

ether. Dry nitrogen was passed through the system, and the mixture was stirred for one-half hour. An ether solution of 9.45 g. (0.041 mole) of methyl 3-hydroxy-2-naphthylglycolate (IIa) was added dropwise to the milky-white suspension, at a rate sufficient to maintain reflux. The turbid reaction mixture was stirred overnight at room temperature. The excess lithium aluminum hydride was decomposed by the slow, dropwise addition of water. The yellow turbid solution was acidified with 150 ml. of 10% hydrochloric acid, and the enolic material isolated from the ether solution by the usual extraction procedure. The crude yellow crystalline triol, m.p. 148–149°, was obtained in quantitative yield (8.4 g.). After recrystallization, as mentioned previously from methanol–benzene, it melted at 152–153°;  $\lambda_{\text{max}}^{\text{sol}}$ , 2.81  $\mu$  (hydroxyl), no carbonyl absorption.<sup>12</sup>

The white product formed a bright green color with ferric chloride solution, reduced Tollens reagent, and yielded a red precipitate upon treatment with benzenediazonium chloride. The compound was unchanged by refluxing for two hours with semicarbazide hydrochloride in ethanol–pyridine.

*Anal.* Calcd. for  $\text{C}_{15}\text{H}_{14}\text{O}_5$ : C, 70.6; H, 5.9. Found: C, 70.3, 70.55; H, 6.0, 5.95.

One milliliter of acetic anhydride was added, dropwise, to a cold solution of 0.24 g. of the compound in 2 ml. of anhydrous pyridine, and the mixture was slowly brought to room temperature and then heated at 35° for one-half hour. Ice shavings were added and the product was extracted with ether and washed well with dilute hydrochloric acid, aqueous sodium carbonate, and finally with water. The white crystalline triacetate weighed 0.86 g. (93%). Recrystallization from benzene–petroleum ether (b.p. 30–60°) did not change the melting point, 87–87.5°,  $\lambda_{\text{max}}^{\text{sol}}$ , 5.76  $\mu$  (carboxylate), no hydroxyl absorption.<sup>13</sup>

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_8\text{O}_5(\text{CH}_3\text{CO})_3$ : C, 65.45; H, 5.5;  $\text{CH}_3\text{CO}$ , 39.1. Found: C, 65.8, 65.6; H, 5.4, 5.5;  $\text{CH}_3\text{CO}$ , 38.65, 38.9.

**3-Hydroxy-2-naphthaldehyde (IV).**—A solution of 268 mg. (0.116 mole) of potassium periodate in 15 ml. of 1 *N* sulfuric acid was added to a solution of 233 mg. (0.00114 mole) of the triol (III) in 12 ml. of 95% ethanol. After ten minutes the orange aldehyde was filtered, washed well with water, and dried; yield 0.12 g. (60%). Recrystallization from aqueous acetic acid gave pure yellow needles of the phenolic aldehyde, m.p. 99–100°. The compound gave a green color with aqueous ferric chloride and formed a red-orange precipitate with benzenediazonium chloride.

The oxime was prepared quantitatively in pyridine–absolute ethanol, and was recrystallized from aqueous ethanol; m.p. 207.5–208° (dec.). The pale yellow needles gave a blue color with ferric chloride solution.

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_8\text{O}_2\text{N}$ : N, 7.5. Found: N, 7.3.

**The Reaction between 2-Tetralone and Bromine.**—An ether solution of 10.7 g. (0.073 mole) of 2-tetralone was treated with 11.66 g. (0.073 mole) of bromine according to the procedure<sup>10</sup> for the bromination of 1-tetralone. Evaporation of the washed extract gave 11.18 g. (106%) of crude 2-naphthol, m.p. 102–108°. Treatment with Norite and alumina, and recrystallization from ether–petroleum ether and benzene–petroleum ether gave the colorless halogen-free product, m.p. and m.m.p. 120–121°; picrate, m.p. 156.5–157.5° (recorded<sup>11</sup> m.p. 155.5°).

(13) O. L. Baril and E. S. Hauber, *THIS JOURNAL*, **53**, 1087 (1931).

