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THE SYNTHESIS AND LITHIUM AMMONIA REDUCTION OF 7-METHOXYCHROMAN[1]

R. T. BLICKENSTAFF and I. Y. C. TAO
Medical Research Laboratory, Veterans Administration Hospital
and
Department of Biochemistry, Indiana University School of Medicine, Indianapolis, Indiana 46202

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Abstract—7-Methoxychroman (II) undergoes Birch reduction to give, among other hydrolysis products, 4a,5,6,7-tetrahydrochroman-7-one (V), which is obtained also by hydrogenation of 4-(γ-hydroxypropyl)-resorcinol (IX) in the presence of rhodium on alumina.

THE Birch reduction has been employed extensively for the conversion of phenolic A-ring steroids into 19-norsteroids.[2] Recent publication of the reduction of 6-oxaestradiol 3-methyl ether[3] prompts us to report our work on a model of this type, namely 7-methoxychroman (II, Scheme 1).

7-Methoxy-4-chromanone (I)[4] was reduced to II with Raney nickel under conditions similar to those used for the reduction of 7-hydroxy-4-chromanone.[5] Some of the preparations contained as a minor constituent an alcohol, which could be separated from II chromatographically and dehydrated with iodine; catalytic hydrogenation of the olefin gave additional II. 7-Methoxychroman was obtained by alumina chromatography as an oil with an IR absorption spectrum identical to that of the distilled, analytical sample.

7-Methoxychroman (II) was reduced with lithium, ammonia and t-butyl alcohol.[6] The reaction appeared to have proceded to completion as judged by loss of the 1620, 1585 and 1504 cm^{-1} bands characteristic of the aromatic ring,[7] but unreduced II was clearly evident in the NMR spectrum,* where a OMe signal at δ 3·7 ppm (completely resolved from the 3·5 ppm OMe of III) represents a mole fraction of 0·04. The dihydro product III could be chromatographed on Florisil, but chromatographic cuts contained traces of II, and on standing in contact with the air they were partially oxidized† to II and partially hydrolyzed to VI.

When the crude reduction product was hydrolyzed in methanolic HCl, chromatography on Florisil gave II, a ketone tentatively identified as 8a-methoxy-4a,5,6,7,8,8a-hexahydrochroman-7-one (IV), 4a,5,6,7-tetrahydrochroman-7-one (V), and 4-(γ-hydroxpropyl)cyclohexane-1,3-dione (VI in one of its tautomeric forms).‡

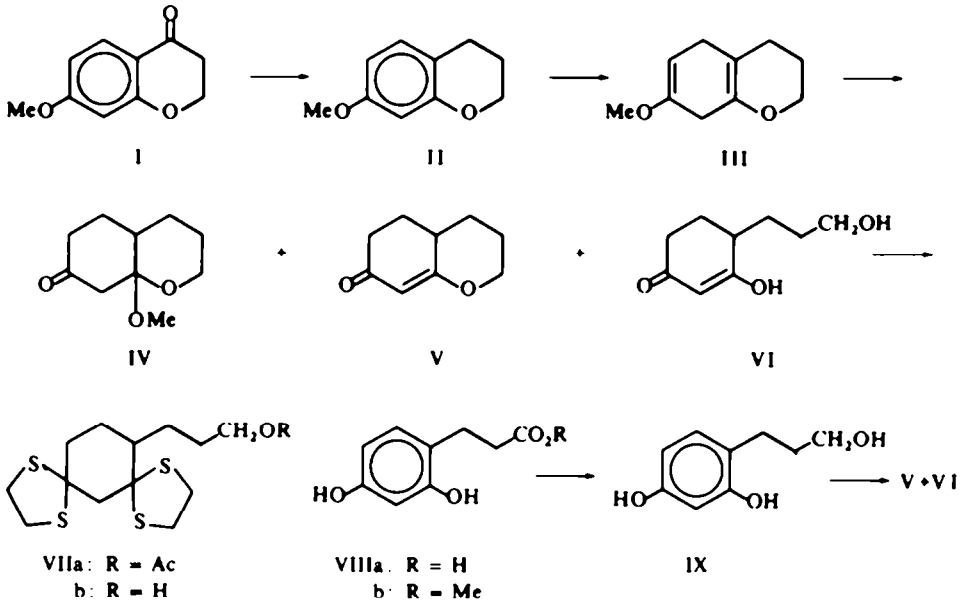
The structure of V is shown by its infrared and NMR spectra and by its synthesis

* We are grateful for advice from the referees on this point.

