many week-end friends, while in the forenoons of the week days Dr. Bogert was found in the woodshed, which had been fitted up as an office, writing for publication, accounts of experimental results and data accumulated during the past academic year by himself and his collaborating research students. The afternoons were given over to fishing and hunting, sports of which he was especially fond, as shown by his membership in the Megantic Fish and Game Club and in the Hunter's Fraternity of America.

DEPARTMENT OF CHEMICAL ENGINEERING
COLUMBIA UNIVERSITY
NEW YORK 27, N. Y. JOHN M. NELSON

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

Studies in Steroid Total Synthesis. I. Resolution of a Bicyclic Intermediate

BY A. JOHN SPEZIALE, JOHN A. STEPHENS AND QUENTIN E. THOMPSON

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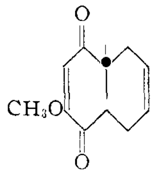
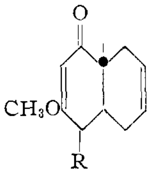
A method for converting Woodward's *dl-trans*-1,4-diketo-2-methoxy-10-methyl-$\Delta^{2,6}$-hexahydronaphthalene (I) into the optically pure enantiomorphs of *trans*-2-keto-10-methyl-$\Delta^{3,6}$-hexahydronaphthalene (IV) in 55–60% over-all yield is described. Stereo-selective reduction of I yielded the monohydric alcohol IIa which was resolved *via* its *d*-camphor-10-sulfonate esters. The pure diastereoisomers were reductively cleaved to (+)- and (−)IIc and thence reduced to the optically active forms of the Woodward bicyclic ketone (IV) with lithium aluminum hydride followed by vigorous acid hydrolysis.

A resolution step is a requirement of any scheme for the total synthesis of naturally occurring steroids. Maximum economy of materials and effort is achieved if resolution can be effected at the earliest possible stage, *i.e.*, at the time of, or closely following, the introduction of the first stable asymmetric center. Present published syntheses of non-aromatic steroids do not contain this feature.[1] When resolution is accomplished it has been done fairly late in the synthetic sequence.

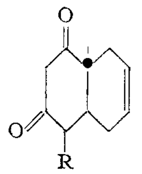
In the present paper we wish to report modification of the Woodward[2] total synthesis to include resolution at the bicyclic stage coupled with an improved method for converting I to IV. Specifically, the racemic Woodward *trans*-adduct (I) has been smoothly and stereo-selectively reduced using zinc and aqueous acetic acid to give *dl-trans*-1-hydroxy-4-keto-2-methoxy-10-methyl-$\Delta^{2,6}$-hexahydronaphthalene (IIa) in approximately 90% yield. That IIa is the correct structure for the reduction product was indicated by cryoscopic molecular weight determination in benzene, infrared spectrum, conversion in good yield to monoesters (acetate, benzoate, *p*-toluenesulfonate) and hydrolysis under mild conditions to a β-diketone IIIa which was soluble in aqueous carbonate and gave a strong ferric chloride test. Subsequent conversions have confirmed these conclusions. Presumably the reduction gives an α-OH although the configuration at C-1 has not been definitely established. Attempts to isolate an epimeric alcohol were unsuccessful. Zinc and acetic acid have been used by numerous investigators to reduce Diels–Alder adducts of this type.[3a,b] In most instances[3a] the conjugated double bond rather than a carbonyl group was reduced. However, Butz and Butz[3b] have reported the reduction of the C-1 carbonyl group of *cis*-1,2,4-triketo-10-methyl-Δ^{6}-octahydronaphthalene in low yield. Nes and Mason[4] observed some reduction of the C-20 carbonyl group of 3α-hydroxy-21-acetoxy-11,20-diketo-12-bromo-$\Delta^{1,16}$-pregnene after treatment with zinc and aqueous acetic acid for 2 hours. Resolution of IIa was accomplished readily by conversion to the *d*-camphor-10-sulfonate esters and separation of the resulting diastereoisomers by fractional crystallization from acetone. Both diastereoisomers have been isolated in good yield (85–90%) with optical purity in excess of 98% in each case.



