potassium hydroxide and crystallization from acetone–alcohol; m.p. 144–146° (not clear above 230°); $[\alpha]_D^{18}$ +35.0° (*c* 0.9 $CHCl_3$), ν_{max} 3380 cm.$^{-1}$ in Nujol. This is a C_8-, C_{11}- or C_{17}-isomer of cholestanol.

Anal. Calcd. for $C_{27}H_{48}O$: C, 83.50; H, 12.37. Found: C, 83.49; G, 12.20.

A later fraction afforded a colorless oil which solidified; crystallization from acetone–alcohol gave silky needles of 15-ketocholestanyl benzoate (XXIV); m.p. 151–152°, yield 190 mg., no ultraviolet spectrum above 230 mμ, ν_{max} 1749 and 1709 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{44}H_{70}O_3$: C, 80.58; H, 9.95. Found: C, 80.12; H, 9.63.

Oxime of XXIV (XXVI).—To a solution of 150 mg. of XXIV in 10 ml. of alcohol–pyridine (1:1) was added 70 mg. of hydroxylamine hydrochloride in 5 ml. of alcohol. The reaction mixture was refluxed for 3 hours and the solution poured into hydrochloric acid. Then the solution was treated as previously described. The residue, obtained by removal of the solvent, was crystallized twice from methanol to yield XXVI, m.p. 236–240°, yield 100 mg., ν_{max} 3360, 1712 and 1669 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{34}H_{51}O_3N$: C, 78.26; H, 9.85; N, 2.68. Found: C, 78.52; H, 10.12; N, 2.79.

Beckmann Rearrangement of XXVI.—The rearrangement was carried out as previously described except that the product was extracted with ether. The oxime tosylate XXVII was obtained, m.p. 172–175°, yield 40 mg. (from 80 mg. of XXVI).

Anal. Calcd. for $C_{41}H_{57}O_5NS$: C, 74.25; H, 8.01; N, 1.96. Found: C, 74.55; H, 8.39; N, 2.06.

YAYOICHO, HONGO, TOKYO, JAPAN

[CONTRIBUTION FROM THE ORGANIC CHEMICALS DIVISION, ST. LOUIS RESEARCH DEPARTMENT, MONSANTO CHEMICAL CO.]

Studies in Steroid Total Synthesis. IV. A Stereoselective Ring A Synthesis[1]

BY LLOYD B. BARKLEY, WILLIAM S. KNOWLES, HAROLD RAFFELSON AND QUENTIN E. THOMPSON

RECEIVED MARCH 23, 1956

In the Woodward steroid total synthesis, the formation of the quaternary center at C-10 from the blocked tricyclic ketone I invariably gives unfavorable stereochemistry (I → II + III). By methylating a keto acid such as XIIIb and thus reversing the order in which the groups forming the quaternary center are attached, a favorable stereochemical result has been obtained. Moreover, it has been found that contraction of ring D prior to the formation of the quaternary center enhances reactivity at the methinyl position so that a blocking group is no longer necessary in the ring A synthesis.

The unfavorable stereochemistry observed in the conversion of the blocked tricyclic system I to the keto acid II marks the weakest point in the Woodward[2] steroid total synthesis approach. Our work[3] and that of others[2,4] has shown that variation of ring D substituents does not improve the existing 2:1 ratio of unnatural to natural isomers.

Since the final group forming the quaternary center preferentially assumes the axial position, introduction of the methyl group last could be expected to give predominantly the natural isomer. The successful achievement of this result forms the subject of this paper.

Our initial approach involved preparation of the tricyclic keto acid VIb by condensation of our basic bicyclic system (−)-*trans*-1,2,4a,5,8,8a-hexahydro-4a-methyl-2-oxo-1-naphthaldehyde (IV) with methyl 5-oxo-6-heptenoate[5] in the presence of benzyltrimethylammonium butoxide.[6]

This adduct V was then cyclized with aqueous base[2,3] to give VIb. The ring C double bond of the keto acid VIb was reduced to give VII and the 3-position was blocked with the methylanilinomethylene group[2,3] to give a non-crystalline derivative which could be methylated in low yield to give some of the desired keto acid II. The stereochemical result was obscured by the low yields of methylated products and by the multiplicity of acidic materials, both methylated and unmethylated, present in the acid fraction. Because of these unpromising results, methylation of a blocked keto acid was abandoned, and it was not until some observations were made in another tricyclic system in which ring D had been contracted to a five-membered ring that a successful stereoselective methylation was accomplished.

At approximately this time, work was begun to ascertain the effect of contracting ring D before construction of ring A. The *dl*-tricyclic ketone VIa[2] was hydroxylated in ring D with silver acetate and iodine in wet acetic acid.[3,7] Reduction of the double bond in ring C to give XIa followed by cleavage of the glycol with lead tetraacetate and ring closure of the dialdehyde by standard methods[2,3] gave the tricyclic system XIIa. The aldehyde group was protected by first reducing the double bond in ring D and then preparing the ethylene glycol acetal XIIIa.[8] Attempts to put the methylanilinomethylene blocking group on XIIIa by con-

(1) The material in this paper was first announced at the Gordon Research Conference A.A.A.S., New Hampton, N. H., August 2–6, 1954.

(2) *Cf.* R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, THIS JOURNAL, **74**, 4223 (1952).

(3) *Cf.* L. B. Barkley, M. W. Farrar, W. S. Knowles, H. Raffelson and Q. E. Thompson, *ibid.*, **76**, 5014 (1954).

(4) P. Wieland, H. Ueberwasser, G. Anner and K. Miescher, *Helv. Chim. Acta*, **36**, 1231 (1953).

(5) (a) P. Wieland, H. Ueberwasser, G. Anner and K. Miescher [*Helv. Chim. Acta*, **36**, 376 (1953)] have prepared ethyl 7-chloro-5-oxoheptanoate and have used the crude β-chloroketone for a condensation similar to that described here. For our purposes the use of the pure vinyl ketone proved more satisfactory. (b) N. Nazarov and S. I. Savyalov [*J. Gen. Chem.* (*USSR*), **23**, 1703 (1953)] made methyl 5-oxo-6-heptenoate ($n^{25}D$ 1.4490, b.p. 102–105° at 15 mm.) by a different route.