† Other examples of the facile oxidation of similar dihydro intermediates are known.[8]

‡ While no detailed analysis of the steps in this hydrolysis has been carried out, the production of these compounds is readily explained along classical lines. Hydrolysis of both vinyl ether linkages of III would be expected to produce VI, whereas hydrolysis of only the methoxyl vinyl ether would produce V. Attack of the methoxyl vinyl ether by methanol rather than water would not be discernible, but attack of other vinyl ether linkage by methanol could lead to IV.

from VIII. Its conversion to the bisdithioketal VII indicates the ease with which the tetrahydropyran ring ruptures. The preparation of V by Birch reduction of 7-methoxychroman is analogous to the reduction of resorcinol dimethyl ether and subsequent hydrolysis to cyclohexane-1,3-dione,[9a] and is similar to the reduction of 2,3-dihydro-5-methoxybenzofuran to 5-methoxy-2,3,4,7-tetrahydrofuran except for the use of ethanol as the proton source.[9b] Reductions of III were carried out in which methanol, 2-propanol or n-butanol replaced t-butyl alcohol, resulting in only minor differences in the relative amounts of products.



SCHEME 1.

An alternative synthesis of V and VI began with 4-(2-carboxyethyl) resorcinol VIIIa,[10] which was reduced as the ester VIIIb with LAH. The triol could be reduced with sodium amalgam, but was reduced in better yield and more conveniently by hydrogenation in the presence of rhodium on alumina.[11] As in the Birch reduction of II, a mixture of V and VI was obtained.

EXPERIMENTAL

M.ps were taken with a unimelt apparatus and are uncorrected. IR spectra were obtained on an Infracord on smears or mineral oil mulls. The NMR spectra were obtained with a Varian A-60 spectrometer using $CDCl_3$ solns and TMS as the standard. Analyses were by Galbraith Laboratories, Knoxville, Tenn., and by Midwest Microlab, Indianapolis, Ind.

7-Methoxychroman (II). A soln of 5·07 g of I[4] in 120 ml EtOH was treated with two teaspoonfuls of Raney Ni[12] and held at 65° for 36 hr. The Ni was filtered and washed thoroughly with hot EtOH; the combined filtrate and washings were evaporated under vacuum to give 4·79 g of liquid lacking CO absorption in the IR. Chromatography on alumina gave II, eluted by petrol (b.p. 30–60°), with IR absorption identical to the analytical sample obtained by distillation: b.p. 273–276°, ν_{max} 1620, 1585, 1504 (aromatic ring), 1156, 1130 and 1112 cm^{-1} (OMe). (Found: C, 73·15; H, 7·30. $C_{10}H_{12}O_2$ requires: C, 73·15; H, 7·37%). When a 24 hr reaction time was used the yield of II was lower and elution of the column with benzene and with ether gave an alcohol which was dehydrated in refluxing benzene containing a trace of I_2 (4 hr).

The benzene soln was washed with 10% $Na_2S_2O_3$ aq, then with water, and dried over $MgSO_4$. Evaporation gave an oily residue which was hydrogenated (PtO_2) in EtOH; chromatography on alumina gave II.