NORTHAMPTON, MASSACHUSETTS

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

## Coumarins as Intermediates in the Synthesis of Colchicine Analogs

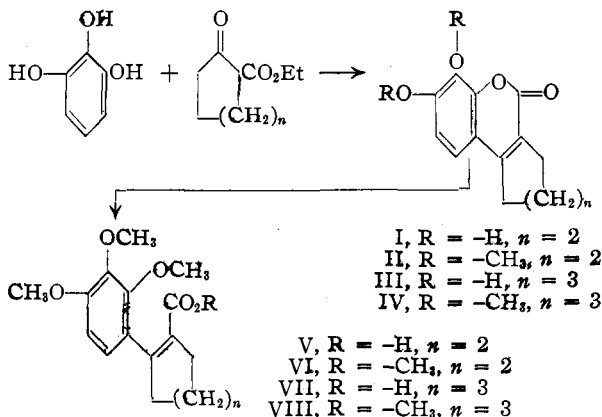
BY V. BOEKELHEIDE AND FRANK C. PENNINGTON<sup>1</sup>

Exploratory work has been carried out to determine the usefulness of the von Pechmann coumarin condensation as a route to the synthesis of derivatives of colchicine. Although it has been possible to prepare a tricyclic molecule (XVI) having some of the structural features present in colchicine, difficulties encountered in attempts to prepare compounds more closely related to colchicine have not yet been resolved.

In a previous study of coumarins as synthetic intermediates<sup>2</sup> the suggestion was made that coumarins would be logical intermediates in the synthesis of molecules related to colchicine. The basis for this suggestion lay in the fact that the synthesis of hydrogenated colchicine derivatives requires the linking together of an alicyclic ring and a methoxylated aromatic ring, and the von Pechmann coumarin condensation is an excellent method for accomplishing this type of union. It is the purpose of this communication to report the results of some exploratory work based on this idea, including the synthesis of a tricyclic compound having some of the structural features present in colchicine.

Since any scheme involving the use of coumarins in a synthesis of this type would require at some stage in the scheme that the lactone ring of the coumarins be cleaved, our first experiments were directed toward the synthesis and ring-opening reactions of some model coumarins. As shown below, pyrogallol underwent condensation smoothly with 2-carbethoxycyclohexanone to give I in good

yield. Methylation of I using potassium carbonate and methyl iodide readily gave II which, in turn, was converted to V by reaction with dimethyl sulfate and strong aqueous base. Although the ring-opening of coumarins using dimethyl sulfate and aqueous base can lead directly to the corresponding ester,<sup>2</sup> it proved to be a better procedure in this case to isolate the acid (V) and convert it to the ester (VI) by reaction with diazomethane.



(1) Predoctoral Research Fellow, National Cancer Institute, Public Health Service, 1950–1951.

(2) V. Boekelheide and A. P. Michels, *THIS JOURNAL*, **74**, 256 (1952).

In view of the fact that ring C of colchicine is now



tempts to accomplish this in the case of XXII have not been successful. Treatment of XXII with perbenzoic acid readily gave the epoxide (XXIII) but attempts to rearrange the epoxide to obtain the corresponding aldehyde did not lead to a useful product. It is possible that other methods of transforming the allyl group would be more successful.

### Experimental<sup>7</sup>

**3,4-Dihydroxy-7,8,9,10-tetrahydro-6-dibenzopyrone (I).**—A mixture of 6.3 g. of pyrogallol and 8.5 g. of 2-carbethoxycyclohexanone was added to 40 ml. of cold 75% (by volume) sulfuric acid and allowed to stand for 15 hours. It was then poured into 200 g. of ice-water and the precipitate, which separated, was removed and washed successively with water, ethanol and ether. The product, after recrystallization from a dioxane-water solution, consisted of 8.9 g. (65%) of white crystals, m.p. 269–276°.

*Anal.*<sup>8</sup> Calcd. for  $C_{18}H_{16}O_4$ : C, 67.21; H, 5.24. Found: C, 66.66; H, 5.10.

**3,4-Dimethoxy-7,8,9,10-tetrahydro-6-dibenzopyrone (II).**—A mixture of 1.90 g. of I, 1.50 g. of potassium carbonate, 10 ml. of methyl iodide, 75 ml. of methanol and 10 ml. of water was boiled under reflux for 16 hours. After removal of the methyl iodide, the dimethoxy compound crystallized from the methanolic solution. There was obtained 1.45 g. (69%) of white crystals, m.p. 126–127°.

