spectrum was identical with that of material prepared by lithium aluminum hydride reduction of methyl 6-methyloctanoate.[2]

6-Methyl-1-octanal (4).—To 450 ml of pyridine was slowly added 45 g of chromic acid with stirring and maintainence of the temperature below 30°. The resulting yellow precipitate was treated with 1 l. of hexane and quickly filtered. The solid was washed with hexane and rapidly dissolved in 900 ml of dichloromethane. 6-Methyloctanol (3) (9 g) was added slowly with stirring and after 10 min the supernatant was decanted from the black, gummy precipitate. The solution was washed with 300 ml of water and 450 ml of 1 *N* HCl and dried ($MgSO_4$). After evaporation of solvent the dark residue was extracted with 100 ml of hexane. The clear solution was evaporated to leave 8.5 g of colorless liquid, which was distilled to yield 6.2 g (69%) of aldehyde, bp 64–66° (6 mm), 2,4-dinitrophenylhydrazone mp 80–82° (*n*-C_3H_7OH).

Anal. Calcd for $C_{15}H_{22}N_4O_4$: C, 55.9; H, 6.88; N, 17.4. Found: C, 55.8; H, 7.01; N, 17.2.

Methyl 14-Methyl-*cis*-8-hexadecenoate (5).—A mixture of 25.0 g of triphenylphosphine, 19.0 g of methyl 8-bromooctanoate, and 250 ml of toluene was refluxed for 24 hr. The cooled supernatant was decanted and the viscous residue was dried to leave 29 g (71%) of the triphenylphosphonium salt. The crude salt (0.058 mol) in 45 ml of dimethylformamide was rapidly added to a suspension of 2.5 g (0.046 mol) of sodium methylate in 50 ml of DMF under nitrogen. After being stirred for 1 hr the yellow mixture was cooled in ice and 5.2 g (0.036 mol) of 6-methyloctanal in 25 ml of DMF was added over 10 min. The mixture was stirred for 18 hr under nitrogen and then chilled and diluted with 400 ml of water. Extraction with 100-ml and two 50-ml portions of hexane was followed by washing with 100 ml of water, drying over magnesium sulfate, and evaporation to leave 7.9 g of yellow liquid.

The crude material was saponified with 2.5 g of potassium hydroxide in 50 ml of 90% methanol to yield 2.80 g of carboxylic acid. Reesterification (methanol–toluenesulfonic acid) gave 2.64 g of ester which was chromatographed on 130 g of silica gel to afford 1.05 g of ester after elution by a 10% ether–90% benzene mixture. Glc (Carbowax 20M) showed the material to be about 90% pure when compared with the natural compound. Infrared spectra were likewise identical except for weak trans C=C at 10.3 μ.

14-Methyl-*cis*-8-hexadecenol (6).—A mixture of 0.75 g of methyl ester 5, 0.30 g of lithium aluminum hydride, and 15 ml of ether was stirred for 20 hr. The mixture was cooled in ice and excess hydride was decomposed with ethanol and water. The white, pasty precipitate was extracted with several portions of ether which were dried over magnesium sulfate and evaporated to leave 0.48 g. Extraction with pentane gave only 0.36 g of soluble material, approximately 90% pure by glc (Carbowax 20M). Further purification was carried out with preparative glc to afford material identical with the natural alcohol with regard to glc retention time, infrared spectrum, and biological activity.

Registry No.—1, 30689-73-7; 2, 30689-74-8; 4, 30689-75-9; 4 2,4-DNP, 30689-76-0; 5, 30689-77-1; 6, 30689-78-2.

Acknowledgment.—The bioassay was conducted by Dr. W. E. Burkholder, University of Wisconsin, USDA Laboratories.