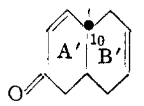
I



IIa, R = OH
b, R = *d*-camphor-10-sulfonyloxy
c, R = H



IIIa, R = OH
b, R = H



IV

It was found that sulfonate esters of IIa could be reductively cleaved by zinc and acetic acid to give high yields of *trans*-4-keto-2-methoxy-10-methyl-$\Delta^{2,6}$-hexahydronaphthalene (IIc) plus the zinc salt of the sulfonic acid. Thus reductive cleavage of the tosylate or the mixture of crude diastereo-

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[1] R. Robinson, *et al.*, *J. Chem. Soc.*, 676 (1946); 1855 (1949); 361 (1953), resolved a tricyclic intermediate while Sarett, *et al.*, THIS JOURNAL, **74**, 1393, 1397, 1401, 1406, 4974 (1952); **75**, 422 (1953); and Woodward (see reference 2) resolved very near the end of their respective syntheses. W. S. Johnson, *et al.*, THIS JOURNAL, **75**, 2275 (1953), and A. L. Wilds, *et al.*, *ibid.*, **72**, 5794 (1950); *ibid.*, **75**, 4878 (1953), have prepared racemic non-aromatic steroids by total synthesis but as yet have not indicated resolution has been effected. It should be noted that in the Johnson synthesis a stable asymmetric center is not present until a tetracyclic system has been prepared, thus resolution prior to that stage is impossible.

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

[3] (a) L. H. Sarett, *et al.*, *ibid.*, **74**, 1393 (1952); K. Alder and G. Stein, *Ann.*, **501**, 247 (1936); C. K. Chuang and C. T. Han, *Ber.*, **68**, 876 (1935); (b) E. W. J. Butz and L. W. Butz, *J. Org. Chem.*, **8**, 497 (1943).

[4] W. R. Nes and H. L. Mason, THIS JOURNAL, **73**, 4765 (1951).

isomeric camphor sulfonate esters gave racemic IIc, m.p. 76–77°. Starting with pure diastereoisomeric camphor sulfonate esters, the more insoluble isomer, m.p. 166–167°, $[\alpha]^{25}\mathrm{D}$ −80.5°, yielded optically active IIc, m.p. 93–94°, $[\alpha]^{25}\mathrm{D}$ −58.9°, while the second diastereoisomer, m.p. 174–175°, $[\alpha]^{25}\mathrm{D}$ +130.2°, gave its enantiomorph, m.p. 93–94°, $[\alpha]^{25}\mathrm{D}$ +58.8°, both in yields of 90–92%. Hydrolysis of the methoxyl group readily occurred when IIc was warmed with dilute mineral acid and was a side reaction in the zinc deacylation if water was present in the acetic acid. Conversion of a sample of the β-diketone IIIb back to the methoxy ketone IIc has been accomplished in 70% yield[5] by refluxing IIIb in anhydrous methanol with an acid catalyst.

Reduction of racemic IIc with lithium aluminum hydride followed by vigorous treatment with mineral acid yielded the racemic ketone IV, identical in all respects with the Woodward[2] bicyclic ketone. In the same manner (−)IIc gave the non-crystalline (m.p. −2°) optically active enantiomorph of IV, b.p. 123–124° (10 mm.), $[\alpha]^{25}\mathrm{D}$ −239°, in excess of 90% yield while (+)IIc yielded (+)IV.

This relatively facile conversion of the Woodward racemic *trans*-adduct to the pure enantiomorphs of IV makes available useful optically active bicyclic steroid intermediates. A distinguishing feature of the Woodward[2] synthesis is the conversion of rings A′ and B′ of IV into rings C and D, respectively, of the steroidal nucleus. Thus, the asymmetric carbon, C-10, of IV becomes C-13 of the finished steroid. Since naturally occurring steroids are optically active and have a common absolute configuration about C-13 (among other positions) that enantiomorph of IV having an identical configuration at C-10 is the desired isomer for use in a synthesis such as Woodward's which involves the conversion of bicyclic A′ and B′ to tetracyclic C and D, respectively. In the present case, it has been determined that the (−) isomer of IV, $[\alpha]^{25}\mathrm{D}$ −239°, is the desired or "natural" isomer for the bicyclic A′B′ to tetracyclic CD conversion. Details of this work are included in a separate paper from this Laboratory.[6]

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.

