(KBr) 3200–3600 (water OH), 2200–3200 (NH_2^+), 1770 (β-lactam C=O), 1730 (imidazolidinyl C=O), 1600 (COO^-), 760, 705 cm^{-1} (C_6H_5–); nmr (DMSO-d_6) δ 7.0–7.6 (m, 20, C_6H_5–), 5.3–6.0 (m, 15, NH_2^+, H_2O, NCHCO), 5.0 (d, 2, NCHS), 3.9 (s, 4, $C_6H_5CH_2N$), 2.6–3.4 (m, 8, $SCH_2C{=}C$, NCH_2CH_2N), 1.9 (s, 18, $CH_3C{=}C$, CH_3CH_3C).

Anal. Calcd for $C_{54}H_{60}N_{10}O_{10}S_2 \cdot 3H_2O$: C, 57.53; H, 5.90; N, 12.43. Found: C, 57.54; H, 6.21; N, 12.71.

The 4 g of the DBED salt of **4** was suspended in 75 ml of water, and 25 ml of 40% H_3PO_4 was added. The mixture was layered with 50 ml of ethyl acetate and shaken vigorously until all the salt dissolved. A final extraction was made with 50 ml of ethyl acetate and the organic layers were collected, washed with water, and evaporated at 40° (15 mm) to obtain a crystalline solid which weighed 2.95 g (32%), mp 175–180°. The ir and nmr spectra were identical with the spectra of authentic **4** prepared from cephalexin.

7β-(D-α-Aminophenylacetamido)-3-methyl-3-cephem-4-carboxylic Acid (Cephalexin) (6) *via* Hetacephalexin (5).—Into a solution of 1 g (0.0025 mol) of **4** in 50 ml of dioxane (purified by running through a column of aluminum oxide) was introduced a stream of dry hydrogen chloride for 5 min at room temperature. The solution was evaporated at 30° (15 mm) to a gum, which was slurried with ethyl acetate and collected. The solid was then dissolved in water (50 ml) and made basic with aqueous sodium bicarbonate solution to pH 4.8. The mixture was filtered, and the filtrate was evaporated at 30° (15 mm) to a glass which was further dried by azeotropic distillation with ethyl acetate. The yield of the sodium salt was 600 mg (63%). The nmr and ir spectra were consistent with the spectra of the acetone condensation product of cephalexin (**5**).

A solution of 1 g (0.0024 mol) of sodium hetacephalexin (**5**) in 5 ml of water was adjusted to pH 3.5 with 6 *N* hydrochloric acid and stirred at room temperature overnight while a stream of nitrogen was bubbled through the solution to remove the acetone formed during the reaction. The white crystalline cephalexin was collected, the filtrate was adjusted to pH 3.5 again and made up to a volume of 5 ml, and the procedure was repeated. The initial crop weighed 350 mg after drying *in vacuo* over P_2O_5. The second crop weighed 240 mg, giving a total yield of 590 mg (70%). The nmr and ir spectra were identical with those of authentic cephalexin.

Cephalexin (6) Prepared Directly from 4.—A solution of 2 g (0.0048 mol) of **4** in 100 ml of peroxide-free dioxane was treated with dry hydrogen chloride for 10 min at room temperature. The solution was evaporated at 35° (15 mm) to a gummy solid. The solid was dissolved in 10 ml of water and filtered, and the pH was raised to 4.5 by the addition of 10% sodium hydroxide solution. The solution was stirred for 48 hr at 30° while a stream of nitrogen was bubbled through the mixture. The white solid was collected and washed with cold water and finally with acetone to yield 550 mg (30%) of pure **6**.

