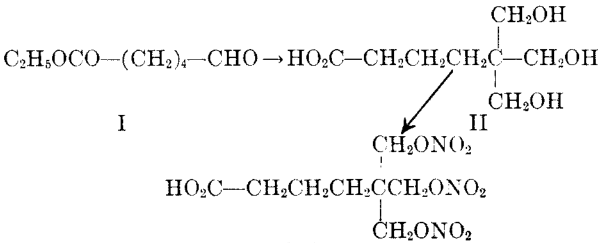
5,5-Dimethylol-6-hydroxyhexanoic Acid and Its Trinitrate Derivative

WILLIAM N. CANNON

Received July 20, 1956

A previous communication described the preparation of several monoacid esters of pentaerythritol trinitrate.[1] These compounds, upon pharmacological examination, exhibited a very pronounced hypotensive action. One compound in particular, pentaerythritol trinitrate hydrogen succinate, proved to be quite interesting physiologically. In view of the pharmacological effects of this series of compounds, it was deemed desirable to prepare similar materials which lacked the internal ester grouping. It was hoped that the absence of this grouping would provide compounds which would be less subject to hydrolytic attack *in vivo*, and would consequently have a longer duration of action. We are therefore reporting the preparation of 5,5-dimethylol-6-hydroxyhexanoic acid (II) and the trinitrate ester (III) of this new polyalcohol.



$$C_2H_5OCO{-}(CH_2)_4{-}CHO \rightarrow HO_2C{-}CH_2CH_2CH_2C(CH_2OH)_3 \rightarrow HO_2C{-}CH_2CH_2CH_2C(CH_2ONO_2)_3$$

I II III

The Rosenmund reduction of ethyl 5-chloroformylvalerate afforded ethyl 5-formylvalerate[2] (I) as the starting material for this work. This aldehyde was chosen to preclude the possibility of lactone formation during the acidic conditions required for the subsequent nitration step. The reaction of ethyl 5-formylvalerate with formaldehyde did not lead to ethyl 5,5-dimethylol-6-hydroxyhexanoate. Instead, in the course of the reaction the ester grouping was hydrolyzed and the desired 5,5-dimethylol-6-hydroxyhexanoic acid (II) was formed directly in low yield. The product was accompanied by the formation of considerable polymeric material. Nitration of this polyalcohol, using 95% nitric acid, produced 5,5-dimethylol-6-hydroxyhexanoic acid trinitrate (III) in good yield.

The preliminary pharmacological examination of this new nitrate ester has shown it to have a very marked hypotensive action.

Acknowledgment. The microanalyses were performed by H. L. Hunter, G. Maciak, and Miss Gloria Beckmann. The author wishes to express his appreciation to Dr. F. G. Henderson for the preliminary pharmacological data.

EXPERIMENTAL[3]

5,5-Dimethylol-6-hydroxyhexanoic acid (II). A mixture of 79 g. (0.5 mole) of ethyl 5-formylvalerate, 210 g. (2.5 moles) of 37% formalin solution, and 300 ml. of water was stirred vigorously. A small volume (25 ml.) of ethanol was added to help effect solution of the aldehyde. Calcium oxide was added in small portions until a total of 74.1 g. (1.0 mole) had been added. This addition caused the temperature to rise to a high of 44°. After all of the calcium oxide had been added, the mixture was stirred at 50° for 3 hours. The mixture was cooled and made slightly acid with 10% sulfuric acid. Filter Aid was added and the precipitated calcium sulfate removed by vacuum filtration. After washing the filter cake with 500 ml. of boiling water, the aqueous filtrate and washings were concentrated *in vacuo* on the steam-bath to a viscous syrup. Upon trituration with 150 ml. of ethanol the syrup quickly changed to a white, amorphous powder. This was collected by filtration and air-dried. After recrystallization from hot water there was obtained 11.6 g. (16.6%) of a white solid; m.p. 157–160°. Several recrystallizations from water were necessary to prepare a pure sample; m.p. 165–166°. Infrared examination indicated the presence of a free carboxylic acid function. Titration data indicated a molecular weight of 200 as compared to the theoretical value of 192.

Anal. Calc'd for $C_8H_{16}O_5$: C, 50.00; H, 8.34. Found: C, 50.09; H, 8.43.

The filtrates from above were evaporated *in vacuo* to give a considerable amount of tacky polymeric material which appeared to lose formaldehyde slowly. This was not investigated further.

5,5-Dimethylol-6-hydroxyhexanoic acid trinitrate (III). To 125 ml. of 95% nitric acid was added 6.6 g. (0.03 mole) of the trihydroxy compound in small portions while keeping the temperature at 0–5°. After all was added, the mixture was stirred for one hour at 0–5°, and then was poured onto 300 g. of crushed ice. This caused the separation of a gummy material which quickly crystallized. The product was collected by filtration and washed on the filter with cold water. After air-drying, the product weighed 8.3 g. (85%); m.p. 109–112°. The sample for analysis was recrystallized twice from absolute ethanol; m.p. 115–116°.

Anal. Calc'd for $C_8H_{13}N_3O_{11}$: C, 29.36; H, 4.00; N, 12.84. Found: C, 29.61; H, 4.12; N, 12.46.

THE LILLY RESEARCH LABORATORIES
INDIANAPOLIS 6, INDIANA

---

[1] Cannon, *J. Am. Chem. Soc.*, **77**, 6369 (1955).

[2] Brown, Armstrong, Moyer, Anslow, Baker, Querry, Bernstein, and Safir, *J. Org. Chem.*, 12, 160 (1947).

[3] Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected.

Polynitrogen Systems from the Hydrazinocarbonic Acids. Part VI. Reactions of Some Amines with Guanyl Azide Nitrate and Nitroguanyl Azide[1]

F. L. SCOTT,[2] F. C. BRITTEN, AND J. REILLY

Received July 23, 1956

In two other papers[3] of this series, we have in-

---

[1] See also F. L. Scott, A. J. Kocjarski, and J. Reilly, *Nature*, (*London*), **170**, 922 (1952).

[2] To whom inquiries concerning reprints are to be sent. Present address, Chemistry Department, University of California at Los Angeles, Los Angeles 24, California.

[3] (a) Part IV, F. L. Scott, A. J. Kocjarski, and J. Reilly, *J. Org. Chem.*, (being prepared for publication); (b) Part V, F. L. Scott, M. T. Scott, and J. Reilly, *J. Am. Chem. Soc.*, (in preparation); (c) See also, F. L. Scott, *Chemistry & Industry*, 959 (1954).