(6) This reagent was shown by Dr. M. W. Farrar in this Laboratory to give about 5% better yields than potassium *t*-butoxide in a similar condensation using ethyl vinyl ketone. It is prepared from 35% benzyltrimethylammonium hydroxide in methanol (obtained from Chemical Development Corp., Danvers, Mass.) by adding *n*-butyl alcohol and distilling out the methanol and water.

(7) *Cf.* D. Ginsburg, THIS JOURNAL, **75**, 5746 (1953).

(8) A number of these tricyclic intermediates with a five-membered ring D were first prepared by R. B. Woodward and A. J. Bose in connection with their study on ring contraction methods; *cf.* footnote 45 in ref. 2. Compound XIIIa was also made from *dl anti-trans*-3a,7,8,9,-9a,9b - hexahydro - 3a,6 - dimethyl - 7 - oxo - (1H)benz[e]indene - 3-carboxaldehyde[2] (m.p. 131–133°), but the one-step reduction of the double bonds in ring C and D proceeded only in low yields since base could not be used because of the sensitive aldehyde group.

ventional methods[2,3] failed and, rather than look for another method, XIIIa was cyanoethylated directly. Using our normal procedure[3] with a large excess of acrylonitrile followed by alkaline hydrolysis, a crude keto acid oil was obtained which showed no α,β-unsaturated ketone in the infrared and had a neutral equivalent corresponding to 1.8 carboxyl groups. A repeat using only one mole of acrylonitrile[9] gave a 65% yield of crystalline keto acid XIVa. Complete absence of any α,β-unsaturated ketone as well as the presence of only one carboxyl function showed that initial attack occurred at the methinyl position and thus no blocking group was necessary when ring D was 5-membered.[10] Acid XIVa was converted to its enol lactone XVa and a study of its infrared spectrum showed it to correspond most closely to enol lactones[2,3] in the 10-*epi* series. In the 7.5 μ region, the unnatural series had a single band and the natural series a double band. Further confirmation that XVa was in the 10-*epi* series was obtained by reaction with methylmagnesium bromide at $-50°$.[3] Under these conditions only alcoholic material was obtained at the tetracyclic stage, as would be predicted for the 10-*epi*-methyl series. None of the natural isomer was isolated, although infrared spectra taken on mother liquors showed evidence of its presence in small amounts.

Since a five-membered ring D enhanced reactivity of the methinyl position in XIIIa, sufficient to eliminate the need for a blocking group, but failed to improve the stereochemistry of the cyanoethylation step, it became obvious that our original approach, *i.e.*, introduction of the methyl group last was again indicated. Thus the tricyclic keto acid VIb was hydroxylated by way of its methyl ester VIc to the oily *cis*-glycol VIIIc. Preparation of the crystalline acetonide IX made possible a purification at this stage. Hydrogenation followed by removal of the acetonide and cleavage of the glycol followed by ring closure of the dialdehyde[2,3] gave XIIb. A second hydrogenation and then reaction with ethylene glycol yielded a crystalline keto ester XIIIb. Methylation using a large excess of methyl iodide and potassium *t*-butoxide gave an oily keto acid in high yield showing no α,β-unsaturated ketone. The structure of this acid was established first by conversion to its oily enol lactone XVb whose infrared spectrum corresponded to the natural series, and reaction of XVb with excess methylmagnesium bromide at $-50°$ to give a crystalline tetracyclic ketone XVI. Final confirmation of the structure of XVI was established by its two-step synthesis from the known Woodward synthetic steroid XVII[2,3] in its dextrorotatory form.

The over-all yield from crystalline XIIIb to XVI was 38%. Since the intermediates were oils and not obtainable pure, this result has to be compared with the conversion of the blocked tricyclic system I to its corresponding tetracyclic ketone.[3] Here the over-all yield is (22) (90) (91) = 18%. Assuming equally high yields for the last two steps in the above case, the yield for the methylation step is 46%. Thus we have clearly doubled the amount of natural isomer.[11] This success was somewhat offset by the generally lower yields experienced when working with tricyclic ketones substituted with carboxyethyl groups in place of a methyl.

(9) *Cf.* A. R. Pinder and R. Robinson, *J. Chem. Soc.*, 1224 (1952).

(10) Use of this one mole cyanoethylation procedure on tricyclic ketone I minus the blocking group resulted in over-cyanoethylation and recovery of starting material.

Experimental

All rotations were measured in chloroform at 2% concentration unless otherwise stated. Analyses were done by Mr. A. Bybell of this Laboratory. Infrared spectra were run on a Perkin–Elmer recording spectrophotometer, model 21.

Crude Methyl 7-Chloro-5-oxoheptanoate.—A solution of 85.5 g. of methyl glutaryl chloride[12] in 150 ml. of dry alcohol-free chloroform was added slowly over 15 minutes to a well-stirred suspension of 134 g. of anhydrous aluminum chloride in 250 ml. of dry alcohol-free chloroform, at 25–30°. Dry ethylene was bubbled into this rapidly stirred slurry. Absorption of ethylene started almost immediately, and the temperature of the reaction rose to 40° where it was maintained by occasional cooling. After 2 hr. the rate of gas absorption slackened and the temperature was allowed to drop gradually to 30° over the next 2 hr. By this time uptake of ethylene had ceased. The reddish colored reaction mixture was quenched by pouring slowly into 1 liter of saturated sodium chloride solution keeping the temperature of the quench solution below 10°. The chloroform layer was separated and the aqueous layer was extracted with two 250-ml. portions of chloroform. The chloroform layers were combined, washed twice with 200-ml. portions of saturated sodium chloride solution and dried. Approximately 5 ml. of pyridine was added to this solution to ensure basicity, and the chloroform was stripped out *in vacuo* keeping the temperature below 45°. This crude mixture consisting of methyl 7-chloro-5-oxoheptanoate, dimethyl glutarate, pyridine and non-volatile polymeric materials was carried directly into the next step.