*Anal.* Calcd. for  $C_{18}H_{16}O_4$ : C, 69.21; H, 6.19. Found: C, 69.04; H, 5.97.

**3,4-Pentamethylene-7,8-dihydroxycoumarin (III).**—This was prepared in the same manner as described for I. From 26.4 g. of 2-carbethoxycycloheptanone there was obtained 23.3 g. (86%) of white crystals, m.p. 266–272°. A further recrystallization of the product from ethanol gave a sample melting at 270–273°.

*Anal.* Calcd. for  $C_{14}H_{14}O_4$ : C, 68.28; H, 5.73. Found: C, 68.00; H, 5.67.

**3,4-Pentamethylene-7,8-dimethoxycoumarin (IV).**—A mixture of 29.5 g. of III, 68 g. of powdered anhydrous potassium carbonate, 35 ml. of redistilled dimethyl sulfate and 600 ml. of dry acetone was boiled under reflux with stirring for seven hours. An additional 15 ml. of dimethyl sulfate and 30 g. of potassium carbonate were added after two hours of heating. The mixture was filtered and the filtrate was diluted with 1200 ml. of water. This caused the separation of 26.2 g. of white crystals, m.p. 132.5–133.5°. When the mother liquor was diluted with 600 ml. more of water, an additional 5.4 g. of product separated. The combined material amounted to 31.6 g. (96%) and was sufficiently pure for use in the next step. A sample, recrystallized from ethanol, gave white crystals, m.p. 134–135°.

*Anal.* Calcd. for  $C_{18}H_{18}O_4$ : C, 70.05; H, 6.62. Found: C, 70.22; H, 6.62.

**2,3,4-Trimethoxy-2'-carboxy-3',4',5',6'-tetrahydrobiphenyl (V).**—A mixture of 1.9 g. of II and 30 ml. of a 20% aqueous potassium hydroxide solution was heated on a steam-bath and stirred while 25 ml. of dimethyl sulfate was added dropwise. Additional alkali (130 ml.) was added from time to time to keep the reaction mixture strongly alkaline. The addition was complete in three hours and the mixture was allowed to stand for another 20 hours. The solution was then filtered and the filtrate was made acidic with dilute hydrochloric acid. The solid, which precipitated, was purified by taking it up in sodium bicarbonate solution and re-acidifying. This gave 1.0 g. (47%) of white crystals, m.p. 127–129°, which on a further crystallization from ethanol melted at 128–130°.

*Anal.* Calcd. for  $C_{18}H_{20}O_5$ : C, 65.74; H, 6.90. Found: C, 65.60, 65.66; H, 6.86, 7.01.

**2,3,4-Trimethoxy-2'-carbomethoxy-3',4',5',6'-tetrahydrobiphenyl (VI).**—A sample of V dissolved in ether was added to an excess of an ethereal solution of diazomethane and the mixture was allowed to stand for 20 hours. The ether solution was then extracted with alkali, washed with

water and dried over anhydrous sodium sulfate. After removal of the ether, crystallization of the residue from pentane gave white crystals, m.p. 70.5–72.5°.

*Anal.* Calcd. for  $C_{17}H_{22}O_5$ : C, 66.65; H, 7.24. Found: C, 66.81; H, 7.37.

**1-Carboxy-2-(2',3',4'-trimethoxyphenyl)-1-cycloheptene (VII).**—This was prepared in the same manner as described for the preparation of V. From 10.0 g. of IV, there was obtained 6.0 g. (54%) of a white solid, m.p. 121–123°. This, on crystallization from ethanol, gave white needles, m.p. 122–122.5°. Acidification of the alkaline extract gave 2.9 g. (29%) of starting material.

*Anal.* Calcd. for  $C_{17}H_{22}O_5$ : C, 66.65; H, 7.24;  $CH_3O-$ , 30.39. Found: C, 66.87; H, 7.27;  $CH_3O-$ , 29.98.

