Conversion of Androstenolone to Pregnenolone

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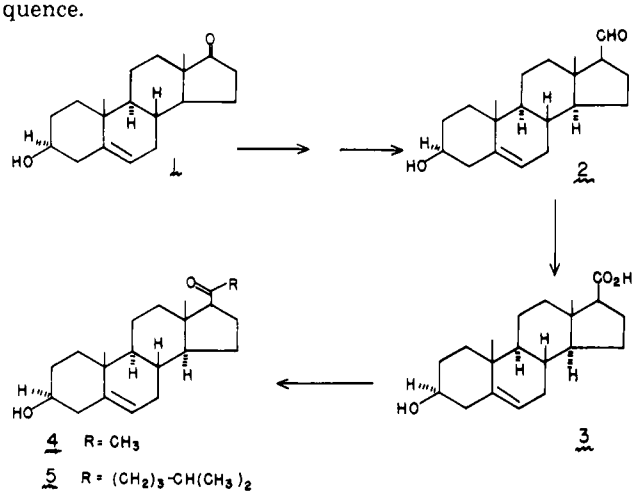
The Butenandt group developed the original methodology for the transformation of androstenolone (1) to pregnenolone (4).[1] Their route involves the reaction of methyl Grignard reagent with a Δ^{16}-17 cyano steroid, which arises from the dehydration ($POCl_3$) of a 17-cyanohydrin. Selective saturation of the Δ^{16} double bond completes the sequence.



The formation of 20-keto steroids has also been achieved[2] via reductive cleavage of a 17α-acetoxy-20-ketone, in turn, derivable from a sequence starting with ethynylation of a 17-ketone. Another route involves the reaction of an etianyl chloride with dimethylcadmium.[3] Oliveto and coworkers have applied ethylidenation (via a Wittig reaction) toward this objective. Oxygen is introduced at C_{20} either through hydroboration[4] or photoxygenation.[5]

As part of our synthetic efforts in steroids, we had need for a short, efficient sequence of reactions which allows for the transformation of a 17- to a 20-keto steroid. An important condition was that the process be compatible with isolated and conjugated double bonds[6] and unprotected alcohols.

We describe below an efficient conversion of 1 to 4. We feel that this route constitutes the simplest way of achieving the objective. Furthermore, considerable synthetic flexibility for the synthesis of steroid side chain analogs is available.

The reaction of 1 with methoxymethylenetriphenylphosphorane[7] in dimethyl sulfoxide[8] followed by acidic hydrolysis via aqueous perchloric acid[9] gives 20β-formylandrost-5-en-3β-ol (2) in 70% yield. The aldehyde was oxidized to a carboxyl group, without protection of the 3β-ol through the action of silver oxide in aqueous methanol. The etianic acid, 3, reacts smoothly with excess methyllithium[10] to afford pregnenolone (80%). The ability to produce the alkyl ketone directly from the alcohol–acid with alkyllithium is an important simplification in that it allows for the avoidance of the blocking and deblocking of the alcohol and activation of the carboxyl involved in the acid chloride routes.[3]

Curiously, the alkyllithium reactions with steroidal carboxylic acids have been conducted only in the *D*-nor series.[11,12] We find that reaction of 3 with excess isohexyllithium gives 20-oxo-21-norcholesterol (5)[13] in 94% yield. The reaction of etianic acids with alkyllithium reagents has considerable utility in the elaboration of sterol side chains.

Experimental Section[13]

Conversion of Androstenolone (1) to 20β-Formylandrost-5-en-3β-ol (2). Sodium hydride (308 mg of a 50% dispersion, 6.4 mmol) was suspended in 5 ml of dry DMSO. Upon warming to 55° and stirring under a nitrogen atmosphere for 40 min, gas was evolved and a pale yellow-green solution resulted. To this solution was slowly added a solution of 2.2 g (6.4 mmol) of methoxymethylenetriphenylphosphonium chloride in 10 ml of DMSO. A deep red coloration developed upon mixing. After 30 min, a solution of 350 mg (1.2 mmol) of androstenolone (1) in 10 ml of DMSO was added. The temperature was raised to 70° and stirring was continued for 10 hr at the same temperature. The reaction mixture was poured into water and the aqueous system was extracted with ethyl acetate. The organic extracts were dried over magnesium sulfate and the volatiles were evaporated at the water pump. To the brown residue was added 20 ml of ether and 5 ml of 70% aqueous perchloric acid. After being stirred at room temperature for 10 hr, the reaction mixture was poured into ice–water. The aqueous system was thoroughly extracted with ethyl acetate. After drying over $MgSO_4$, the organic extracts were evaporated and the residue was chromatographed on silica gel. Elution with 3:1 *n*-hexane–ethyl acetate gave 254 mg of 2 (70%). Recrystallization from EtOH–H_2O gave plates: mp 155–157°; $[\alpha]D$ (room temperature) −21.0° (*c* 0.1, $CHCl_3$) [lit.[14] mp 148–153°, $[\alpha]^{21}D$ 14.5° ($CHCl_3$)]; $\bar{\nu}$ 3450, 1710 cm^{-1}; *m/e* 302 (parent); NMR δ ($CDCl_3$) 0.80 (s, 3, C_{13} Me), 1.05 (s, 3, C_{10} Me), 3.45 (m, 1, CHOH), 9.80 [s (broad), 1, CHO].