Isolation of Betamethasone 17,21-Orthobenzoate

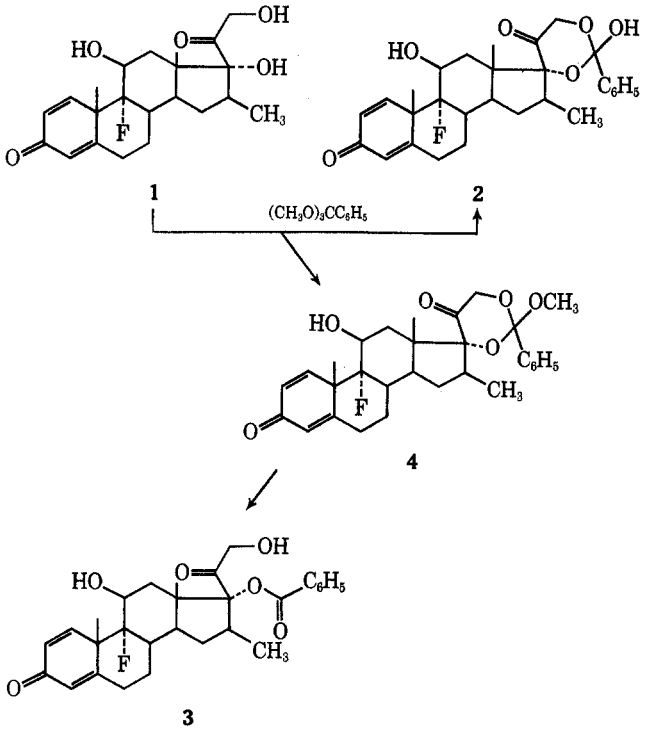
EDWARD J. MERRILL* AND GERALD G. VERNICE[1]

Department of Analytical/Physical Chemistry, Warner-Lambert Company, Morris Plains, New Jersey 07950

Received December 11, 1970

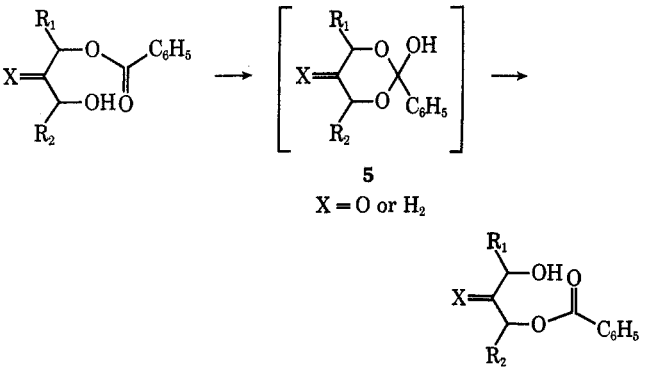
The preparation of betamethasone 17-benzoate (9α-fluoro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17-benzoate) (3) labeled with tritium was required in order to determine its excretion pattern and to elucidate its metabolite(s) in various animal species and man. The synthesis of the radioactive drug is reported elsewhere.[2] During the preliminary work with nonradioactive compounds, on the same small scale required for the radioactive synthesis, an unknown was isolated which possessed an unusual structure.

SCHEME I



This synthesis, as shown in Scheme I, necessitated the preparation of betamethasone 17,21-(methyl orthobenzoate) (4). This reaction produced, in addition to 4, about an equal weight of a more polar compound. The structure of this compound was shown to be betamethasone 17,21-orthobenzoate (2). Compound 2 is novel because it contains the ortho ester structure of the normally unstable intermediate 5 in the generalized migration depicted in Scheme II.

SCHEME II



(1) Hoffman-La Roche, Inc., Nutley, N. J. 07110.

(2) E. J. Merrill and G. G. Vernice, *J. Label. Compounds*, in press.