Experimental[7]

The *dl-trans*-1-Hydroxy-4-keto-2-methoxy-10-methyl-$\Delta^{2,6}$-hexahydronaphthalene (IIa).—To a solution of 50 g. of *trans*-1,4-diketo-2-methoxy-10-methyl-$\Delta^{2,6}$-hexahydronaphthalene[2] (I) in 162 ml. of water and 500 ml. of glacial acetic acid, was added 100 g. of zinc dust at 20–25° over a 15-minute period. The mixture was stirred vigorously for 5 hours at 20–25° and filtered to remove unreacted zinc. The filter cake was washed with 100 ml. of methanol, and the combined filtrate and washings were reduced to about one-third of the original volume by distillation under reduced pressure. The residue was dissolved in 150 ml. of chloroform and 150 ml. of water. The aqueous layer was separated and extracted with 100 ml. of chloroform. The chloroform solutions were combined, washed with water and 5% sodium bicarbonate solution, and after drying over sodium sulfate and removal of the solvent under reduced pressure, there remained 45.2 g. (90% yield) of IIa as a viscous liquid which set to a hard mass, m.p. 78–82°. Recrystallization from a variety of solvents—(benzene, cyclohexane, petroleum ether (b.p. 60–68°), benzene and diisopropyl ether)—afforded IIa in 80% recovery; m.p. 81–83°. The analytical sample was prepared by recrystallization from petroleum ether or petroleum ether–benzene mixtures, m.p. 82–83°.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74; CH_3O–, 14.90; mol. wt., 208. Found: C, 68.94; H, 7.84; CH_3O–, 14.81; mol. wt., 200.

The following esters of IIa were prepared in the conventional manner by reaction of the alcohol in pyridine with acetic anhydride, benzoyl chloride and *p*-toluenesulfonyl chloride, respectively.

Acetate: essentially quantitative yield; recrystallized from isopropyl ether, m.p. 84–85°.

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.24; CH_3O–, 12.39. Found: C, 67.49; H, 7.46; CH_3O–, 12.85.

Benzoate: yield 92%; recrystallized from methanol and finally isopropyl ether, m.p. 146.6–147.8°.

Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.05; H, 6.45; CH_3O–, 9.92. Found: C, 73.18; H, 6.93; CH_3O–, 10.16.

***p*-Toluenesulfonate:** yield 90%; recrystallized from methyl isobutyl ketone, m.p. 145.4–146.4°.

Anal. Calcd. for $C_{19}H_{22}O_5S$: C, 62.96; H, 6.12; CH_3O–, 8.56; S, 8.84. Found: C, 63.37; H, 6.32; CH_3O–, 9.09; S, 8.77.

Preparation and Separation of Camphor Sulfonate Diastereoisomers IIb.—Crude *dl-trans*-1-hydroxy-4-keto-2-methoxy-10-methyl-$\Delta^{2,6}$-hexahydronaphthalene (IIa) from the reduction step (104 g., m.p. 78–82°) dissolved in 200 ml. of anhydrous pyridine was treated in several portions with 125.4 g. of *d*-camphor-10-sulfonyl chloride[8] (m.p. 67–70°) over a 15-min. period. The temperature of the reaction was allowed to rise spontaneously to 60° where it was maintained, first by cooling and later by warming, for 1 hr. during which time considerable ester separated. The mushy mixture was allowed to cool to 30° over a 3-hr. period and was quenched by slowly adding 900 ml. of cold (10°) water. The light tan mixture of diastereoisomers which separated amounted to 180 g. (85%), m.p. 130–150°, $[\alpha]^{25}\mathrm{D}$ +24 ± 1° after being collected, washed with water and dried. In other experiments using purified IIa, the yields of esters were around 95%.

Separation of the diastereoisomers may be effected by crystallization from a number of common solvents (benzene, toluene, xylene, ethyl acetate, methyl ethyl ketone, methyl isobutyl ketone, carbon tetrachloride) but acetone, in which the ratio of solubilities of the dextro diastereoisomer to the levo was approximately 2.7:1, appeared to be the solvent of choice. Thus, in the present case, the 180 g. of crude mixture was dissolved in 630 ml. of hot acetone, decolorized with about 2 g. of carbon, filtered and allowed to cool to 25° with stirring. Levo rotating diastereoisomer of approximately 90–95% optical purity precipitated in the first crop. Concentration and collection of additional crops gave samples with a wide range of diastereoisomeric composition. When the ratio of dextro to levo isomer in solution approached 2.7:1, the levo compound tended to supersaturate allowing essentially pure crops of the more soluble dextro isomer to be collected. Thus, by recrystallization in a systematic fashion, both of the pure esters could be obtained. The yield of essentially pure levo diastereoisomer, m.p. 166–167°, $[\alpha]^{25}\mathrm{D}$ −80.5°, was approximately 90%

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(5) H. Conroy, THIS JOURNAL, **74**, 3046 (1952), observed that the ethoxylation of *cis*-8-methylhydrindan-5,7-dione occurred exclusively at the 5-position, thus being substantially in agreement with our results. However, in our case, a small amount of an oily product was isolated from the reaction mixture which appeared to contain the isomeric 4-methoxy ketone. Further study of the methoxylation of IIIb is under investigation in this Laboratory.

