.35; CH_3, 5.08.

9α-Fluoro-11β-hydroxy-16α-methoxyandrost-1,4-diene-3,17-dione (IV). To a solution of 0.6 g. of 9α-fluoro-11β,17α,-21-trihydroxy-16α-methoxypregn-1,4-diene-3,20-dione (Ic) in 60 ml. of 50% aqueous acetic acid was added 12 g. of sodium bismuthate. The mixture was stirred for 30 min. at room temperature whereupon 10% sodium hydroxide solution was added in sufficient quantity to almost neutralize the mixture. Chloroform (500 ml.) was added, the mixture was shaken up and filtered, and the filter cake was washed with chloroform. The product was worked up into a chloroform extract which was washed with sodium bicarbonate solution and water until neutral, dried, and evaporated to give an oil (0.40 g.). An ether slurry yielded 0.21 g. of IV; m.p. 228–231°. Several crystallizations from acetone-petroleum ether raised the melt to 233–235°; λ_{max} 237 mμ (ε 15,200); ν_{max} 3480, 1748, 1670, 1637, and 1615 cm.$^{-1}$; $[\alpha]_D^{25}$ +112° (chloroform).

Anal. Calcd. for $C_{20}H_{25}O_4F$ (348.40): C, 68.94; H, 7.23; F, 5.45; CH_3, 4.31. Found: C, 68.72; H, 7.46; F, 5.28; CH_3, 6.95, 6.97.

21-Acetoxy-9α-fluoro-11β,17α-dihydroxy-16α-methoxypregn-4-ene-3,20-dione (Ie). To a solution of 2.5 g. of 21-acetoxy-9α-fluoro-11β,16α,17α-trihydroxypregn-4-ene-3,20-dione (Id) in 1.5 liters of methylene chloride was added 2.5 ml. of fluoroboric acid solution (see the preparation of Ib) and 50 ml. of diazomethane solution. After 1 hr. the yellow color was discharged with fluoroboric acid and an additional 50 ml. of diazomethane solution was added. After 2 hr. this was repeated again and after the fourth hr. a final addition was made. The reaction mixture was allowed to stand for 16 hrs. at which time it was colorless. The polymethylene was filtered off, and the methylene chloride solution was washed with aqueous sodium bicarbonate and water until neutral. Evaporation gave an oil which was partition chromatographed on Celite[17] using the system: heptane–methylene chloride–ethylene glycol (70:30:10). Evaporation of holdback volume two gave 0.53 g. of solid, m.p. 204–208°. Four crystallizations from acetone–petroleum ether gave 0.22 g. of Ie, m.p. 212–214°; λ_{max} 238 mμ (ε 18,000); ν_{max} 3480, 3370 (shoulder), 1755, 1728, 1670 and 1628 (shoulder) cm.$^{-1}$; $[\alpha]_D^{30}$ +98° (chloroform).

Anal. Calcd. for $C_{24}H_{33}O_7F$ (452.50): C, 63.70; H, 7.35;

(16) Florisil is the Floridin Company's registered trademark for a synthetic magnesium silicate.

(17) Celite is Johns-Manville's registered trademark for diatomaceous silica products.

(18) The Zeisel methoxy determination was calculated as CH_3. It should be further noted that many of these determinations are extraordinarily high. The reason for this is not understood.

F, 4.20; CH_3, 3.32. Found: C, 63.86; H, 7.43; F, 4.22; CH_3, 3.38.

9α-Fluoro-11β,17α,21-trihydroxy-16α-methoxypregn-4-ene-3,20-dione (If). To a solution of 400 mg. of 21-acetoxy-9α - fluoro - 11β,17α - dihydroxy - 16α - methoxypregn-4-ene-3,20-dione (Ie) in 40 ml. of methanol kept under nitrogen was added 1.0 ml. of 10% aqueous potassium carbonate. The reaction mixture was allowed to stand for 20 min. at room temperature, at which time it was neutralized with acetic acid and evaporated until solid had formed. Water was added and the crystals were filtered off and washed with water to give 300 mg. of If, m.p. 240–245°. Several crystallizations from acetone-petroleum ether raised the melting point to 246–249°; λ_{max} 239 mμ (ε 17,800); ν_{max} 3490, 1711, 1680, and 1635 cm.$^{-1}$; $[\alpha]_D^{25}$ +108° (methanol).

Anal. Calcd. for $C_{22}H_{31}O_6F$ (410.47): C, 64.37; H, 7.61; F, 4.63; CH_3, 3.66. Found: C, 64.78; H, 7.93; F, 4.53; CH_3, 3.62.

Compound V. To a solution of 0.64 g. of II in 150 ml. of methanol, previously flushed with nitrogen, was added 2.1 ml. of 10% aqueous potassium carbonate. The reaction mixture was allowed to stand for 20 min. at room temperature and was then neutralized with acetic acid. Evaporation and addition of water gave 0.57 g., m.p. 267–270°. Several crystallizations from acetone–petroleum ether gave compound V, m.p. 277–280°; λ_{max} 240 mμ ($E_{1cm.}^{1\%}$ 378); ν_{max} 3450, 1729, 1670, 1640, and 1620 cm.$^{-1}$; $[\alpha]_D^{25}$ +47° (pyridine).