Oxidation of 2. Formation of 3β-Hydroxyeti-5-enoic Acid (3). Silver nitrate (3.4 g, 20 mmol) was dissolved in 60 ml of deionized water. To this was added 30 ml of 10% aqueous sodium hydroxide. A brown precipitate formed immediately. To this system was slowly added 75 ml of dilute ammonia, thus giving a clear solution. To this was added a solution of aldehyde 2 (1 g, 3.3 mmol) in 25 ml of methanol and the system was stirred at 80–90° for 6 hr. The reaction mixture was poured into ice–water, acidified with 10% aqueous HCl, and extracted with ethyl acetate. After the organic extract was dried over magnesium sulfate, the volatiles were removed at the water pump. The residual yellow powder was recrystallized from ethanol–water to give 800 mg (76% yield) of 3. Recrystallization from ethanol gave 3 as needles, mp 282–283° dec, $[\alpha]D$ (room temperature) −20° (*c* 0.2, EtOH) (lit.[15] mp 280–281°, no reported rotation).

Conversion of 3 to Pregnenolone (4). To 100 mg (0.32 mmol) of acid 3 was added via syringe 4 ml of 1.0 *M* methyllithium in hexane. The reaction mixture was maintained under a nitrogen atmosphere and allowed to stir for 15 hr at room temperature. The contents were poured into ice–water and the aqueous system was extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated at the water pump. The residue was chromatographed on silica gel. Elution with 3:1 *n*-hexane–ethyl acetate gave 81 mg (81%) of pregnenolone (4), mp 190–192°, $[\alpha]D$ (room temperature) (*c* 0.15, EtOH) [lit.[16] mp 193°, $[\alpha]D$ +28° (EtOH)].

Reaction of Hydroxy Acid 3 with Isohexyllithium. Formation of 21-Nor-20-oxochlesterol (5). A solution of isohexyllithium in ether was prepared by dropwise addition of a solution of isohexyl bromide (10 g) in 10 ml of anhydrous ether to lithium wire (1.3 g) covered with 40 ml of ether. The temperature was maintained at 10–15° and stirring was continued for 3 hr. The titer (0.8 *M*) was established according to Gilman.[17]

To compound 3 (700 mg, 2.2 mmol), under nitrogen and with rigorous exclusion of moisture, was added via syringe a solution of isohexyllithium (22 mmol) in ether. The system was stirred at room temperature for 50 hr.

The reaction mixture was poured into ice and the aqueous phase was extracted with ether. The combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation of the volatiles left a crystalline residue (840 mg, 99%). Recrystallization from 3-hexane gave 5 (800 mg, 94%): mp 138–139° (lit.[18] mp 139–140°); $[\alpha]D$ (room temperature) +20° ($CHCl_3$, *c* 0.2) [lit. $[\alpha]^{25}D$ +20° ($CHCl_3$, *c* 1.22)]; $\bar{\nu}$ (Nujol) 1710 cm^{-1}; *m/e* 386 (parent).

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Registry No.—1, 53-43-0; 2, 55029-99-7; 3, 10325-79-8; 4, 145-13-1; 5, 38673-20-0.

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Iodide Catalysis of Oxidations with Dimethyl Sulfoxide. A Convenient Two-Step Synthesis of α Diketones from α-Methylene Ketones