4a,5,6,7-Tetrahydrochroman-7-one (V) *and 4-(γ-hydroxypropyl)cyclohexane-1,3-dione* (VI) *by Birch reduction.* Ammonia (50 ml) was distilled into the apparatus described by Sandoval.[13] Li wire (0·694 g, 0·01 eq) was added in pieces while the mixture was stirred magnetically. A soln of 7-methoxychroman (4·102 g, 0·025 mole) in 5 ml of t-BuOH (dried over $CaSO_4$) was added dropwise over a period of 10 min, then another 5 ml of t-BuOH was added similarly to rinse the addition funnel. The blue mixture was stirred 4 hr, after which water (75 ml) was added cautiously. The aqueous mixture was extracted with 3 portions (150 ml) of ether; the ethereal layer was washed with 4 portions (150 ml) of water, the fourth wash being neutral. Evaporation of the dried (Na_2SO_4) ether soln left 4·024 g of an oil with strong IR bands at 1712 and 1670 cm^{-1}, and with barely discernible deflections in place of the 1620, 1585 and 1504 cm^{-1} peaks of II. Chromatography of a portion (800 mg) of the crude dihydro product on 40 g of Florisil gave 673 mg of III, eluted by benzene–petrol 1:1 and by benzene, whose NMR spectrum shows signals at δ 1·9 (C_5,C_6 methylenes), 2·7 (C_5,C_8 methylenes), 3·5 (O—CH_3), 3·7 (impurity), 4·0 (O—CH_2) and 4·6 ppm (C=CH). A chromatographic cut which stood for a day exposed to the air, after being recovered from the NMR determination, exhibited new IR bands at 3500, 1642 and 1608 (VI), and 1585 (shoulder) and 1504 cm^{-1} (II).

In a similar Birch reduction the crude dihydro product (from 1·044 g of II) was hydrolyzed by stirring its soln in MeOH (18 ml) containing conc HCl (1·2 ml) and water (0·8 ml) at room temp for 3 hr. Ether extraction and drying gave an oil with strong IR absorption at 3500, 1638 and 1600 cm^{-1}. Its chromatography on alumina gave the following fractions: 1. eluted by benzene, 0·09 g, largely II; 2. benzene, 0·12 g, oil with ν_{max} 1724 (C=O) cm^{-1}; 3. benzene, 0·15 g, intermediate mixture; 4. MeOH, 0·41 g, oil with ν_{max} 3500 (OH), 1635 and 1605 (O=C—C=C—O), 1241, 1174 cm^{-1}, V and VI; 5. MeOH, 0·16 g, impure VI. Rechromatography of fraction 2 on alumina gave IV, an oil with IR maxima at 1724, 1993 and 1052 cm^{-1} and with NMR signals at δ 3·2 (ketal O—CH_3) and 3·6 ppm (O–CH_2). (Found: C, 65·43; H, 8·97; O, 25·57. $C_{10}H_{16}O_3$ requires: C, 65·19; H, 8·75; O, 26·05%). Acid hydrolysis of IV in the absence of MeOH converts it to V and VI. Rechromatography of fraction 4 on Florisil gave a fraction, eluted by benzene–ether 1:1 and by ether, which solidified. It was recrystallized from ether to give V, m.p. 55–56°, IR and NMR identical to that prepared by hydrogenation of IX.

4-(β-Carbomethoxyethyl)resorcinol (VIIIb). Anhyd HCl introduced into a soln of VIIIa,[10] (28·38 g) in MeOH (100 ml); after 24 hr at room temp the solvent was evaporated under vacuum and the residue was chromatographed on Florisil (300 g). Elution with ether gave five fractions (29·81 g) which crystallized on standing and were sufficiently pure for the next step. Two recrystallizations from benzene of fraction 1 gave plates, m.p. 81·0–82·0°, ν_{max} 3390 and 3280 (OH), 1690 (C=O), 1630, 1610, 1530, 1308, 1214, 1102, 971, 851 cm^{-1}. (Found: C, 61·40; H, 6·12. $C_{10}H_{12}O_4$ requires: C, 61·22; H, 6·17%).