**1-Carbomethoxy-2-(2',3',4'-trimethoxyphenyl)-1-cycloheptene (VIII).**—A mixture of 15.8 g. of VII, 500 ml. of methanol and 5 ml. of concd. sulfuric acid was boiled under reflux for 24 hours. About 200 ml. of alcohol was then distilled, the remaining solution was diluted with 1200 ml. of water and the resulting solution was extracted three times with 350-ml. portions of ether. The combined ether extracts were washed successively with water, sodium bicarbonate solution and water, and were then dried over potassium carbonate. After removal of the ether, the residue was crystallized from pentane to yield 14.0 g. (85%) of white crystals, m.p. 63–64°.

*Anal.* Calcd. for  $C_{18}H_{24}O_6$ : C, 67.48; H, 7.55. Found: C, 67.71; H, 7.68.

**3-Methoxy-4,5-diacetoxycinnamic Acid (X).**—A mixture of 21.5 g. of 3-methoxy-4,5-dihydroxybenzaldehyde,<sup>9</sup> 30 g. of freshly used sodium acetate and 60 ml. of acetic anhydride was boiled under reflux for 15 hours. The hot reaction mixture was carefully poured into 1200 ml. of nearly boiling water and the solution was boiled and stirred for several minutes. The hot solution, after filtration and cooling, deposited the solid crude cinnamic acid. After the product had been further purified by taking it up in sodium bicarbonate solution and re-acidifying, there was obtained 10.0 g. (26.6%) of white crystals, m.p. 154.5–159°. A further recrystallization from water gave a sample that melted at 161.5–163°.

*Anal.* Calcd. for  $C_{14}H_{14}O_7$ : C, 57.14; H, 4.80. Found: C, 57.09; H, 4.63.

From the neutral product after extraction with sodium bicarbonate solution there was isolated 1.5 g. of a white crystalline solid, m.p. 128–129°. From its composition (*Anal.* Calcd. for  $C_{16}H_{18}O_9$ : C, 54.24; H, 5.12. Found: C, 54.38; H, 5.12) and by analogy with other examples of the Perkin reaction,<sup>10,11</sup> this has been assumed to be the tetraacetate of 3-methoxy-4,5-dihydroxybenzaldehyde.

Several other procedures for preparing X were tried without success. Although Rosenmund's procedure<sup>12</sup> for condensing gallaldehyde and malonic acid failed in the case of IX, his procedure using ethyl cyanoacetate was found to be successful in yielding ethyl  $\alpha$ -cyano- $\beta$ -(3-methoxy-4,5-dihydroxy)-acrylate as yellow crystals (from chloroform), m.p. 179.5–181° (*Anal.* Calcd. for  $C_{18}H_{18}NO_5$ : C, 59.31; H, 4.98. Found: C, 58.98; H, 4.83). Hydrolysis of this ester occurred readily to give the acid as yellow crystals (from water), m.p. 195–199° dec. (*Anal.* Calcd. for  $C_{11}H_9NO_3$ : C, 56.18; H, 3.86. Found: C, 56.49; H, 4.12), but decarboxylation of the acid did not proceed cleanly and other attempts to utilize this compound were unpromising.

**3-Methoxy-4,5-diacetoxyhydrocinnamic Acid (XI).**—To a mixture of 0.3 g. of prerduced Adams catalyst in 50 ml. of ethanol there was added 1.95 g. of X and the mixture was subjected to hydrogenation at atmospheric pressure of hydrogen and room temperature. A molar equivalent of hydrogen was absorbed in one-half hour. After removal of the catalyst and solvent, the residual solid was taken up in a benzene-hexane mixture and, on crystallization, it gave 1.45 g. (74%) of white crystals, m.p. 97–102°. Further crystallization of this material from an ether-pentane mixture gave a sample that melted at 102–104°.

(9) W. Bradley, R. Robinson and G. Schwarzenbach, *J. Chem. Soc.*, 811 (1930).

(10) J. Shinoda, M. Kawagai and D. Sato, *J. Pharm. Soc. Japan*, **51**, 249 (1921).

(11) C. A., **25**, 3979 (1931).

(12) E. W. Rosenmund and T. Boehm, *Ann.*, **437**, 125 (1924).