(6) L. B. Barkley, M. W. Farrar, W. S. Knowles, H. Raffelson and Q. E. Thompson, THIS JOURNAL, **76**, 5014 (1954).

(7) Melting points are uncorrected. Optical rotations were carried out in chloroform solution at 2% concentration unless otherwise specified. Analyses were done by Mr. A. Bybell of this Laboratory.

(8) S. Smiles and T. P. Hilditch, *J. Chem. Soc.*, **91**, 519 (1907).

(based on crude ester) while that of the dextro isomer, m.p. 174–175°, $[\alpha]^{25}\text{D}$ +130°, was 80–85%.

Anal. Calcd. for $C_{22}H_{30}O_6S$: C, 62.57; H, 7.16. Found (levo isomer): C, 62.62; H, 7.31; (dextro isomer): C, 62.63; H, 7.07.

trans-**4-Keto-2-methoxy-10-methyl-$\Delta^{2,6}$-hexahydronaphthalene (IIc)**.—A suspension of 0.05 mole of a sulfonate ester of IIa (toluenesulfonate or mixed camphor sulfonates for racemic IIc and pure dextro or levo diastereoisomeric camphor sulfonates for the (+) and (−) enantiomorphs, respectively) was prepared in 25 ml. of glacial acetic acid (99.5%) and 2 ml. of acetic anhydride. Zinc dust (6.5 g.) was added with vigorous agitation and the temperature carefully raised to 60–80° whereupon the reaction became self-sustaining. The temperature was allowed to rise to 100° and was held in the range 100–110° for 2 hr. first by occasional cooling and then, after about 20 min., by gentle heating. The mixture was then cooled to room temperature and filtered to remove zinc (also some zinc toluenesulfonate when the tosylate ester was used). The filter cake was washed with 5–10 ml. of acetic acid and the combined filtrate and washings were quenched by pouring slowly into 170 ml. of cold (10°) water. In either optically active series, approximately 8.6–8.8 g. (90–92%) of very good quality, m.p. 92–94°, (+)- or (−)IIc separated. A single recrystallization from petroleum ether (b.p. 60–68°) gave pure colorless needles, m.p. 93–94°, $[\alpha]^{25}\text{D}$ ±58.8°. Racemic IIc being lower melting tended to separate as an oil but almost immediately crystallized. Yields from either the pure toluenesulfonate or the crude mixed camphorsulfonates were around 80%, m.p. 72–75° (crude). One or two recrystallizations from petroleum ether (b.p. 60–68°) gave pure material, m.p. 76–77°.

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.98; H, 8.39; CH_3O–, 16.15. Found: (*dl*) C, 74.98; H, 8.46; CH_3O–, 16.21 (+) series; C, 75.05; H, 8.19.

trans-**1-Hydroxy-2,4-diketo-10-methyl-Δ^6-octahydronaphthalene (IIIa)**.—A mixture consisting of 1.7 g. of IIa (m.p. 81.8–82.2°), 10 ml. of methanol, 9 ml. of water and 0.5 ml. of sulfuric acid was stirred at room temperature for 23 hours. The solution was concentrated under reduced pressure to an oily residue and dissolved in 50 ml. of ether. The ether solution was washed with water and dried over anhydrous sodium sulfate. After evaporation of the solvent, there remained 1.4 g. (88%) of IIIa. A sample recrystallized from ethyl acetate melted at 155–156°.