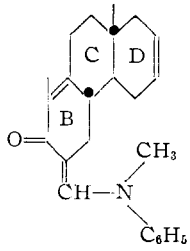
Methyl 5-Oxo-6-heptenoate.[5b]—Crude chloroketone as obtained in the previous preparation was dissolved in 60 g. of triethylamine and stirred for 4 hr. During this time, the temperature was allowed to rise to 45° as triethylamine hydrochloride separated. At the end of the dehydrohalogenation period, the temperature had fallen to 30° and the reaction mixture had become a thick slurry. Approximately 500 ml. of ether was added and triethylamine hydrochloride (36 g.) was collected by filtration and washed with ether. The filtrate and washings were combined, washed thoroughly with water and dried. Ether and the bulk of the volatile materials were removed on a water-bath and finally under water-pump vacuum. The reddish-brown residue, amounting to about 80 g. and consisting of dimethyl glutarate, methyl 5-oxo-6-heptenoate, a little pyridine and considerable high boiling material, was subjected to vacuum take-over distillation. The main fraction, b.p. 69–85° (1.5 mm.), amounted to 44.7 g. of clear oil, $n^{25}D$ 1.4422, $\lambda_{max}^{H_2O}$ 213 mμ, ϵ 7020, and consisted of a mixture of dimethyl glutarate (20–25%) and the desired vinyl ketone (75–80%).[13]

(−)-Methyl *trans*-1-Formyl-1,2,4a,5,8,8a-hexahydro-4a-methyl-δ,2-dioxo-1-naphthaleneheptanoate (V).—The 44.7 g. of crude methyl 5-oxo-6-heptenoate (0.22 mole of vinyl ketone) was dissolved in 50 ml. of anhydrous *t*-butyl alcohol along with 38 g. (0.20 mole) of IV. To this solution, under nitrogen, was added 8 ml. of a 30% solution of benzyl trimethylammonium butoxide[6] in *n*-butyl alcohol. After a

(11) In a recent communication Stork and co-workers [G. Stork, H. J. E. Loewenthal and P. C. Mukharji, THIS JOURNAL, **78**, 501 (1956)] reported work on a closely similar tricyclic system. Introducing the methyl group at C-10 last gave them in one case equal amounts of isomers and in another a ratio of two to one favoring the natural form. These data are in reasonably close agreement with ours.

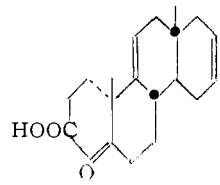
(12) R. F. Naylor, *J. Chem. Soc.*, 1106 (1947).

(13) Fractionation studies by Miss Eva Pohlen of this Laboratory have shown that dimethyl glutarate is essentially the sole impurity in the crude vinyl ketone at this point. A fairly pure sample of methyl 5-oxo-6-heptenoate ($n^{25}D$ 1.4475, $\lambda_{max}^{H_2O}$ 213 mμ, ϵ 9220, sapn. equiv. 152, calcd. 156) was obtained in these studies. This material served as a standard for an ultraviolet assay. It was later found that the dimethyl glutarate content could be determined equally well by refractive index, that of pure dimethyl glutarate being $n^{25}D$ 1.4221 and the vinyl ketone $n^{25}D$ 1.4475.

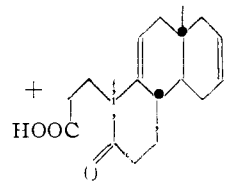


I

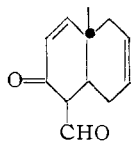
1, CH_2=CHCN
2, NaOH



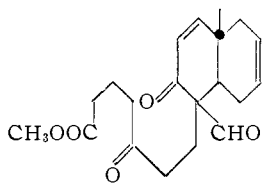
II 22%



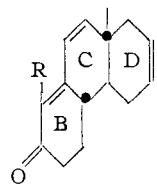
III, 45%



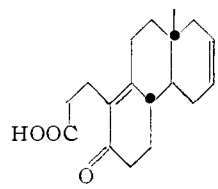
IV



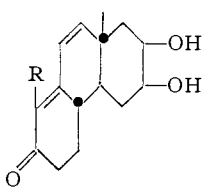
V



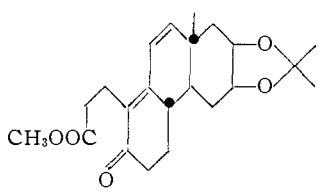
VIa, R = CH_3
b, R = CH_2CH_2COOH
c, R = $CH_2CH_2COOCH_3$



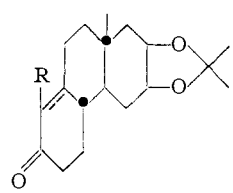
VII



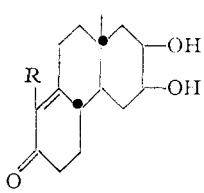
VIIIa, R = CH_3
b, R = CH_2CH_2COOH
c, R = $CH_2CH_2COOCH_3$