(7) Analyses by Miss Claire King and the Micro-Tech Laboratories.

(8) We are indebted to Mr. A. P. Michels for the first preparations of I and II.

*Anal.* Calcd. for  $C_{14}H_{16}O_7$ : C, 56.75; H, 5.45. Found: C, 57.10; H, 5.70.

**3,4-Tetramethylene-5-( $\beta$ -carboxyethyl)-7-methoxy-8-hydroxycoumarin (XII).**—A cooled mixture of 9.80 g. of XI and 5.63 g. of 2-carbethoxycyclohexanone was carefully added to 50 ml. of commercial methanesulfonic acid.<sup>13</sup> After the mixture had stood for 20 hours, it was poured into 600 ml. of ice-water causing the separation of the solid coumarin. This was removed by filtration and purified by taking it up in sodium bicarbonate solution and re-acidifying. The resulting solid, on recrystallization from ethanol, yielded 1.10 g. (10.4%) of faintly yellow crystals, m.p. 278–284° dec. A further recrystallization from ethanol gave a sample that melted at 284–288° dec.

When two equivalents of 2-carbethoxycyclohexanone were used, the yield was raised to 12.5%. Also, 75% sulfuric acid could be used but the yields were much lower.

*Anal.* Calcd. for  $C_{17}H_{18}O_8$ : C, 64.14; H, 5.70. Found: C, 64.25; H, 5.91.

When the above reaction was tried using 2-carbethoxycycloheptanone in place of 2-carbethoxycyclohexanone, none of the desired coumarin was formed, but the neutral fraction, insoluble in sodium carbonate solution, gave a white solid. This, after recrystallization from ethanol, gave white crystals melting at 152.5–154.5°. This material was soluble in 10% sodium hydroxide solution, gave a dark green ferric chloride test, and showed the right composition (*Anal.* Calcd. for  $C_{16}H_{16}O_4$ : C, 61.85; H, 5.19;  $CH_3O$ -, 15.98. Found: C, 62.07; H, 5.40;  $CH_3O$ -, 15.16) for 1,2-dihydroxy-3-methoxy-7-hydrindanone.

**3,4-Tetramethylene-5-( $\beta$ -carboxyethyl)-7,8-dimethoxycoumarin (XIII).**—To a solution of 100 mg. of XII in 4 ml. of methanol, dimethyl sulfate and a 20% solution of potassium hydroxide were added alternately in a dropwise fashion. The reaction mixture was kept at 50 to 55° during the addition and sufficient dimethyl sulfate (threefold excess) was added at the end to render the solution acidic. After removal of the methanol, the residual solid was extracted and the ethereal extract was washed successively with water, dilute sodium hydroxide and water. Concentration of the ethereal solution gave a solid which, on crystallization from methanol, gave 9 mg. of white needles, m.p. 133–134.5°.

*Anal.* Calcd. for  $C_{18}H_{22}O_8$ : C, 65.88; H, 6.40. Found: C, 65.63; H, 6.61.

**1-Carboxy-2-(2',3',4'-trimethoxy-6-( $\beta$ -carboxyethyl)-phenyl)-1-cyclohexene (XIV).**—It was more convenient to prepare XIV directly from XII rather than from XIII. To a mixture of 1.10 g. of XII and 40 ml. of a 20% solution of potassium hydroxide heated on a steam-bath under an atmosphere of nitrogen there was added 25 ml. of dimethyl sulfate. Then while maintaining these conditions, an additional 110 ml. of potassium hydroxide solution and 35 ml. of dimethyl sulfate were added alternately in a dropwise fashion over a period of three hours. After the solution had been allowed to stand at room temperature overnight, it was decanted from the inorganic salts and acidified with dilute hydrochloric acid. The crude acid, which separated, was recrystallized from aqueous ethanol, yielding 1.00 g. (79%) of white crystals, m.p. 153–155°. Further recrystallization from aqueous ethanol gave a sample melting at 156.5–157.5°.

*Anal.* Calcd. for  $C_{19}H_{24}O_7$ : C, 62.62; H, 6.64;  $CH_3O$ -, 25.55; neut. equiv., 182. Found: C, 63.06; H, 6.61;  $CH_3O$ -, 24.64; neut. equiv., 182.