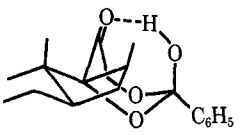
This generalized migration of an acyl group from one hydroxyl group to the other has been observed with 1,2- and 1,3-dihydroxy compounds.[3-7] This is one of the few examples of the isolation of such an ortho ester.[8]

Betamethasone (**1**), when allowed to react with freshly distilled trimethyl orthobenzoate in dimethylformamide in the presence of 3% *p*-toluenesulfonic acid (*p*-TsOH) as described by Ercoli and Gardi,[9,10] gave both **2** and **4**, each in about 30% yield. This reaction was reinvestigated with the aim of increasing the yield of **2**. Varying the amount of *p*-TsOH had no effect on either the yield or the products. However, the yield of **2** was increased to 50–60% merely by using the practical grade of trimethyl orthobenzoate as supplied by the manufacturer.[11] Gas chromatography demonstrated that the trimethyl orthobenzoate, as received, contained about 5% methyl benzoate and less than 1% methanol.[12] When methyl benzoate was substituted for the trimethyl orthobenzoate, no reaction occurred. When synthetic mixtures of methyl benzoate with trimethyl orthobenzoate were allowed to react with **1**, the yields decreased as the amount of methyl benzoate increased. However, the products **2** and **4** were always present in an approximate ratio of 1:1. These results eliminate methyl benzoate as the reactant in the formation of **2**. This aspect of the work must still be clarified.

It was noted during the isolation that impure **2** was unstable and rapidly hydrolyzed to **1** either in solution or in the solid state. The stability of **2** was increased greatly by incorporating 0.5% pyridine into any solvent in which it was dissolved. When pure, **2** was stable for several months.

The infrared spectrum of **2** was similar to **4** but with fewer bands in the C–O stretch region (1020–1120 cm^{-1}) and demonstrated the absence of a benzoate carbonyl band and that the A ring dienone system was unchanged. The ultraviolet spectrum of **2** confirmed the latter observation. The nmr spectrum showed (a) the presence of a phenyl group (δ 7.30–8.10), (b) the presence of three vinyl protons at C-1, 2, and 4 (δ 6.00–6.25, 7.34), (c) the absence of the O–CH_3 group, whose protons in **4** appear at δ 2.92 and 3.00 attributable to the two epimeric forms,[13] and (d) a slight shift in the position of the C-16 methyl protons (δ 1.01) from **3** (δ 1.41) but very similar to **4** whose protons appear at δ 1.08 and 1.28 also attributable to the epimeric forms. A molecular ion could not be obtained as **2** immediately fragmented in the mass spectrometer. However, a prominent fragment having a *m/e* ratio of 105 was evident as expected for the $C_6H_5CO^+$ ion.

A study of the infrared spectra, which resulted from serial dilutions of **2** in $CHCl_3$, demonstrated that strong intramolecular hydrogen bonding was present. This must account for the stability of this ortho ester. The postulated partial structure **6** is shown below.



6

Several hydrolysis experiments were performed in order to show the differences between **2** and **4**. The hydrolysis conditions were chosen to allow a reasonable comparison of the two samples. It should be emphasized that the reported products were the only ones observed either before or after the time period reported.

After 20 min at room temperature, a 2% solution of **4** in a mixture of 10 parts of chloroform, 35 parts of methanol, 3.5 parts of water, and 2.4 parts of concentrated hydrochloric acid gave about 80% of **3** and about 10% of both **1** and betamethasone 21-benzoate (**7**). Under the same conditions, **2** gave about 70% of **1** and about 30% of **7**. No **3** could be detected.

As a 1% solution in 0.2 *N* methanolic potassium hydroxide, no change was detected in either **2** or **4** after 2.5 days at room temperature.

To ensure identification, both **1** and **7**, which resulted from the acid hydrolysis of **2**, were eluted from the tlc plate. An infrared spectrum of each compound was determined as a micro KBr pellet. Both spectra exhibited the same maxima and minima as their respective authentic samples.

Experimental Section

Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. Uv and ir spectra were determined with Beckman DK-1A and Perkin-Elmer 621 or Baird 4-55 spectrophotometers. Nmr results were obtained with a Varian A-60 spectrometer using tetramethylsilane as an internal standard.