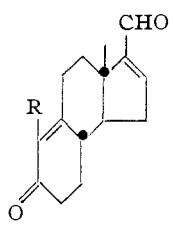
IX



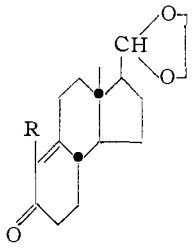
Xa, R = CH_3
b, R = $CH_2CH_2COOCH_3$



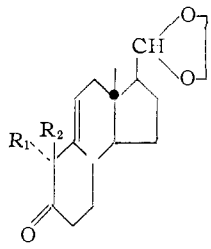
XIa, R = CH_3
b, R = $CH_2CH_2COOCH_3$



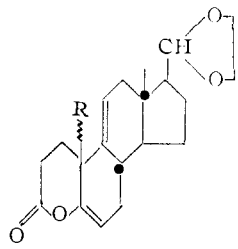
XIIa, R = CH_3
b, R = $CH_2CH_2COOCH_3$



XIIIa, R = CH_3
b, R = $CH_2CH_2COOCH_3$

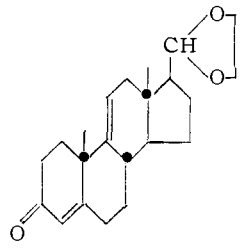


XIVa, R_1 = α-CH_3
R_2 = β-CH_2CH_2COOH
b, R_1 = α-CH_2CH_2COOH
R_2 = β-CH_3



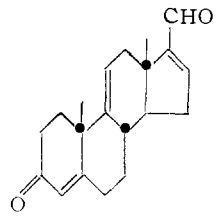
XVa, R = α-CH_3
b, R = β-CH_3

XVb 2 Steps



XVI

2 Steps



XVII

short time, a green color developed. The mixture was allowed to stand at 25° under nitrogen for 40 hr. Approximately 200 ml. of petroleum ether (b.p. 60–68°) was then added dropwise over about an hour while the greenish solution was cooled to 5° with good stirring. At the start of the addition of petroleum ether seed crystals were obtained. The main batch was seeded and allowed to crystallize slowly as the petroleum ether was being added. The pale blue-green crystalline adduct which separated was collected by filtration and then slurried for 5 minutes in 100 ml. of a cold (0–5°) mixture of isopropyl alcohol (80 ml.) and methanol (20 ml.). The crystals were again collected by filtration and were washed with another 25 ml. of the cold mixed solvent. The white product obtained by this treatment amounted to 41.2 g. (59%), m.p. 66–67°, and appeared to be of excellent quality. The analytical sample was prepared by twice recrystallizing this material from petroleum ether (b.p. 60–68°), m.p. 66.5–67.5°, $[\alpha]^{25}D$ −206°.

Anal. Calcd. for $C_{20}H_{26}O_5$: C, 69.3; H, 7.6. Found: C, 69.4; H, 7.7.

(−)-*anti-trans*-2,3,4,4a,4b,5,8,8a-Octahydro-8a-methyl-2-oxophenanthrene-1-propionic Acid (VIb).—The crude crystalline adduct (41.2 g.) obtained in the previous step was added to 250 ml. of 1.6 *M* aqueous sodium hydroxide solution and the mixture was stirred overnight at room tem-

perature under nitrogen. Within a few hours the solid had dissolved giving a light brown aqueous solution. At the end of the reaction period, the aqueous solution was extracted once with 100 ml. of ether to remove neutral materials. The ether phase was discarded and the aqueous phase was acidified with cold concentrated hydrochloric acid. The oily acid which separated was taken up in ether (approximately 200 ml. in several portions). The ether extracts were washed with water, dried and the ether removed on a steam-bath. The pale yellow glassy residue was boiled with 100 ml. of petroleum ether containing about 15% diethyl ether and then allowed to cool. A drop of the heavy yellow oil was placed on a watch glass under petroleum ether, cooled and scratched to obtain seeds. The oily acid in petroleum ether–ether solution was then seeded and allowed to crystallize slowly over 24 hr. During this time a hard mass of large crystals formed. These were collected and washed quickly with 25 ml. of cold ether to remove adhering oil. This crop amounted to 21.2 g., m.p. 100–102°. A second crop amounting to 10.2 g. of lower quality acid, m.p. 93–100°, was obtained from the filtrate and washings making the total yield of crystalline product approximately 92%. The analytical sample was prepared by recrystallizing first crop material twice from petroleum ether (b.p. 90–100°), m.p. 101–102°, $[\alpha]^{25}D$ −374°, λ_{max}^{alc} 290 mμ, ε 24,900.

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.5; H, 7.7. Found: C, 75.4; H, 7.8.

(−)-*anti-trans*-2,3,4,4a,4b,5,8,8a,9,10-Decahydro-8a-methyl-2-oxophenanthrene-1-propionic Acid (VII).—To a solution of 3.64 ml. of 2.74 *N* NaOH in 30 ml. of water was added 0.28 g. of palladium-on-strontium carbonate containing 2% palladium. After the catalyst had been reduced, 2.8 g. of VIb was added, and hydrogenation was carried out at atmospheric pressure at 25°. When one molecular equivalent of hydrogen had been added, the mixture was filtered, acidified and extracted with ether. The ether layer was washed with water and dried. The crystals obtained (2.5 g., 89%) after removing the ether were recrystallized from Skellysolve C, m.p. 120–122°, $[\alpha]^{25}D$ −113°.

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 75.0; H, 8.4. Found: C, 74.9; H, 8.5.

(−)-*anti-trans*-1,2,3,4,4a,4b,5,8,8a,9-Decahydro-1β,8a-dimethyl-2-oxophenanthrene-1-propionic Acid (II).—The methylanilinomethylene blocking group was introduced in the 3-position of VII in the usual manner.[2,3] Both the formyl compound and the methylanilinomethylene compound were oils. The yields were essentially quantitative, but the compounds were not purified. The methyl group was introduced by adding to a slurry of 0.57 g. of potassium amide in 100 ml. of ether 1.4 g. of the blocked VII. The mixture was refluxed for 3 hr., cooled to 25° and 3.0 g. of methyl iodide in 10 ml. of ether was added. The mixture was stirred for 16 hr. Water was then added, the layers separated and the aqueous layer was acidified and stirred with ether for 1 hr. to cleave N-methylaniline from the molecule. The ether layer was separated and the ether was removed *in vacuo*. The residual oil was refluxed for 3 hr. with 50 ml. of a 15% KOH solution. The solution was cooled, acidified, extracted with ether and the ether solution was washed with water and dried. One gram of oily material was obtained from the ether. The desired acid II was isolated from the mixture by using the quinine salt method of separation,[2] yield 0.12 g. (11.5%), m.p. 123–126°. Mixed melting point showed no depression with material previously prepared.[2]

***dl-anti-trans*-4,4a,4b,5,6,7,8,8a-Octahydro-6β,7β-dihydroxy-1,8a-dimethyl-2(3H)phenanthrone (VIIIa).**[2]—This material was made from the tricyclic ketone VIa using either osmium tetroxide according to the Woodward[2] procedure or better with silver acetate and iodine (reference 3, footnote 9). For the most part, we used the β-*cis*-glycol which corresponded to the minor osmium product of Woodward, although the α-*cis*-glycol worked equally well.