**1-Carbomethoxy-2-(2',3',4'-trimethoxy-6-( $\beta$ -carbomethoxyethyl)-phenyl)-1-cyclohexene (XV).**—A suspension of 731 mg. of XIV in ether was slowly treated with a standardized ether solution containing two equivalents of diazomethane. After the solution had stood overnight, it was filtered and dried over anhydrous potassium carbonate. Concentration of the ethereal solution gave an oil which, on distillation using a molecular still, gave 576 mg. of colorless oil, b.p. 210–230° (bath temp.) at 2 mm.

*Anal.* Calcd. for  $C_{21}H_{26}O_7$ : C, 64.27; H, 7.19. Found: C, 64.05; H, 7.31.

**1,2,3-Trimethoxy-5,6,8,9,10,11-hexahydrodibenzo[a,c]cycloheptatrienone-7 (XVI).**—To a solution prepared by add-

ing one drop of methanol to a hot mixture of 0.25 g. of potassium in 5 ml. of toluene there was added a solution of 576 mg. of XV in 5 ml. of toluene. The reaction mixture was boiled under reflux for 11 hours, diluted with benzene and the excess potassium was destroyed by addition of water. After removal of solvent, the residue was taken up in 5 ml. of a 0.5 *N* solution of ethanolic potassium hydroxide and allowed to stand overnight. The ethanol was then removed and the residue was treated with a boiling solution of dilute hydrochloric acid for a short period of time. The neutral material was extracted with benzene, washed with water and dried. Removal of the benzene left 133 mg. of a crude oil.

A solution of 87 mg. of the crude oil in 0.5 ml. of absolute ethanol was boiled under reflux with 111 mg. of hydroxylamine hydrochloride and 0.5 ml. of pyridine for two hours. After removal of the solvent, the remaining oil was triturated with aqueous methanol and gave a solid oxime. This solid, on recrystallization from aqueous methanol, gave 49 mg. of white crystals, m.p. 122.5–125°.

*Anal.* Calcd. for  $C_{18}H_{22}NO_4$ : C, 68.12; H, 7.30; N, 4.42;  $CH_3O$ -, 29.34. Found: C, 67.96; H, 7.26; N, 4.53;  $CH_3O$ -, 30.32.

The 2,4-dinitrophenylhydrazone of XVI was prepared by adding a solution of one drop of XVI in ethanol to freshly prepared 2,4-dinitrophenylhydrazine reagent. The resulting solid, after recrystallization from ethanol, gave orange-red crystals, m.p. 142.5–143.5°.

*Anal.* Calcd. for  $C_{24}H_{26}N_4O_7$ : C, 59.74; H, 5.43. Found: C, 59.63; H, 5.48.

**3-Methoxy-4-hydroxy-7,8,9,10-tetrahydro-6-dibenzopyrone (XVIII).**—A solution of 67.0 g. of 1-methoxy-2,3-dihydroxybenzene<sup>14</sup> and 81.4 g. of 2-carbethoxycyclohexanone was carefully added to 480 ml. of a 75% (by volume) sulfuric acid solution and the mixture was allowed to stand for 24 hours. When the mixture was poured into 2000 ml. of hot water, a solid separated which was collected, washed with water, and recrystallized from ethanol. There was obtained 78.0 g. (66%) of faintly yellow crystals, m.p. 194–196°. Attempts to cause XVIII to undergo substitution by means of the Mannich reaction, chloromethylation, formylation or the Gattermann reaction were unsuccessful.

*Anal.* Calcd. for  $C_{14}H_{14}O_4$ : C, 68.28; H, 5.73. Found: C, 68.03; H, 5.57.

**3-Methoxy-4-propionyloxy-7,8,9,10-tetrahydro-6-dibenzopyrone (XIX).**—A mixture of 2.5 g. of XVIII, 25 ml. of propionic anhydride and 3 drops of concd. sulfuric acid was allowed to stand for 24 hours and was then diluted with 100 ml. of water. The solid, which separated over a period of several hours, was collected and recrystallized from ethanol, yielding 2.1 g. (69%) of white crystals, m.p. 141–142°.