7β-(D-2,2-Dimethyl-3-nitroso-5-oxo-4-phenyl-1-imidazolidinyl)-3-methyl-3-cephem-4-carboxylic Acid (4) from Cephalexin.—To a mixture of 10 g (0.03 mol) of (7-D-α-aminophenylacetamido)-3-methyl-3-cephem-4-carboxylic acid in 100 ml of water was added 10% sodium hydroxide solution until pH 7.8 was attained. To this solution was added 40 ml of acetone, and the reaction mixture was stored overnight. The solvent was evaporated, leaving behind a frothy, amorphous solid which was dissolved in 200 ml of water and acidified to pH 2 with 6 *N* hydrochloric acid, and layered with 200 ml of ethyl acetate. The solution was cooled in an ice bath to 5°, and 2.1 g (0.03 mol) of sodium nitrite was added. After stirring for 0.5 hr, the ethyl acetate was separated, washed with water, and evaporated under reduced pressure to an oil. The oil solidified on slurrying with ether to give 2.5 g of an amorphous solid. During storage overnight, a second crop separated, which was crystalline and weighed 1.2 g. The crops were combined and recrystallized from ethyl acetate and ether to obtain 3.2 g (26%). The analytical sample was recrystallized from boiling methanol: mp 175–180° dec; ir (KBr) 2500–3500 (carboxyl OH), 1780 (β-lactam C=O), 1720 and 1730 (imidazolidinyl C=O and carboxyl C=O), 700 cm^{-1} (C_6H_5–); nmr (DMSO-d_6) δ 7.31 (s, 5, C_6H_5), 5.68 (s, 1, C_6H_5CHN), 5.55 (d, 1, J = 4.5 cps, NCHCO), 5.15 (d, 1, J = 4.5 cps, NCHS), 2.9–3.6 (m, 2, SCH_2), 1.8–2.3 (m, 9, CH_3CH_3CN and $CH_3C{=}$).

Anal. Calcd for $C_{19}H_{20}N_4O_5S \cdot {}^1/_2H_2O$: C, 53.73; H, 4.74; N, 13.17. Found: C, 53.90; H, 4.96; N, 13.48.

6α-(D-2,2-Dimethyl-3-nitroso-5-oxo-4-phenyl-1-imidazolidinyl)-penicillanic Acid Sulfoxide (6 Epimer of 2).—To a solution of 20 g (0.048 mol) of **2** in 500 ml of water made basic to pH 9 by the addition of 10% sodium hydroxide was added 12 g (0.056 mol) of sodium metaperiodate. After stirring for 2 hr at pH 7, the solution was acidified to pH 2 with 40% H_3PO_4 and the crystalline solid was collected, washed with water, and dried *in vacuo* over P_2O_5 to yield 14 g (67%): mp 201° dec; ir (KBr) 2990 and 2950 (CH_3), 1795 (β-lactam C=O), 1735 (imidazolidinyl C=O and carboxyl C=O), 705 (monosubstituted phenyl); nmr ($CDCl_3$ and DMSO-d_6) δ 7.0–7.76 (m, 5, C_6H_5), 5.7 (d, J = 2 Hz, 1, C_6H), 5.6 (s, 1, C_6H_5CH), 4.9 (d, J = 2 Hz, 1, C_5H), 4.3 (s, 1, C_3H), 1.9–2.2 (m, CH_3CH_3CN), 1.65 and 1.3 (2 s, 3, 3, CH_3CH_3CS).

Anal. Calcd for $C_{19}H_{22}N_4O_6S \cdot 2H_2O$: C, 48.51; H, 5.57; N, 11.91. Found: C, 48.47; H, 5.23; N, 11.79.

Registry No.—**1**, 14537-96-3; **2**, 34959-70-1; **2** (6 epimer), 34959-71-2; **3**, 34982-12-2; **4**, 34959-72-3; **4** DBED salt, 34959-73-4; **6**, 15686-71-2.