Preparative tlc was done using 20 × 20 cm glass plates coated with a 250-μ thick layer of silica gel GF (Analtech, Inc.) prewashed with methanol and reactivated by heating at 100° for 1 hr. The solvent used for development was a mixture[14] of 80 parts of benzene and 20 parts of acetone. All the solvents were specially purified.[15] Typical R_f values obtained with this system for **1**, **2**, **3**, **4**, and **7** were 0.20, 0.50, 0.55, 0.45, and 0.60, respectively. The spots were visualized under short-wave uv light or by spraying with a 50% solution of concentrated sulfuric acid in methanol and then heating at 110° for about 15 min. A deep blue color resulted.

Betamethasone 17,21-(Methyl orthobenzoate)[9] (**4**).—To 0.53 g (2.9 mmol) of redistilled trimethyl orthobenzoate and 1.5 mg (0.0079 mmol) of *p*-TsOH in a 5-ml round-bottom flask with a condenser was added a solution of 50 mg (0.127 mmol) of **1** in 1.5 ml of dimethylformamide.[16] taken from a newly opened bottle. A stream of nitrogen was slowly bubbled through the solution while the reaction was heated in an oil bath at 105° for

(3) J. F. King and A. D. Allbutt, *Can. J. Chem.*, **48**, 1754 (1970).
(4) R. Gardi, R. Vitali, and A. Ercoli, *Tetrahedron Lett.*, No. 13, 448 (1961).
(5) H. Gilman, "Organic Chemistry," Vol. II, 2nd ed, Wiley, New York, N. Y., 1947, p 1610.
(6) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 680.
(7) D. J. Cram and G. S. Hammond, "Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1964, p 486.
(8) H. W. Post, "The Chemistry of the Aliphatic Orthoesters," ACS Monograph Series No. 92, Reinhold, New York, N. Y., 1943, pp 24, 38.
(9) A. Ercoli and R. Gardi, South Africa Patent 68/1303 (Sept 10, 1968).
(10) A. Ercoli and R. Gardi, U. S. Patent 3,147,249 (Sept 1, 1964).
(11) Purchased from Eastman Organic Chemicals, Rochester, N. Y., 14650.
(12) Mr. R. Sprissler of these laboratories accomplished this separation on a 6-ft glass column of 2% Carbowax on 80–100 mesh Gas-Chrom Q programmed for a temperature rise of 10°/min at a helium flow of about 50 ml/min. The sample was introduced at 150° and a flame detector was used.
(13) Ercoli and Gardi[4] have isolated the epimeric forms of several steroidal 17α,21-ethylorthoformates.
(14) A. D. Lewis and M. Goodenough, these laboratories, private communication.
(15) For a discussion about purification of solvents, see E. J. Merrill and G. G. Vernice, *J. Label. Compounds*, **6**, 269 (1970).
(16) Purchased from Fisher Scientific Co., Fair Lawn, N. J.

20 hr. The reaction was cooled to room temperature and 2 drops of pyridine added. Tetrachloroethylene was added to aid in the removal of the solvents *in vacuo* at <35°. The oily residue was dissolved in 0.7 ml of chloroform and purified *via* preparative tlc. The crude **4** was then dissolved in 0.35 ml of peroxide-free diethyl ether and percolated through a 3-g alumina column (Merck) deactivated with 3% water followed by more diethyl ether. The eluate (20 ml) was collected and the solvent removed. The residue weighed 32.4 mg (50%). A tlc exhibited a single uv absorbing spot. This material was sufficiently pure and was used to prepare **3**: ir (KBr) 3450, 1740–1725, 1665, 1635–1605, 1290, 1130–1005, 890, 695 cm^{-1}; nmr (DMSO-d_6) δ 7.20–7.70 (m, 5), 7.25 (d, 1, J = 10 Hz), 6.00–6.25 (m, 2), 5.29 (d, 1, J = 5 Hz), 4.33 (s, 1), 4.15 (s, 2), 2.92 and 3.00 (s, 1), 1.48 (s, 3), 1.08 and 1.28 (d, 2, J = 6 Hz), 1.0 (s, 3); uv max (CH_3OH) 238–240 nm (a 29.7).

