per cent of asymmetric reduction is greater in the presence of THF than of diethyl ether (Table III).

This conformational analysis was restricted only to the examination of the steric interactions between the alkyl phenyl ketone and the reacting 2-methylbutyl group bound to aluminum atom, although the other two optically active alkyl groups were able, in principle, to exert a further control on the stereochemistry of the reduction. The linear relationship we have observed between the per cent of enantiomeric excess of the carbinol and optical purity of (+)-tris-[(*S*)-2-methylbutyl]aluminum in the reduction of *tert*-butyl phenyl ketone (Figure 1) excludes effectively that the two unreacting optically active alkyl groups control the asymmetric reduction of ketones. This result agrees with the data, previously reported, on the reduction of methyl *tert*-butyl ketone by bis[(*S*)-2-methylbutyl]magnesium and by the corresponding Grignard reagent, reduction which occurs with the same stereoselectivity.[35]

Registry No.—α-Tetralone, 529-34-0; α-tetralol, 530-91-6.

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Remote Oxidation with Photoexcited Nitrobenzene Derivatives

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Remote oxidation of unactivated carbon–hydrogen bonds by photoexcited nitrobenzene derivatives is described. The procedure is illustrated by the key step in the conversion of 5α-androstan-3α-ol (**3**) to 5α-androst-14-en-3-one (**6**). Introduction of unsaturation into the steroid D ring is accomplished by irradiation of the β-(*p*-nitrophenyl)propionate ester of **3** (compound **2**). As in previously reported remote oxidations utilizing benzophenone derivatives, the selectivity of the reaction is controlled by mutual orientation of the oxidizing agent and the substrate. The advantages and limitations of nitro compounds as reagents for remote oxidation are discussed.

Remote oxidation is a process in which unactivated carbon–hydrogen bonds are selectively oxidized at substrate sites remote from existing functionality.[1] Selectivity is achieved by attaching the substrate and oxidizing agent, thus mutually orienting them. The oxidation is then initiated by irradiation, and the reaction is carried out in sufficiently dilute solution that intramolecular reactions predominate. Previous examples have employed the benzophenone phototriplet as the oxidizing agent, and a common occurrence in such reactions is the formation of a new carbon–carbon bond which must then be cleaved to remove the residue of the oxidizing agent.

We have been seeking alternative remote oxidizing agents with which carbon–carbon bond formation would not be a problem, and we report here the first successful reaction with an attached reagent other than the benzophenone group.[2]

There is precedent in the literature for believing that the photoexcited aromatic nitro group would be able to abstract hydrogen from saturated carbon. Thus nitrobenzene is reduced when irradiated in "petroleum,"[3] and irradiation of 2,5-di-*tert*-butylnitrobenzene results in oxidation of one of the methyl carbons on the 2-*tert*-butyl group and reduction of the nitro group.[4]

Results and Discussion

To test the utility of the nitro function as a remote oxidizing agent, 5α-androstan-3α-yl *p*-nitrobenzoate (**1**) was first studied. Irradiation of **1** did not result in oxidation of the steroid at unactivated positions. Instead, reaction took place at the ester group to afford, after hydrolysis, the 3α and 3β alcohols, the 3 ketone, and the Δ^2 and Δ^3 olefins.

The next compound studied was 5α-androstan-3α-yl β-(*p*-nitrophenyl)propionate (**2**). It was believed that the methylene groups would decrease the reactivity of the ester function by isolating it from the nitroaromatic chromophore, and, at the same time, provide flexibility in the attachment of the oxidizing agent, a property shown to be of importance in the benzophenone reactions.[1b]

Irradiation of **2** was first carried out using a Corex filter. The reaction product was treated with iodine–acetic acid to dehydrate any tertiary alcohols, and the ester function was saponified. The nuclear magnetic resonance (nmr) spectrum of the neutral fraction thus obtained suggested the presence of 5α-androst-14-en-3α-ol (**5**) (vinyl signal at δ 5.18).[5] Hydroboration–

(1) (a) R. Breslow and M. A. Winnik, *J. Amer. Chem. Soc.*, **91**, 3083 (1969); (b) R. Breslow and S. W. Baldwin, *ibid.*, **92**, 732 (1970); (c) R. Breslow and P. C. Scholl, *ibid.*, **93**, 2331 (1971); (d) R. Breslow and P. Kalicky, *ibid.*, **93**, 3540 (1971); (e) J. E. Baldwin, A. R. Bhatnagar, and R. W. Harper, *Chem. Commun.*, 659 (1970).

(2) There are reports in which selective oxidations are achieved by means other than direct attachment of reagent and substrate. Selective radical chlorination resulted when only one end of a straight-chain substrate was exposed to chlorine dissolved in CCl_4, the other substrate end being adsorbed on a solid surface: N. C. Deno, R. Fishbein, and C. Pierson, *J. Amer. Chem. Soc.*, **92**, 1451 (1970). Reports of intermolecular oxidations which are selective at steroid position 14 have also appeared: R. Breslow, J. A. Dale, P. Kalicky, S. Y. Liu, and W. N. Washburn, *J. Amer. Chem. Soc.*, **94**, 3276 (1972); A. Rotman and Y. Mazur, *ibid.*, **94**, 6228 (1972).

(3) J. A. Barltrop and N. J. Bunce, *J. Chem. Soc. C*, 1467 (1968).

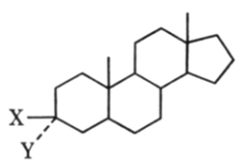
(4) D. Dopp, *Chem. Commun.*, 1284 (1968).