Synthesis of Compounds Structurally Related to Poison Ivy Urushiol. V.[1a] A Novel Synthesis of 3-*n*-(1′,2′-Dehydro)pentadecylcatechol (3β-Alkylvinylcatechols) *via* Dehydration of a Bis(trimethylsilyl) Intermediate[1b]

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Received July 2, 1971

In connection with recent studies[1a] of the role of the side chain in the dermatological activity of 3-alkylcatechols, it became necessary to develop a practical synthesis of 3-*n*-(1′,2′-dehydro)pentadecylcatechol (**1a**), the styrenic analog of the saturated component of poison ivy urushiol, 3-*n*-pentadecylcatechol (3-PDC). A search of the literature revealed that no efficient synthesis of compounds of the general type, 3β-alkylvinylcatechol, had previously been reported.

While the dimethyl (**1b**) and dibenzyl (**1c**) ethers of **1a** can easily be prepared by conventional routes from, respectively, 2,3-dimethoxybenzaldehyde and 2,3-dibenzyloxybenzaldehyde,[2] neither **1b** nor **1c** can be converted to the free dihydroxybenzene derivative, **1a**.[3]

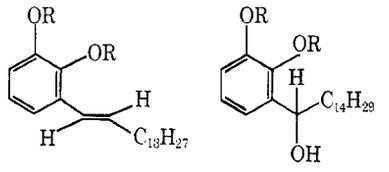
Exploratory experimentation confirmed the results of earlier studies in which it had been found that 3-*n*-

(1) (a) Previous paper in the series (IV): A. P. Kurtz and C. R. Dawson, *J. Med. Chem.*, **14**, 733 (1971). (b) These investigations were supported by Contract PH-43-64-76 with the Division of Biologics Standards of the National Institutes of Health. (c) National Institutes of Health Predoctoral Fellow, 1965–1968.

(2) (a) H. J. Backer and N. H. Haack, *Recl. Trav. Chim. Pays-Bas*, **57**, 225 (1938); (b) B. Loev and C. R. Dawson, *J. Amer. Chem. Soc.*, **78**, 6095 (1956).

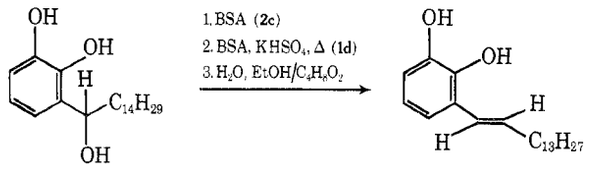
(3) Prior to the development of the synthetic route with which this report is concerned, a series of experiments were conducted testing methods of cleavage of **1b** and **1c** to **1a**. Use of a variety of agents, including $AlCl_3$–chlorobenzene, HBr–HOAc, pyridinium chloride, and others for the cleavage of **1b** gave high yields of polymer when conditions vigorous enough to effect cleavage were employed. Reductive cleavage of **1c** using either Na–1-butanol or hydrogenolysis (10% Pd/C) yielded only the saturated 3-PDC.

(1′-hydroxy)pentadecylcatechol (**2a**)[4] cannot be successfully dehydrated without extensive cyclization or polymerization.[5]



1a, R = H
b, R = CH_3
c, R = CH_2Ph
d, R = $Si(CH_3)_3$

2a, R = H
b, R = CH_2Ph
c, R = $Si(CH_3)_3$



2a **1a**

3-*n*-(1′,2′-Dehydro)pentadecylcatechol (**1a**) was successfully synthesized in the present investigation from **2a**[4] according to the route shown *via* the bis(trimethylsilyl) intermediates **2c** and **1d**. As reported in the Experimental Section, bis(trimethylsilyl)acetamide (BSA)[6] was used first as a reagent to form **2c**, an analog of **2a** having protected phenolic hydroxyl groups, and secondly as a water scavenger during the pyrolytic dehydration of **2c**. It is interesting to note that our mild silylation procedure did not effect etherification of the sterically hindered 1′-hydroxyl group in **2a** (see nmr data for **2c**). Use of BSA as a water scavenger apparently precludes *in situ* hydrolysis of the protecting TMS groups during the dehydration. Concomitant cyclization or polymerization is thus avoided. By this route **1d** was obtained from **2a** in an overall yield of 60%; both **2c** and **1d** were easily purified by fractional distillation. The bis(trimethylsilyl) compound, **1d**, was quantitatively hydrolyzed to the alkylvinylcatechol, **1a**, using aqueous ethanol–dioxane at 100° as given in the Experimental Section.