The β-diketone alcohol IIIa gave a red color with ferric chloride solution, was soluble in dilute sodium carbonate solution and was precipitated on addition of dilute acetic acid.[9]

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.99; H, 7.28.

trans-**2,4-Diketo-10-methyl-Δ^6-octahydronaphthalene (IIIb)**.—To a solution of 24.0 g. of (−)IIc (m.p. 93–94°) in 100 ml. of dioxane was added a solution of 12.2 g. of concentrated sulfuric acid in 75 ml. of water at 25°. The clear solution was allowed to stand overnight. Crystals were deposited 40 minutes after the reactants were mixed. The solvent was removed under reduced pressure and 200 ml. of water was added to the residue. The mixture was cooled in an ice-bath for several hours, filtered and washed with water giving 22 g. (99%) of colorless (−)IIIb melting at 185–188°. The analytical sample was prepared by recrystallization from aqueous isopropyl alcohol, m.p. 187.2–189.2°, $[\alpha]^{25}\text{D}$ −96.6° (1% soln. in chloroform) or $[\alpha]^{25}\text{D}$ −154° (2% soln. in methanol). Racemic IIIb was prepared in a similar fashion in 94% yield; m.p. 150–151°. A sample was recrystallized from ethyl acetate; m.p. 151–152°.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.12; H, 7.98. Found (*dl*): C, 74.13; H, 8.10, (−)series: C, 74.06; H, 8.03.

Conversion of (−)IIIb to (−)IIc.—A solution consisting of 2.0 g. of (−)IIIb, 25 ml. of anhydrous methanol, 40 ml. of dry benzene and 0.5 g. of *p*-toluenesulfonic acid was heated to reflux and the solvent removed by slow distillation. After 6 hours an additional 10 ml. of methanol and 40 ml. of benzene were added and distillation was continued for an additional 11 hours. The solution was cooled, neutralized with solid potassium carbonate, transferred to a separatory funnel, and diluted with 50 ml. of ether. The solution was washed with three 10-ml. portions of 2.5% aqueous sodium carbonate solution and water. Acidification of the carbonate washes gave a negligible amount of unreacted diketone. The benzene–ether solution was dried over magnesium sulfate. After removal of the solvent under reduced pressure, there remained 2.1 g. (100%) of white solid material. Recrystallization from petroleum ether (b.p. 60–68°) gave 1.5 g. (71%), m.p. 89–91°. There was no depression on admixture with (−)IIc (m.p. 91–92°).

A small amount of oil was isolated from the mother liquors and preliminary investigation by infrared analysis indicated this may contain some of the isomeric 4-methoxy ketone.

trans-**2-Keto-methyl-$\Delta^{3,6}$-hexahydronaphthalene (IV)**.—A solution of 23.7 g. of IIc (racemic or optically active) in 165 ml. of anhydrous diethyl ether was added to a solution of lithium aluminum hydride (3.02 g.) in 150 ml. of anhydrous diethyl ether over 28 min. The reaction was carried out in an atmosphere of dry nitrogen. The mixture was stirred for 1.5 hr. after the addition was complete. Water (15 ml.) was added dropwise to destroy the unreacted hydride and the mixture cooled to 5°. A solution of 16.2 g. of concentrated sulfuric acid in 85 ml. of water was added to dissolve the inorganic hydroxides and the mixture allowed to settle. The aqueous layer was separated and washed with two 30-ml. portions of diethyl ether, and the wash liquors were added to the above ethereal solution. When the solvent was removed under reduced pressure, a viscous, yellow oil remained. The oil was mixed with a solution of 5.5 g. of concentrated sulfuric acid in 27 ml. of water, and the resulting suspension was heated at 95–103° for 2.5 hr. with vigorous agitation. The mixture was cooled and extracted with two 50-ml. portions of diethyl ether. The combined extracts were washed with water and dilute sodium bicarbonate solution and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure (50° at 30 mm.). The yield of IV was around 19.5 g. With racemic materials the crude ketone crystallized readily upon standing at room temperature, m.p. 34–36° (crude), $n^{25}\text{D}$ 1.5193. A mixed m.p. with *dl-trans*-2-keto-10-methyl-$\Delta^{3,6}$-hexahydronaphthalene, m.p. 34.5–36°, prepared by the method of Woodward,[2] showed no depression. In addition a semicarbazone of our (±)IV, m.p. 178–179°, agreed with that reported by Woodward. In the optically active series, (−)IIc yielded liquid IV, m.p. −4 to −2° (crude) and −2° (pure), b.p. 123–124° (10 mm.), $[\alpha]^{25}\text{D}$ −239°, $n^{25}\text{D}$ 1.5197. In the same manner (+)IV was obtained from (+)IIc. Infrared spectra of pure samples of our (+)-, (−)- and (±)IV were identical with each other and with racemic material prepared by Woodward's method.

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.43; H, 8.70. Found (−) series: C, 81.41; H, 8.99.

St. Louis, Missouri

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[9] E. W. J. Butz and L. W. Butz[3b] describe some properties for *cis*-IIIa.