4-(γ-Hydroxypropyl)resorcinol (IX). A soln of VIIIb (18·00 g) in anhyd ether (540 ml) was added to a stirred suspension of LAH (12·00 g) in ether (450 ml) and the mixture refluxed 20 hr. Water (150 ml) and conc H_2SO_4 were added dropwise, the layers were separated and the acidic aq layer was extracted twice with ether. Drying and evaporating the ether soln left 15·20 g of liquid residue with a weak 1690 cm^{-1} band. A portion was crystallized with difficulty from acetone–benzene and from ether; the analytical sample crystallized from ether–toluene to give prisms, m.p. 94·0–95·0°, ν_{max} 3412 (OH), 1612, 1512, 1563, 1111, 1057, 972 cm^{-1} (Found: C, 64·43; H, 7·11. $C_9H_{12}O_3$ requires: C, 64·27; H, 7·19%). To obtain IX for subsequent reduction it was preferable to chromatograph the crude product on Florisil and elute with ether–benzene mixtures and with ether. These fractions, with IR spectra identical to that of the analytical sample, were suitable as such or could be triturated in toluene–ethyl acetate to give IX with m.p. 97–99°.

4a,5,6,7-Tetrahydrochroman-7-one (V) *and 4-(γ-hydroxopropyl)cyclohexane-1,3-dione.* (VI) *by hydrogenation.* Rhodium on alumina (10% K & K, 350 mg) was added to a soln of IX (5·72 g) in water (7·1 ml) containing NaOH (1·64 g). The mixture was hydrogenated at 50 PSI for 24 hr, then filtered. The catalyst was washed with H_2O, diluting the filtrate to 50 ml. This soln was acidified with cold, conc H_2SO_4 and extracted four times with ether–EtOAc 1:1. Evaporation of the dried soln (Na_2SO_4) left 4·64 g of a liquid residue which was chromatographed (acetone–ether) on Florisil. Ether containing 1% MeOH eluted 0·85 g of a mixture that is predominately IX; ether containing 2% MeOH eluted a 0·39 g intermediate fraction. The major product, VI (2·26 g), was eluted by 3–5% MeOH in ether; it is a liquid with ν_{max} 3450 (OH), 1620 and 1600 (O=C–C=C—O), 1222, 1170 cm^{-1}. During evaporation of the eluting solvents some of the VI is converted into its anhydro derivative V. Consequently, some of these fractions deposited crystals which, when collected and recrystallized from petrol m. 57–58°; ν_{max} 3310 (wk), 1642, 1600,

1220, 1162, 1083, 1050, 965, 861, 840 cm^{-1}, δ 4·1 (O—CH_2) 5·4 ppm (C=CH). (Found: C, 71·18; H, 8·09. $C_9H_{12}O_2$ requires: C, 71·03; H, 7·05%). Recrystallization from water gave another form of V, m.p. 49–50°, with identical IR. (Found: C, 71·07; H, 7·95%).

4-(γ-Acetoxypropyl)cyclohexane-1,3-dione bisethylenedithioketal (VIIa). A soln of crude VI (prepared by hydrogenation and unchromatographed, 2·35 g), ethanedithiol (8 ml), and BF_3-etherate (4 ml) in AcOH (60 ml) stood at room temp overnight. Dilution with water and refrigeration pptd crude VIIa, which m 108–109° after recrystallization in MeOH (2·71 g). The analytical sample, out of acetone–water, m.p. 107–108°, ν_{max} 1740 (C=O) and 1262 cm^{-1}. (Found: C, 49·24; H, 6·35; S, 35·46. $C_{15}H_{24}O_2S_4$ requires: C, 49·41; H, 6·63; S, 35·18%). The same product is obtained from a chromatographic fraction of V.

4-(γ-Hydroxypropyl)cyclohexane-1,3-dione bisethylenedithioketal (VIIb). A soln of VIIa (2·67 g), NaOH (2·7 g) and water (3 ml) in MeOH (270 ml) was refluxed 15 min, diluted with water (270 ml) and refrigerated. The crude product was recrystallized in MeOH to give VIIb, m.p. 114–116° (cooling the melt gave a form with m.p. 123–125°), ν_{max} 3560, 1280, 1041, 1031 and 1009 cm^{-1}. (Found: C, 48·21; H, 6·73; S, 40·00. $C_{13}H_{22}OS_4$ requires: C, 48·40; H, 6·87; S, 39·76%). The same compound is formed directly from VI when the reaction with ethanedithiol is carried out in ether rather than acetic acid.

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