The success of this synthesis suggests its general applicability to the synthesis of 3β-alkylvinylcatechols, hitherto very elusive compounds.

Experimental Section

Precursors to 3-*n*-(1′,2′-Dehydro)pentadecylcatechol.—A sample of 8.0 g (0.024 mol) of 3-*n*-(1′-hydroxy)pentadecylcatechol (**2a**),[4] mp 90.0–91.0° (lit.[7] mp 89.6–90.5°), was dissolved in 100 ml of anhydrous benzene and stirred under a nitrogen blanket at room temperature. Over a 2-min period, 10.6 g of bis(trimethylsilyl)acetamide (BSA)[6] was added with ice bath cooling as necessary to maintain the temperature of the reaction near 50°. The resulting solution was stirred for about 20 min until the exothermic reaction was complete and allowed to stand under nitrogen for 18 hr. About 1 g of acetamide, mp 68–79°, was filtered off, and the filtrate was evaporated *in vacuo* using an 80° bath to give 17.08 g of a thick oil.

Part (7.25 g) of this oil was cleanly distilled *in vacuo* using a small Vigreux column to give a viscous oil, bis(trimethylsilyl)-3-*n*-(1′-hydroxy)pentadecylcatechol (**2c**): 4.5 g (93% yield); ir (neat) 2.86 (w, sharp), 2.8–3.0 (vw, broad), 3.45 (s, sharp), shoulder 3.53 (s, sharp), 6.29 (w), 6.78 (vs, broad), 7.36 (w, broad), 7.80 (m, broad), 8.01 (vs, sharp), 8.23 (m, broad), 9.0–9.5 (m, very broad), 9.8–10.5 (m, very broad), 10.9 (s, broad), 11.2–12.2 (vs, very broad), 13.0–13.7 (m, very broad); nmr (CCl_4) τ 2.83–3.55 (multiplet, 3 H, aromatic), 5.07 (center of poorly defined triplet, 1 H, benzylic), 7.57 (s, 1 H, hydroxyl), 8.0–9.5 (broad singlet and distorted triplet, 29 H, $C_{14}H_{29}$), 9.78 [center of jagged singlet, 18 H, bis-$Si(CH_3)_3$].

A sample of 8.0 g of the crude (not purified by distillation) **2c** was pipetted into a 125-ml erlenmeyer flask fitted with a gas inlet tube reaching to the bottom and to one side of the flask. While this material was flushed with bubbling nitrogen, 3.4 g of BSA and 0.5 g of powdered $KHSO_4$ were added. With agitation *via* the nitrogen bubbling, the contents of the flask were heated for 30 min using a 150–200° bath. The progress of the dehydration was monitored by observation of frothing and reflux of low-boiling materials. Following this pyrolysis period, 3.4 g further of BSA was added and the contents of the flask were heated for 10 min at 150°. The resulting clear, slightly yellow oil was transferred to a pointed flask and distilled *in vacuo* through a Vigreux column. Following collection of a low-boiling fraction including excess BSA, 2.99 g (60% yield from **2a**) of a clear, slightly yellow oil was obtained, bis(trimethylsilyl(-3-*n*-(1′,2′-dehydro)pentadecylcatechol (**1d**): bp 185–190° (0.1 mm); one spot on tlc analysis (extremely mobile); ir (neat) essentially identical with spectrum for **2c** except no OH bands in the present spectrum (2.86, 2.80, 3.0, 7.36, 9.0–9.5 μ bands absent); nmr (CCl_4) τ 2.8–3.2 (multiplet, 5 H, aromatic and vinyl), 7.4–8.0 (broad resonance, allylic), 8.0–9.3 (broad singlet and distorted triplet, $C_{12}H_{25}$), signals at τ 7.4–9.3 integrated for 27 H, 9.80 and 9.83 (two sharp singlets, 18 H, bis-TMS). A 10.3 μ band in the ir spectrum was diagnostic for predominance of the trans isomer.