***dl-anti-trans*-4,4a,4b,5,6,7,8,8a,9,10-Decahydro-6β,7β-dihydroxy-1,8a-dimethyl-2-(3H)phenanthrone (XIa).**—A slurry of 7.0 g. of palladium-on-strontium carbonate containing 2% palladium in 300 ml. of isopropyl alcohol was pre-reduced with hydrogen. Then 3.27 ml. of 10% sodium hydroxide and 32.7 g. (0.125 mole) of VIIIa were added and 0.125 mole of hydrogen was absorbed at 25°. The mixture was filtered and the filtrate was neutralized with acetic acid. After removing the solvent *in vacuo*, the residue was dissolved in chloroform, washed with dilute sodium carbonate and water. The dried solvent was removed and the crystalline residue was triturated with hot ethyl acetate and cooled. Filtration and drying of the crystals gave 22.4 g. (68%) of the monounsaturated β-glycol XIa. This compound which showed an indefinite melting point of 110–120° was characterized as the nicely crystalline acetonide Xa, m.p. 157–160°.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 75.0; H, 9.3. Found: C, 75.3; H, 9.2.

***dl-anti-trans*-3a,4,5,7,8,9,9a,9b-Octahydro-3a,6-dimethyl-7-oxo-(1H)benz[e]indene-3-carboxaldehyde (XIIa).**[3]—The crude β-glycol XIa (20.8 g.) was dissolved in 800 ml. of 50% acetic acid and, after cooling the mixture to 0–5°, 35 g. of lead tetraacetate was added and the mixture was stirred for 1 hr. at 0–5°. Subsequently, 400 ml. of water was added, and the solution was extracted twice with 200 ml. of chloroform. The combined extracts were washed four times with 100-ml. portions of distilled water, twice with 100-ml. portions of 5% sodium bicarbonate, dried and the solvent was removed *in vacuo*. The residue was taken up in 1,050 ml. of benzene and, after heating the solution to 60°, 7.8 ml. of acetic acid and 5.5 ml. of piperidine were added and the benzene–water azeotrope was distilled in a slow stream of nitrogen during a 1-hr. period. The reaction mixture was cooled, washed successively with dilute hydrochloric acid, dilute sodium bicarbonate, water and finally dried. After removal of the solvent *in vacuo* and recrystallization of the residue from isopropyl alcohol, there was obtained 8.4 g. (44%) of the keto aldehyde XIIa, m.p. 117–119°.

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 78.7; H, 8.2. Found: C, 78.5; H, 8.2.

***dl-anti-trans*-2,3,3a,4,5,7,8,9,9a,9b-Decahydro-3a,6-dimethyl-7-oxo-(1H)benz[e]indene-3-carboxaldehyde Ethylene Glycol Acetal (XIIIa).**[3]—The keto aldehyde XIIa (4.00 g., 0.0164 mole) was added to 100 ml. of an isopropyl alcohol slurry of 0.70 g. of pre-reduced palladium–strontium carbonate catalyst containing 2% palladium, and 0.0164 mole of hydrogen was introduced at atmospheric pressure and 25°. The catalyst was removed by filtration, and the solvent was removed *in vacuo* to give the oily saturated aldehyde. Without purification, this oil was dissolved in 50 ml. of dioxane, and 100 ml. of benzene was added along with 1.0 ml. of ethylene glycol and 0.12 g. of *p*-toluenesulfonic acid. The reaction mixture was heated and the water azeotrope slowly distilled during a 1 hr. period. After the remainder of the solvents were removed *in vacuo*, the residue was taken up in chloroform and washed with 5% sodium bicarbonate solution and water. Evaporation of the dried solvent gave 3.26 g. (69%) of the ethyleneglycol acetal XIIIa, m.p. 138–139°.

Anal. Calcd. for $C_{18}H_{26}O_3$: C, 74.4; H, 9.0. Found: C, 74.4; H, 9.0.

***dl-anti-trans*-(1,3-Dioxolane-2-yl)-2,3,3a,4,6,7,8,9,9a,9b-decahydro-6α,3a-dimethyl-7-oxo-(1H)benz[e]indene-6-propionic Acid (XIVa).**—To a solution of 35 ml. of dioxane containing 0.60 ml. of acrylonitrile was added 2.00 g. of XIIIa, and the solution was cooled to 0–5°. Then 0.5 ml. of Triton B was added and the mixture was stirred at room temperature under a nitrogen atmosphere for 65 hours.[9] Dioxane was removed *in vacuo*, and the residue was taken up in 60 ml. of chloroform, washed thrice with 20-ml. portions of saturated sodium chloride, dried and the solvent was removed *in vacuo* to give an oily nitrile. The nitrile (2.086 g.) was refluxed with 50 ml. of 10% potassium hydroxide for 8 hr. under nitrogen. The alkaline aqueous phase was extracted with ether, and the ether phase was worked up to give 0.260 g. of starting material. To the aqueous phase was added 100 ml. of ether, and after cooling to 0–5°, the mixture was acidified with cold dilute sulfuric acid. After separating the layers, the ethereal extract was washed with water, dried and the solvent was removed to give 1.892 g. of acids. Trituration with ether and filtration gave 1.067 g. (57.5%) of acid XIVa, m.p. 158–161°.

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.6; H, 8.3. Found: C, 69.7; H, 8.5.