Anal. Found: C, 65.67, 65.66; H, 7.51, 7.43; F, 4.34, 4.23; CH_3, 8.01.

Acknowledgment. We wish to thank Louis M. Brancone and associates for the analytical data, William Fulmor and associates for the spectral and optical rotational data, and Charles Pidacks and associates for the partition chromatographic separations.

ORGANIC CHEMICAL RESEARCH SECTION
LEDERLE LABORATORIES
A DIVISION OF AMERICAN CYANAMID CO.
PEARL RIVER, N. Y.

Polynitro Aliphatic Esters

MILTON B. FRANKEL[1]

Received August 14, 1961

The selective reduction of polynitro acid chlorides to the alcohols with sodium borohydride was reported.[2] The conversion of these alcohols to the nitrate esters and of the acid chlorides to the 2,2,2-trinitroethyl esters is described in the present paper.

4,4-Dinitro-1,7-heptane dinitrate (I), 4,4,6,8,8-pentanitro-1,11-undecane dinitrate (II), 4,4,6,6,8,8-hexanitro-1,11-undecane dinitrate (III), 4,4,6,8,8-pentanitro-6-aza-1,11-undecane dinitrate (IV), and 3,5,5-trinitro-3-aza-1-hexane nitrate (V) were prepared in quantitative yields by treating the corresponding alcohols with absolute nitric acid (Table I). Generally nitrates have a lower melting point than the corresponding alcohols. This was confirmed in compounds I, II, and III which melt 25–47° lower than the alcohols from which they were prepared. However, compounds IV and V melt considerably higher than the corresponding alcohols, a significant factor which must be attributed to the presence of the nitramino group. This is of interest because it is believed that there is a correlation between the melting point and thermal stability of a compound, the higher melting compound being more thermally stable provided that other factors are the same.

The 2,2,2-trinitroethyl esters were generally prepared according to the procedure of Hill,[3] by treating the acid chlorides with 2,2,2-trinitroethanol in the presence of a catalytic amount of aluminum chloride. In this manner bis(2,2,2-trinitroethyl) 4,4-dinitroheptanedioate, bis(2,2,2-trinitroethyl)-4-nitrazaheptanedioate, bis(2,2,2-trinitroethyl) 4,7-dinitrazadecanedioate, and 2,2,2-trinitroethyl 3,5,5-trinitro-3-azahexanoate were synthesized. Bis(2,2,2-trinitroethyl) 4,4,6,6,8,8-hexanitroundecanedioate was prepared from 4,4,6,6,8,8-hexanitroundecanedioic acid and 2,2,2-trinitroethanol using 100% sulfuric acid as the ionizing solvent. The results are summarized in Table II.

EXPERIMENTAL[4,5]

Nitrate esters. The preparation of 4,4,6,6,8,8-hexanitro-1,-11-undecane dinitrate is typical. In a 300-ml. three-necked flask, fitted with a mechanical stirrer and thermometer, was placed 100 ml. of 100% technical nitric acid. The flask was immersed in an ice bath and 10 g. of 4,4,6,6,8,8-hexanitro-1,11-undecanediol was added portionwise in 10 min. The solution was stirred for 10 min. longer at this temperature and poured on ice. The white solid was collected, washed with water, and dried *in vacuo* over potassium hydroxide. The yield of 4,4,6,6,8,8-hexanitro-1,11-undecane dinitrate was 11.4 g. (95.2%).

2,2,2-Trinitroethyl esters. In a 100-ml. round-bottom flask, fitted with a condenser and drying tube, was placed a solution of 3.62 g. (0.02 mole) of 2,2,2-trinitroethanol in 50 ml. of dry ethylene dichloride. Anhydrous aluminum chloride, 0.27 g. (0.002 mole), was added, and the solution turned yellow. To the solution was added 3.31 g. (0.01 mole) of 4,7-dinitrazadecanedioyl chloride. The reaction mixture was refluxed until evolution of hydrogen chloride gas had ceased. The black mixture was cooled and filtered, the solid was washed with cold dilute hydrochloric acid, with water, then dried and recrystallized from ethylene dichloride using charcoal to give 5.3 g. (85.5%) of white crystals, m.p. 126–128°.

In a 500-ml. Erlenmeyer flask was placed 100 g. of 100% sulfuric acid, 18.0 g. (0.1 mole) of 2,2,2-trinitroethanol, followed by 24.3 g. (0.05 mole) of 4,4,6,6,8,8-hexanitroundecanedioic acid and 50 ml. of chloroform. After standing for 5 days with occasional shaking, the copious white solid was collected, washed with ice water, and dried, 35.6 g. (87.8%), m.p. 114–116. Recrystallization from chloroform raised the melting point to 117–118°.

(1) Present address: Stanford Research Institute, Menlo Park, Calif.

(2) G. B. Linden and M. H. Gold, to be published.

(3) M. E. Hill, *J. Am. Chem. Soc.*, **75**, 3020 (1953); **76**, 2329 (1954).

(4) All melting points are uncorrected.

(5) Microanalysis by Elek Microanalytical Laboratories, Los Angeles, Calif.