*Anal.* Calcd. for  $C_{17}H_{18}O_6$ : C, 67.54; H, 6.00. Found: C, 67.66; H, 6.30.

**3-Methoxy-4-allyloxy-7,8,9,10-tetrahydro-6-dibenzopyrone (XX).**—A mixture of 4.7 g. of XVIII, 2.4 g. of allyl bromide, 25 ml. of methanol, 15 ml. of water and 5.0 g. of potassium carbonate was boiled under reflux for seven hours with stirring. When the reaction mixture was diluted with water and cooled, a solid separated which was collected, washed with water and recrystallized from hexane. There was obtained 3.8 g. (70%) of white crystals, m.p. 96–100°. Further recrystallization from hexane gave a sample melting at 97.5–100.5°.

*Anal.* Calcd. for  $C_{17}H_{18}O_4$ : C, 71.31; H, 6.34. Found: C, 71.51; H, 6.35.

**1-Allyl-3-methoxy-4-hydroxy-7,8,9,10-tetrahydrodibenzo-6-pyrone (XXI).**—A solution of 1.95 g. of XX in 15 ml. of dimethylaniline was boiled under reflux for eight hours. The reaction mixture was then poured into excess dilute hydrochloric acid and the solid, which separated, was collected by filtration. Recrystallization of the solid from ethanol gave 1.00 g. (51%) of white crystals, m.p. 180–185°. Further recrystallization from ethanol gave a sample melting at 184.5–186.5°.

*Anal.* Calcd. for  $C_{17}H_{18}O_4$ : C, 71.31; H, 6.34. Found: C, 71.22; H, 6.35.

**1-Allyl-3,4-dimethoxy-7,8,9,10-tetrahydro-6-dibenzopyrone (XXII).**—A mixture of 24.0 g. of XXI, 10 ml. of methyl

(13) Indiol Chemical Co., Chicago, Ill. The commercial product was used directly as obtained. When the methanesulfonic acid was purified prior to use, the yield of desired product was negligible.

(14) A. R. Surrey, *Org. Syntheses*, **26**, 90 (1946).

iodide, 20 g. of potassium carbonate, 225 ml. of methanol and 75 ml. of water was boiled under reflux for 11 hours. After removal of most of the methanol, the mixture was diluted with water and cooled. The solid which separated was recrystallized from hexane and yielded 13.2 g. (55%) of white crystals, m.p. 144–146.5°. Further recrystallization gave a sample melting at 148–149°.

Attempts to carry out a Willgerodt reaction with XXII gave only dithiooxalodimorpholide, a compound previously observed in this type of reaction by McMillan and King.<sup>15</sup>

*Anal.* Calcd. for  $C_{18}H_{20}O_4$ : C, 71.98; H, 6.71. Found: C, 72.08; H, 6.75.

1-( $\beta,\gamma$ -Epoxypropyl)-3,4-dimethoxy-7,8,9,10-tetrahydro-6-dibenzopyrone (XXIII).—To a solution of 11.3 g. of XXII in 200 ml. of chloroform there was added 100 ml. of

(15) F. H. McMillan and J. A. King, *THIS JOURNAL*, **69**, 1207 (1947).

a 0.374 *M* chloroform solution of perbenzoic acid and the mixture was allowed to stand for 3 days. The chloroform solution was then extracted with sodium bicarbonate solution, washed with water and dried over sodium sulfate. After removal of the chloroform, the residue was extracted with hot hexane to remove any starting material and recrystallized from ethanol. There resulted 7.4 g. (62%) of white crystals, m.p. 144–148°. Further recrystallization from ethanol gave a sample melting at 149–150°.

Attempts to rearrange XXIII in the usual way<sup>16</sup> did not yield aldehydic material.

*Anal.* Calcd. for  $C_{18}H_{20}O_5$ : C, 68.34; H, 6.37. Found: C, 68.60; H, 6.36.

(16) M. Tiffeneau, P. Weill and B. Tchoubar, *Compt. rend.*, **205**, 54 (1937); R. A. Barnes and W. M. Budde, *THIS JOURNAL*, **68**, 2339 (1946); and E. Mosettig, *Ber.*, **62**, 1274 (1929).