***dl-anti-trans*-(1,3-Dioxolane-2-yl)-2,3,3a,4,6,9,9a,9b-octahydro-7-hydroxy-6α,3a-dimethyl-(1H)benz[e]indene-6-propionic Acid δ-Lactone (XVa).**—The crystalline keto acid XIVa (0.300 g.) was dissolved in 20 ml. of acetic anhydride

containing 0.010 g. of anhydrous sodium acetate and the mixture was refluxed for 4 hr. under an atmosphere of nitrogen. After the acetic anhydride was removed *in vacuo*, the residue was taken up in ether and washed with 5% sodium carbonate solution and water. Drying and removal of the solvent gave a crystalline residue. The residue was dissolved in 2.0 ml. of acetone, 2.0 ml. of Skellysolve B was then added and the solution was refrigerated overnight. After filtering and drying, there was obtained 0.230 g. (80.7%) of enol lactone XVa, m.p. 151.5–153°.

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.4; H, 8.2. Found: C, 73.6; H, 8.5.

Treatment of this enol lactone according to the procedure given for the preparation of tetracyclic ketone XVI gave a crystalline compound whose infrared spectrum showed strong hydroxyl absorption and the absence of α,β-unsaturated carbonyl absorption. This fact in addition to the similarity of infrared spectra of XVa in the 7.5 μ region with the enol lactone from III showed that this enol lactone was in the 10-*epi*-methyl or unnatural series.[2,3]

(−)-Methyl *anti-trans*-2,3,4,4a,4b,5,8,8a-Octahydro-8a-methyl-2-oxo-1-phenanthrenepropionate (VIc).—Thirty grams of VIb was esterified by refluxing for 2.5 hr. with 312 g. of methanol and 17 g. of dry hydrogen chloride. The excess methanol was removed *in vacuo*, and the residue was taken up in ether and washed with 5% bicarbonate solution and then with water. Removal of the ether gave 31.7 g. of oil (100%) which did not crystallize and was used without purification.

(−)-Methyl *anti-trans*-1,2,3,6a,7,7a,10a,11,11a,11b-Decahydro-3-oxo-6a,9,9-trimethylphenanthro-[2,3]-[1,3]-dioxole-4-propionate (IX).—To a solution of 31.7 g. of ester VIc in 1165 ml. of glacial acetic acid and 3.6 ml. of water was added 38.2 g. of silver acetate and over a period of 30 minutes, 27.2 g. of iodine. The mixture was stirred 1 hr. at 20–25° to consume all the iodine and then was heated at 90–95° for 3 hr. After cooling and filtering, the bulk of the acetic acid was removed *in vacuo*. The residue was dissolved in 500 ml. of methanol, filtered and neutralized to *p*H 9 with methanolic potassium hydroxide. An additional 13.6 g. of potassium hydroxide in 300 ml. of methanol was added and the mixture stirred 16 hr. under nitrogen at 25°. After neutralizing with acetic acid, the methanol was removed under vacuum and the crude *cis*-glycol was taken up in chloroform. The organic phase after washing with water and bicarbonate was dried and evaporated under vacuum to give 20.6 g. of crude neutral glycol VIIIc. Acidification of the bicarbonate wash yielded a thick water-insoluble gum. This acidic material (VIIIb) was re-esterified by first dehydrating with benzene and then treating with methanolic hydrogen chloride as above to give more neutral oily glycol VIIIc, making a total of 31.8 g.

Since this glycol resisted all attempts at crystallization, it was converted to its acetonide IX with acetone and anhydrous copper sulfate.[2,3] The crude crystalline acetonide after trituration with ether weighed 21.1 g., m.p. 120–122°. Chromatography of the mother liquors gave 0.8 g. more, amounting to 55% over-all yield from the acid VIb. Recrystallization from methanol gave a pure sample of the acetonide, m.p. 123–124°, $[\alpha]^{25}D$ −242°.

Anal. Calcd. for $C_{22}H_{30}O_5$: C, 70.6; H, 8.1. Found: C, 70.7; H, 8.1.

(−)-Methyl *anti-trans*-1,2,3,5,6,6a,7,7a,10a,11,11a,11b-Dodecahydro-3-oxo-6a,9,9-trimethylphenanthro-[2,3]-[1,3]-dioxole-4-propionate (Xb).—IX was reduced by the procedure described for XIa to give a 70% yield of Xb, m.p. 106.5–108°, $[\alpha]^{25}D$ −98.5°.

Anal. Calcd. for $C_{22}H_{32}O_5$: C, 70.2; H, 8.1. Found: C, 69.9; H, 8.5.

(+)-Methyl 3-Formyl-3a,4,5,7,8,9,9a,9b-octahydro-3a-methyl-7-oxo-(1H)benz[e]indene-6-propionate (XIIb).—The keto ester Xb (7.91 g.) was dissolved in 75 ml. of acetic acid and 75 ml. of water. The reaction mixture then was heated on a steam-bath for a period of 1 hr. to remove the acetonide group giving the glycol XIb. Subsequently, 300 ml. of 50% acetic acid was added, the reaction mixture was cooled to 0–5° and 9.9 g. of lead tetraacetate was added. After stirring for 15 minutes, 250 ml. of ice-water was added and the mixture was extracted twice with 100 ml. of chloroform. The combined chloroform extract was washed successively with water, dilute sodium bicarbonate solution, dilute sulfuric acid solution, water and finally dried. The solvent was removed *in vacuo* and the residue was taken up in 600 ml. of benzene. After heating the solution to 60°, 4 ml. of acetic acid and 2.8 ml. of piperidine were added, and the water was azeotroped out in a slow stream of nitrogen during a 1-hr. period. The reaction mixture was cooled, washed successively with dilute hydrochloric acid, dilute sodium bicarbonate solution, water and finally dried. After removal of the solvent *in vacuo* and trituration of the residue with ether–Skellysolve B, there was obtained 2.13 g. (32%) of XIIb, m.p. 71–73°, $[\alpha]^{25}D$ +61.3°.