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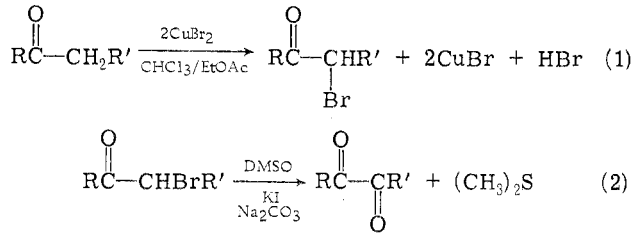
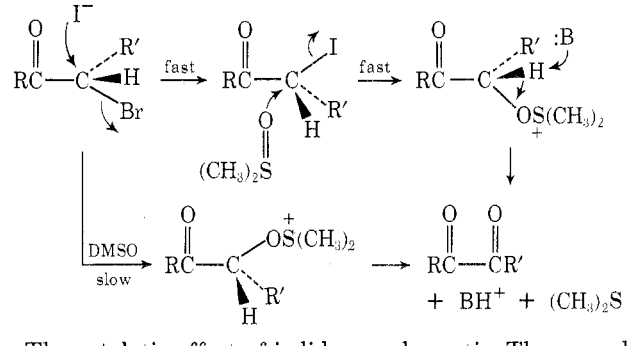
α diketones are not only interesting with regard to conformational analysis,[1] electronic spectroscopy,[2] and photochemistry,[3] but also because they are versatile synthetic intermediates and they undergo a variety of unique reactions, including the benzil–benzilic acid rearrangement[4] and dioxaphospholene formation.[5]

In connection with our synthesis of macrotricyclic hydrocarbons, we needed large amounts of several cyclic α diketones, including 1,2-cyclooctanedione and 1,2-cyclododecanedione. One synthesis involved an acyloin condensation, followed by oxidation with cupric acetate;[6,7] another was the selenium dioxide oxidation of the corresponding cyclic ketones.[7] Our attempts to reproduce the selenium dioxide oxidations led to products in moderate yields, but these products were contaminated with selenium which proved extremely difficult to remove.[8] The acyloin condensation, while providing higher purity, was much more difficult to carry out and gave frustratingly low yields. The observation that primary and secondary halides and sulfonate esters could be oxidized to aldehydes and ketones with dimethyl sulfoxide (DMSO)[9] led several groups to prepare α diketones via the DMSO oxidation of α-bromo ketones.[10] Unfortunately, the DMSO oxidation, because it requires SN2 attack by the sulfoxide oxygen at the brominated carbon, is sensitive to the steric environment of that center. Thus, while primary halides and tosylates provide aldehydes in decent yields, oxidation of secondary systems, as required to make diketones, is often sluggish. This low reactivity can be partially overcome by promoting the oxidation with silver salts such as silver perchlorate[11] or silver nitrate,[12] but such reagents are not economical on the mole scale. We wish to report a convenient, high-yield process for conversion of α-methylene ketones to α diketones, using only inexpensive, common reagents.



Of the many ways to α-brominate ketones, we have had uniformly excellent results with cupric bromide in refluxing chloroform–ethyl acetate.[13] For the five ketones listed in Table I, the isolated yield of α-bromo ketone ranged from 90 to 97%, and the slowest reaction required 8 hr (2,2,5,5-tetramethyl-3-hexanone). The success of the sequence thus depended only on the oxidation step. Our attempts to oxidize these α-bromo ketones directly with DMSO gave only slow reactions in the cases of the third and fourth entries in Table I, and essentially no reaction in the first, second, and fifth cases.

It has been noted[14] that DMSO is a weaker nucleophile than even bicarbonate in at least one instance. It seemed reasonable that the oxidation step could be catalyzed by a species that was a better nucleophile than DMSO and a better leaving group than bromide. Iodide ion fits this description well, for it is not only a powerful nucleophile (by virtue of high polarizability and low solvation), but also a highly reactive leaving group in nucleophilic displacements (because of the weakness of the C–I bond).[15] Thus, the slow direct attack by DMSO on the α-bromo ketone could be circumvented by two faster displacements involving iodide.



The catalytic effect of iodide was dramatic. The second, third, and fourth entries in Table I reacted completely within 10 min at ambient temperature. The first entry, for reasons that are not clear, required 60 min at 120°, but still gave a reasonable yield. Not unexpectedly the 4-bromo-2,2,5,5-tetramethyl-3-hexanone (a new compound, entry 5) failed to react even after 25 hr at 150°. Although there was evidence that attack by iodide occurred (see Experimental Section), attack by DMSO was apparently precluded by the neopentyl nature of the reaction center.[16] We *were* able to oxidize 4-bromo-2,2,5,5-tetramethyl-3-hexanone in 47% yield using silver nitrate in DMSO.[12] This is probably the method of choice when dealing with highly hindered α-halo ketones.

With the exception of the above compound, overall yields of the α diketones ranged from 65 to 92%. Both reactions are simple to perform and the required reagents and solvents are economical to use. The only disadvantages of this procedure are (1) certain α-bromo ketones (Table I, entries 1 and 2) are somewhat unstable and should not be stored for long periods before carrying out the oxidation, (2) some α-bromo ketones and α diketones undergo side reactions such as aldol condensations in DMSO, so the oxi-