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## A Further Study on the Reduction of Steroid Semicarbazones

BY HUANG-MINLON AND RUSSELL H. PETTEBONE

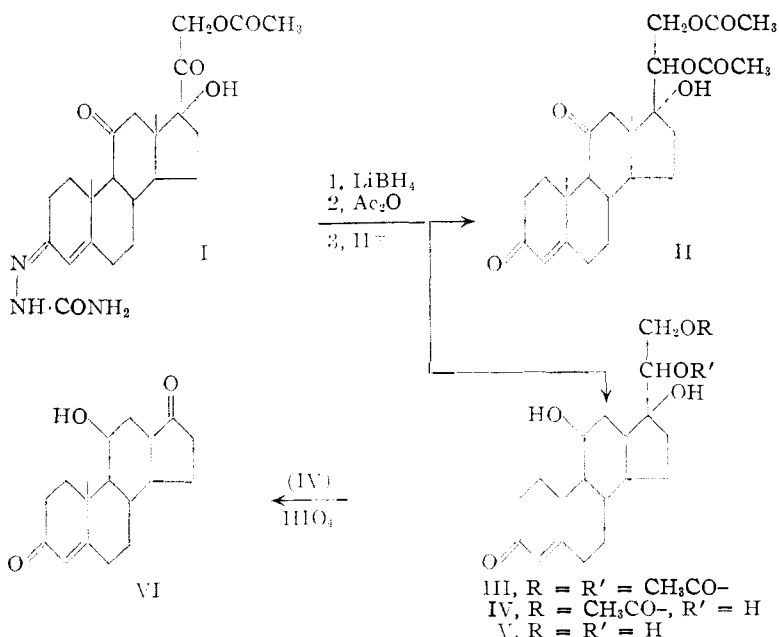
A product isolated from the reaction mixture of cortisone acetate 3-semicarbazone after  $LiBH_4$  reduction followed by acetylation and regeneration has been proved to be 4-pregnane-11,17,20,21-tetrol-3-one-21-acetate (Reichstein's substance E 21-acetate). The route to the formation of this new substance has been studied.

The synthesis from cortisone of 4-pregnene-11,17,20,21-tetrol-3-one 20,21-diacetate and 4-pregnene-17,20,21-triol-3,11-dione 20,21-diacetate (Reichstein's Substances E and U diacetate) was the subject *inter alia* of a recent communication.<sup>1</sup> This transformation consisted in the reduction of cortisone acetate 3-semicarbazone (I) with lithium

one 21-acetate (IV), previously not described in the literature. This substance has been found, moreover, to be the predominant product from this synthesis under properly chosen conditions.

Saponification of (IV) yielded 4-pregnene-11,17,20,21-tetrol-3-one (V) and acetylation produced the diacetate (III). Periodic acid oxidation converted (IV) to 11-dihydroadrenosterone<sup>2</sup> (VI) thereby establishing the structure of this compound.

It seemed desirable to ascertain whether the acetyl group of (IV) originated from the starting material (I) or had been replaced by the subsequent acetylation step following the hydride reduction of (I). The latter possibility implies that the 21-acetyl group of (I) was lost during the treatment with lithium borohydride. In support thereof it was found that omission of the acetylation step produced (V) as the major product. Furthermore, when the crude reduction product obtained from (I) was acetylated under *mild* conditions there resulted a twofold increase of (IV) in the final product. It therefore appears that the 21-acetyl group of (IV) arises through partial acetylation of an intermediate tetrol (VII) which we have not been able to



borohydride and subsequent acetylation and removal of the semicarbazone grouping. Since the time of the completion of this work a third substance has been isolated from this reaction sequence and identified as 4-pregnene-11,17,20,21-tetrol-3-

obtain in crystalline form.

### Experimental

**4-Pregnene-11,17,20,21-tetrol-3-one 21-Monoacetate (IV).**—A solution of 1.00 g. of cortisone acetate 3-semicarbazone (I) in 175 cc. of dry tetrahydrofuran was added with stirring

(1) N. L. Wendler, Huang-Minlon and M. Tishler, *THIS JOURNAL*, **73**, 3818 (1951).

(2) T. Reichstein, *Helv. Chim. Acta*, **20**, 978 (1937).