Anal. Calcd. for $C_{19}H_{24}O_4$: C, 72.1; H, 7.7. Found: C, 72.1; H, 7.8.

(−)-Methyl *anti-trans*-3-(1,3-Dioxolane-2-yl)-2,3,3a,-4,5,7,8,9,9a,9b-decahydro-3a-methyl-7-oxo-(1H)benz[e]-indene-6-propionate (XIIIb).—The aldehyde XIIb was converted by the procedure used for XIIa to XIIIa, involving first a reduction and then reaction with ethylene glycol, to XIIIb, m.p. 100–101°, $[\alpha]^{25}D$ −21.5°.

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.6; H, 8.3. Found: C, 69.5; H, 8.3.

***anti-trans*-3-(1,3-Dioxolane-2-yl)-2,3,3a,4,6,7,8,9,9a,9b-decahydro-6β,3a-dimethyl-7-oxo(1H)benz[e]indene-6-propionic Acid (XIVb).**—The keto ester XIIIb (1.222 g.) was dissolved in 40 ml. of benzene containing 14 ml. of *t*-butyl alcohol, and 28.4 ml. of 0.467 *N* potassium *t*-butoxide solution was added. The mixture was refluxed under a nitrogen atmosphere, and 1.8 ml. of methyl iodide was added. After refluxing for 5 minutes, 20 ml. of water was added, and the mixture was stirred for 20 minutes while it was cooling to room temperature. The layers were separated and after the aqueous layer was extracted with ether, it was cooled to 0–5° and acidified in the presence of 50 ml. of ether with dilute sulfuric acid. After the layers were separated, the aqueous layer was extracted with 50 ml. of ether and the combined extracts were washed with water and dried. Removal of the solvent gave 1.196 g. (97.8%) of an oil whose infrared spectrum showed no α,β-unsaturated carbonyl group. This oil was used in the next step without purification.

***anti-trans*-3-(1,3-Dioxolane-2-yl)2,3,3a,4,6,9,9a,9b-octahydro-7-hydroxy-6β,3a-dimethyl-(1H)benz[e]indene-6-propionic Acid δ-Lactone (XVb).**—The oily keto acid XIVb (1.191 g.) was dissolved in 15 ml. of acetic anhydride containing 0.010 g. of anhydrous sodium acetate, and the mixture was refluxed for 4 hr. under an atmosphere of nitrogen. After the acetic anhydride was removed *in vacuo*, the residue was taken up in ether and washed with 5% sodium carbonate and water. Drying and removal of the solvent gave 0.995 g. (88%) of an oil whose infrared spectrum showed that it was mainly the enol lactone XVb but that it contained some anhydrides as well as some enol lactone XVa. This oil was used in the next step without further purification.

(+)$\Delta^{9,11}$-Dehydro-21-norprogesterone-20-ethylene Glycol Acetal (XVI).—The previously obtained crude oily β-enol lactone XVb (0.896 g.) was dissolved in 100 ml. of ether containing 30 ml. of benzene, and after cooling the mixture to −50°, 3.0 ml. of 4.0 *M* methylmagnesium bromide solution was added over a 20-minute period. The mixture was stirred for 1 hr. at −50°, and then 2.0 ml. of acetone and 10 ml. of 20% acetic acid were added. The mixture was warmed to 5° and the layers were separated. The aqueous layer was extracted with 15 ml. of chloroform and the combined extracts were washed with 5% sodium carbonate solution, water and then dried. After removing the solvents *in vacuo*, the residue was dissolved in 60 ml. of methanol and a solution of 2.0 g. of potassium hydroxide in 6.0 ml. of water was added. The mixture was refluxed for 2 hr. under a nitrogen atmosphere and the methanol was removed *in vacuo*. Subsequently, water and ether were added to the residue and the ether layer was separated and dried. Removal of the solvent gave an oil (0.711 g.) which partially crystallized. The total residue was taken up in benzene and put on a basic alumina column. Elution with ether and recrystallization from methanol gave 0.340 g. (38.2% from XIIIb) of tetracyclic ketone XVI, m.p. 176–179°, $[\alpha]^{25}D$ +76°.

The m.p., mixed m.p., optical rotation and infrared spectrum were identical with those of the tetracyclic ketone derived from Woodward's (+)$\Delta^{9(11),16}$-bisdehydro-21-norprogesterone, whose preparation is described below.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.2; H, 8.8. Found: C, 77.0; H, 8.9.

$\Delta^{9(11)}$-Dehydro-21-norprogesterone.—A slurry of 0.08 g. of palladium-on-strontium carbonate containing 2% palladium in 4 ml. of isopropyl alcohol was hydrogenated at atmospheric pressure at 25°. Then 0.350 g. of $\Delta^{9(11),16}$-bisdehydro-21-norprogesterone (XVII) was added and washed in with 2 ml. of isopropyl alcohol, and the hydrogenation was continued until one molecular equivalent of hydrogen was added. The reaction mixture was filtered and the isopropyl alcohol was removed *in vacuo*. Trituration with ether yielded 0.17 g. of crystals, m.p. 127–131°, $[\alpha]^{25}D$ +120°.

$\Delta^{9(11)}$-Dehydro-21-norprogesterone-20-ethylene Glycol Acetal (XVI).—The procedure for the reaction between $\Delta^{9(11)}$-dehydro-21-norprogesterone and ethylene glycol was the same as for the preparation of XIII. A 71% yield of XVI was obtained, m.p. 173–176°. The analytical sample was recrystallized from methanol, m.p. 177–180°, $[\alpha]^{25}D$ +79.1°.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.2; H, 8.8. Found: C, 76.8; H, 8.9.

Acknowledgment.—We thank Dr. R. H. Munch, Mr. G. W. Ashworth and Mr. O. E. Kinast for their help with the numerous spectra required in this work. We are also indebted to Dr. R. B. Woodward for much valuable advice and assistance and to Dr. O. J. Weinkauff, Associate Director of Research, whose interest and coöperation made this work possible.