3-*n*-(1′,2′-Dehydro)pentadecylcatechol (1a).—A sample of 3.18 g of **1d** was dissolved in 30 ml of dioxane containing 10 ml of 95% ethanol. The solution was brought to reflux under nitrogen with stirring. A total of about 15 ml of water was dripped in gradually over 2 hr at a rate slow enough so that the solution never became turbid. Water and ether were added, the phases were separated, and a conventional work-up was performed. A white solid was obtained, 1.95 g, which showed no TMS resonances in the nmr (quantitative hydrolysis). Recrystallization from ligroin gave pure **1a**: 1.75 g; mp 56.5–57.4°; ir (CCl_4) 2.76–3.26 (s, broad), 3.45 (s, sharp), shoulder (3.53 (sharp), 6.13 and 6.24 (pair of medium sharp peaks), 6.78 (vs, broad), 7.2–9.0 (broad band of multiple peaks), 9.35 (w, broad), 10.25 (vs, broad) (diagnostic for trans double bond); no detail in fingerprint region; nmr (CCl_4) τ 3.0–4.1 (multiplet, aromatic and vinyl), 4.29 (broad singlet, hydrolysis), signals at 3.0–4.5 integrated for 7 H, 7.60–8.15 (broad jagged resonance, 2 H, allylic), 8.73 (center of broad singlet, $C_{11}H_{22}$), 9.10 (center of distorted triplet, terminal methyl); signals at 7.6–9.2 integrated for 25 H.

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.12; H, 10.73.

Hydrogenation of **1d** gave bis(trimethylsilyl)-3-*n*-pentadecylcatechol, identical (spectra) with the product of the reaction between 3-PDC and BSA. The hydrogenation required exactly 1 equiv of hydrogen. Similarly, **1a** took up exactly 1 equiv of hydrogen over 10% Pd/C to give 3-PDC, identical in melting point (58–59°) (lit.[8] mp 59–60°) and spectra (ir and nmr) with an authentic sample.

Registry No.—**1a**, 34910-28-6; **1d**, 34910-29-7.

(4) The trihydroxy compound, **2a**, was obtained in the present investigation according to the method of Loev and Dawson (see ref 2b and the Ph.D. Dissertation of B. Loev, Columbia University, 1952). Quantitative hydrogenolysis of 2,3-dibenzyloxy(1′-hydroxy)pentadecylbenzene (**2b**), a precursor of **1c**, at 1 atm over 10% Pd/C gave **2a**. **2b** had been obtained in two steps in an overall yield of 58% from *o*-catechualdehyde according to the method given in ref 2b.

(5) Ortho-allyl and propenyl phenols are very susceptible to cyclization to form dihydrobenzofurans under the influence of heat and/or acidic catalysts. Such reactions are usually accompanied by formation of large amounts of polymer. See (a) D. S. Tarbell, *Chem. Rev.*, **27**, 287 (1940); (b) Q. R. Bartz, R. F. Miller, and R. Adams, *J. Amer. Chem. Soc.*, **57**, 371 (1935); (c) D. S. Tarbell, *Org. React.*, **2**, 1 (1944); (d) C. D. Hurd and L. Schmerling, *J. Amer. Chem. Soc.*, **59**, 107 (1937).

(6) (a) Aldrich Chemical Co., $CH_3(COTMS)$=NTMS; (b) J. F. Klebe, H. Finkbeiner, and D. M. White, *ibid.*, **88**, 3390 (1966); (c) L. Birkofer and A. Ritter, *Angew. Chem., Int. Ed. Engl.*, **4**, 417 (1965).

(7) B. Loev and C. R. Dawson, *J. Org. Chem.*, **24**, 980 (1959).

(8) H. Keil, D. Wasserman, and C. R. Dawson, *J. Amer. Chem. Soc.*, **68**, 534 (1946).