Betamethasone 17-Benzoate[9] (**3**).—A solution of 32.4 mg (0.064 mmol) of **4** in 6.5 ml of methanol and 2.59 ml of a Sorensen citrate buffer[17] at pH 3.7 was heated in an oil bath at 50° for 30 min. The solvents were removed and the residue was dissolved in 25 ml of chloroform. This was washed with three 10-ml portions of distilled water, dried ($MgSO_4$), and filtered, and the solvent removed. The residue was redisssolved in a small amount of chloroform and purified by preparative tlc.

This gave 11.8 mg (38%) of **3** as a white solid: uv max (CH_3OH) 233 nm (a 53.4);[18] ir (KBr) 3470, 3230, 1740–1715, 1670, 1620, 1610, 1280, 1105–1060, 890, 710 cm^{-1}; nmr (DMSO-d_6) δ 7.35–8.15 (m, 5), 7.37 (d, 1, J = 10 Hz), 6.10–6.20 (m, 2), 5.33 (broad, 1), 5.05 (t, 1, J = 6 Hz), 4.36 (broad 1), 4.05 (d, 2, J = 6 Hz), 1.55 (s, 3), 1.41 (d, 3, J = 5 Hz), 0.97 (s, 3). A tlc exhibited a single uv-absorbing spot.

Betamethasone 17α,21-Orthobenzoate (**2**).—This material was prepared in an identical manner as described for **4** except that the trimethyl orthobenzoate was used without purification. The product of this reaction, as an oily residue, was dissolved in ethyl acetate and distributed equally on the appropriate number of 20 × 20 cm plates for preparative tlc. The compound was eluted from the adsorbent with benzene–acetone (1:2). The solvent was removed from the combined eluate and the solid recrystallized from about 30 parts of ethyl acetate. Recoveries of about 70% were obtained from each of the two recrystallizations usually required to raise the melting point to 213–215°. Additional quantities of less pure material may be obtained by adding an equal volume of Skellysolve B to the filtrates.

In a typical reaction, 17.7 mg (28%) of **2** was obtained from 50 mg (0.127 mmol) of **1** after preparative tlc. Two recrystallizations from 30 parts of ethyl acetate gave the analytical sample which melts at 213–215° after drying *in vacuo* at 37° for 20 hr. A tlc was developed after spotting 500 μg and a single uv-absorbing spot was observed: uv max (CH_3OH) 232 nm (a 54.3); ir (KBr) 3350 (broad), 1735–1720, 1660, 1640, 1600, 1280, 1120–1020, 890, 710 cm^{-1}; nmr (DMSO-d_6) δ 7.30–8.10 (m, 5), 7.34 (d, 1, J = 10 Hz), 6.00–6.25 (broad, 2), 4.98 (d, 1, J = 6 Hz), 4.42 (broad, 1), 1.49 (s, 3), 1.01 (s, 3), 0.90 (s, 3). The ir continued to exhibit a broad band at 3440 cm^{-1} at concentrations of 2.58, 1.29, 0.65, and 0.32% (w/v) in $CHCl_3$ using a 0.5-mm cell.

Anal. Calcd for $C_{29}H_{33}FO_6 \cdot C_6H_6$: C, 72.98; H, 6.82; F, 3.31. Found: C, 73.04; H, 6.73; F, 3.26.

Prolonged heating at elevated temperatures in an attempt to remove the solvate caused decomposition.

Registry No.—**2**, 31020-75-4; **3**, 22298-29-9; **4**, 31020-77-6.