ST. LOUIS 4, MO.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

Occurrence of the (1 → 3)-Linkage in Starches[1]

BY M. L. WOLFROM AND A. THOMPSON[2]

RECEIVED FEBRUARY 2, 1956

The presence of a small number of α-D-(1 → 3)-linkages in amylopectin is shown by the isolation, by means of carbon and silicate column chromatography, of 3-*O*-α-D-glucopyranosyl-D-glucose (nigerose), as its β-D-octaacetate, from the acid hydrolyzate of amylopectin under conditions in which its formation by reversion is negligible.

It is now generally accepted, on the basis of methylation[3–5] and rotational[6] studies, that the principal linkage in starch is α-D-(1 → 4), in agreement with the long known fact that enzymic degradation of starch produces maltose[7] as the major product. Freudenberg and co-workers[4] found that completely methylated potato starch, upon hydrolysis, yields 90% of 2,3,6-tri-*O*-methyl-D-glucose, 5% of 2,3,4,6-tetra-*O*-methyl-D-glucose and approximately 5% of a mixture of di-*O*-methyl-D-glucoses, consisting mainly of 2,3-di-*O*-methyl-D-glucose. These data indicate that a glycosidic linkage may occur at both carbons 6 and 4 in a small proportion of the D-glucose units later shown[8] to be located in the predominant amylopectin fraction of the starch. This observation has been confirmed by later workers[9] who have isolated isomaltose (6-*O*-α-D-glycopyranosyl-D-glucose) as its crystalline β-D-octaacetate from the acetylated acid hydrolyzate of amylopectin, prepared under conditions minimizing reversion products to a negligible quantity.[10]

Evidence obtained from periodate oxidation[11] indicates that some of the dextrans contain (1 → 2)- or (1 → 3)-linkages. Nigerose[12] ("sakebiose"[13] or the sugar of the "γ-acetate,"[14,15] 3-*O*-α-D-glucopyranosyl-D-glucose) has been isolated[12] from the acid hydrolyzate of the polysaccharide "mycodextran" or "nigeran" produced by the action of *Aspergillus niger* on sucrose. Periodate oxidation of amylopectin[16] followed by reduction and hydrolysis produces a small amount of D-glucose, which, assuming complete reaction, indicates the presence of either (1 → 3)-linkage alone or of both (1 → 2)- or (1 → 3)- and (1 → 4)-linkages in the same D-glucopyranose unit.

We wish to present herein definitive evidence for the presence of the 3-*O*-α-D-glucopyranosyl linkage in the amylopectin molecule. This evidence consists of the isolation of 3-*O*-α-D-glucopyranosyl-D-glucose as its crystalline β-D-octaacetate from an amylopectin (waxy maize starch) acid hydrolyzate produced under conditions in which the formation of this disaccharide during the hydrolysis is negligible.[10,14] Therefore, a small amount of an α-D-(1 → 3)-linkage exists preformed in the amylopectin molecule. The finding[17] that intestinal extracts hydrolyze nigerose offers further support for the presence of this linkage in starches.

Experimental

3-*O*-α-D-Glucopyranosyl-β-D-glucose Octaacetate from Amylopectin Acid Hydrolyzate.—Amylopectin (32.4 g. of waxy maize starch, equivalent to 36 g. of D-glucose) was suspended in 9000 ml. of 0.1 *N* hydrochloric acid solution and stirred in a boiling water-bath. The hydrolysis was followed by

(1) Preliminary communication: M. L. Wolfrom and A. Thompson, THIS JOURNAL, **77**, 6403 (1955).

(2) Research Associate of the Corn Industries Research Foundation.

(3) W. N. Haworth, E. L. Hirst and J. I. Webb, *J. Chem. Soc.*, 2681 (1928).

(4) K. Freudenberg and H. Boppel, *Ber.*, **73**, 609 (1940); K. Freudenberg and G. Hüll, *ibid.*, **74**, 237 (1941); K. Freudenberg, *ibid.*, **76A**, 71 (1943).

(5) C. C. Barker, E. L. Hirst and G. T. Young, *Nature*, **147**, 296 (1941).

(6) K. Freudenberg, *Chem.-Ztg.*, **60**, 853, 875 (1936).

(7) C. O'Sullivan, *J. Chem. Soc.*, **25**, 579 (1872); **29**, 478 (1876).

(8) K. Meyer, M. Wertheim and P. Bernfeld, *Helv. Chim. Acta*, **23**, 865 (1940).

(9) M. L. Wolfrom, J. T. Tyree, T. T. Galkowski and A. N. O'Neill, THIS JOURNAL, **72**, 1427 (1950); **73**, 4927 (1951).

(10) A. Thompson, M. L. Wolfrom and E. J. Quinn, *ibid.*, **75**, 3003 (1953).

(11) Allene Jeans, W. C. Haynes, C. A. Wilham, J. C. Rankin, E. H. Melvin, Marjorie J. Austin, J. E. Cluskey, B. E. Fisher, H. M. Tsuchiya and C. E. Rist, *ibid.*, **76**, 5041 (1954).

(12) S. A. Barker, E. J. Bourne and M. Stacey, *J. Chem. Soc.*, 3084 (1953).

(13) K. Matsuda, G. Hiroshima, K. Shibasaki and K. Aso, *J. Fermentation Technol.* (Japan), **32**, 498 (1954); *Tohoku J. Agr. Research*, **5**, 239 (1954); *C. A.*, **49**, 8554 (1955).

(14) A. Thompson, Kimiko Anno, M. L. Wolfrom and M. Inatome, THIS JOURNAL, **76**, 1309 (1954).

(15) S. Peat, W. J. Whelan and Kathleen A. Hinson, *Chemistry & Industry*, 385 (1955).

(16) M. Abdel-Akher, J. K. Hamilton, R. Montgomery and F. Smith, THIS JOURNAL, **74**, 4970 (1952).

(17) J. Larner and R. E. Gillespie, *ibid.*, **78**, 882 (1956).