Acknowledgment.—The authors wish to acknowledge the technical assistance of Mrs. N. Eltvedt. We also are indebted to Mr. A. D. Lewis, Director of Analytical/Physical Chemistry, and his associates, Dr. R. C. Greenough for providing and aiding in the interpretation of the spectral data, and Mrs. U. Zeek for the microanalyses. We also wish to thank Dr. E. A. Eliel for helpful discussions.

(17) W. M. Clark, "Determination of Hydrogen Ions," Williams and Wilkens Co., Baltimore, Md., 1927, p 114.

(18) This was 97.7% of an authentic sample.

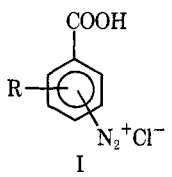
Thermal Decomposition Reactions of Carboxybenzenediazonium Salts. III. Attempts to Generate 1,3-Dehydrobenzene in Solution[1]

ROBERTO A. ROSSI, RITA HOYOS DE ROSSI, AND HECTOR E. BERTORELLO*

Departamento de Química Orgánica, Instituto de Ciencias Químicas, Universidad Nacional de Córdoba, Córdoba, Argentina

Received September 11, 1970

Many efforts have been made to know more about 1,2-dehydrobenzene (benzyne) and its derivatives,[2] but not much progress has been made on other dehydroaromatic intermediates such as 1,8-dehydronaphthalene[3] and 2,6-dehydropyridine.[4] 1,3- and 1,4-dehydrobenzene were formed from flash photolysis of *m*- and *p*-benzenediazoniumcarboxylates.[5,6] We have postulated 1,3 and 1,4 dehydroaromatics as intermediates in the thermal decomposition of dry carboxybenzenediazonium salts of type I in the solid state.[1,7]



I

It was proposed that the thermal decomposition of I led to a carbonium ion after evolution of nitrogen and hydrogen chloride, which then decomposes losing carbon dioxide to give the respective dehydroaromatic compound. The yield of carbon dioxide evolved depends principally on the position of the positive charge, the substituent R, and the possibility of reaction between the carbonium ion and other species in the reaction medium.[1,7]

The study of these reactions offers some advantages in the elucidation of the substituent effects and intermediates involved, since solvation effects are absent,[8] but these reactions are not useful for kinetic studies because they proceed explosively.

The reaction of 3-carboxy-4-nitrobenzenediazonium chloride (II) suspended in different solvents was examined, in search for the possibility of repressing the explosive decomposition. Unfortunately, in the solvents used, the proportion of carbon dioxide evolved is far from that observed when solid diazonium salt was decomposed. Moreover, in most of the solvents used the

(1) Part II: H. E. Bertorello, R. A. Rossi, and R. H. de Rossi, *J. Org. Chem.*, **35**, 3332 (1970).

(2) For reviews see (a) R. W. Hoffmann, "Dehydrobenzene and Cycloalkynes," Academic Press, New York, N. Y., 1967; (b) J. F. Bunnett, *J. Chem. Educ.*, **38**, 278 (1961); (c) H. Heaney, *Chem. Rev.*, **62**, 81 (1962).

(3) (a) C. W. Rees and R. C. Storr, *J. Chem. Soc. C*, 760 (1969); (b) R. W. Hoffmann, G. Guhn, M. Preiss, and B. Dittrich, *ibid.*, 769 (1969); (c) R. W. Hoffmann and W. Sieber, *Angew. Chem., Int. Ed. Engl.*, **4**, 786 (1965).

(4) T. Kauffmann, *ibid.*, **4**, 543 (1965).

(5) R. S. Berry, M. Clardy, and M. E. Schafer, *Tetrahedron Lett.*, 1011 (1965).

(6) R. S. Berry, M. Clardy, and M. E. Schafer, *ibid.*, 1003 (1965).

(7) R. H. de Rossi, H. E. Bertorello, and R. A. Rossi, *J. Org. Chem.*, **35**, 3328 (1970).

(8) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 568.