(5) L. Mamlok, *Bull. Soc. Chim. Fr.*, 3827 (1967).

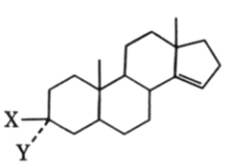
oxidation of this mixture and chromatography afforded 5α,14β-androstane-3,15-dione (**7**).

The yield of the remote oxidation product **7** was only 11%, even though isolation of only 18% of 5α-androstan-3-one (**4**) indicated that most (82%) of the starting steroid had undergone photooxidation.

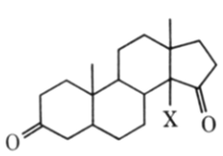
Two obvious difficulties existed with the above set of reactions, and no doubt contributed to the low yield. First, the photoreaction was not very "clean." Insoluble material had precipitated during the irradiation, requiring frequent cleaning of the lamp well, and much of the neutral fraction obtained upon work-up appeared to consist of a complex mixture of steroid components and polymer. The second difficulty was concerned with the sequence of reactions designed to aid the separation and characterization of products. The 14 olefin **5** was probably converted by the hydroboration–oxidation sequence into both **7** and its 14α epimer, **8**. Compound **8**, if produced, could not be isolated in pure form and characterized. Conditions for a "cleaner" photooxidation and an improved method of product characterization were therefore sought.



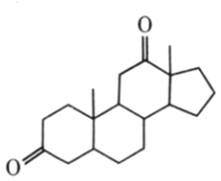
1, X = H; Y = $OCOC_6H_4NO_2$
2, X = H; Y = $OCOCH_2CH_2C_6H_4NO_2$
3, X = H; Y = OH
4, X, Y = O



5, X = H; Y = OH
6, X, Y = O



7, X = β-H
8, X = α-H



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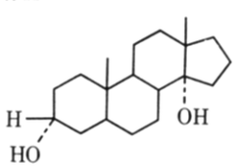

10

The photoreaction of **2** could be effected under milder conditions (lower energy light) with a Pyrex filter. Under these conditions no solid separated, although the solution changed from colorless to deep yellow during the 12-hr reaction. Dehydration, saponification, and chromatography of the neutral fraction gave a mixture of 5α-androstan-3α-ol (**3**) and 5α-androst-14-en-3α-ol (**5**), and a mixture of more polar components. The mixture of **3** and **5** could not be separated, but the corresponding ketones **4** and **6**, prepared by cautious Jones oxidation of the alcohol mixture, were readily separated by chromatography on silver nitrate impregnated silica gel.[6] This sequence afforded a 26% yield of 5α-androst-14-en-3-one (**7**) and 39% of 5α-androstan-3-one (**4**).

(6) Oxidation to ketones rather than the more common practice of masking the hydroxyl groups as acetates or methyl ethers was chosen since **6** is a known compound.

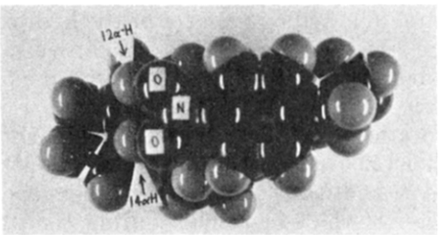

Figure 1.—Space-filling model of 5α-androstan-3α-yl β-(*p*-nitrophenyl)propionate (**2**) with the *p*-nitrophenyl moiety in position for oxidation of the steroid. View is from the α side of the steroid, with the D ring to the left and rotated slightly toward the viewer. Note the proximity of the nitro group oxygens and the steroid 12α and 14α hydrogens.

The more polar fraction isolated from the initial chromatography appeared to consist of a complex mixture of diols and polymer. Oxidation of this fraction with Jones reagent gave a mixture of diketones (and polymer). This mixture was complex, but the predominant isomer is probably 5α-androstan-3,12-dione (**9**) as evidenced by the position of the angular methyl signals in nmr spectra determined in deuteriochloroform and in benzene. Oxidation of the steroid 12 position in addition to position 14 is consistent with predictions based on space filling molecular models, as illustrated in Figure 1. Also, preference for oxidation at these positions has been observed in the analogous benzophenone photooxidation.[1b]

In addition to the above components isolated from the neutral fraction after saponification, it should be noted that *ca.* 10% of the steroid was found in the acid layer. This observation suggested that some of the steroid was undergoing multiple oxidation. It is likely that the more polar component of the neutral fraction also contained steroids which had undergone multiple oxidations. This conclusion was inferred from several vinyl proton signals, albeit faint, observed in the nmr spectrum, and from the polarity of the fraction which requires an oxygen function in addition to the 3α-hydroxyl group. The presence of both a second oxygen function and carbon–carbon unsaturation requires a multiple oxidation. This finding was not surprising, since the color of the solution after irradiation and the intense color of the acid fraction after saponification suggested reduction of the nitro group to azo- and/or azoxybenzene derivatives. Increasing the time of irradiation to 18, 24, or 48 hr resulted in more steroid undergoing photooxidation, as indicated by the isolation of smaller amounts of **4**, but the yield of compound **6** was not improved, more tarry material being formed instead. In the 48-hr experiment, for example, 12% of **4** and 24% of **6** were obtained.

Material balances in these experiments were usually better than 90% when the steroid found in the acid fraction and the neutral polymeric material was included.

Acetonitrile appears to be the best solvent for the photoreaction. In acetone or benzene little oxidation of the steroid occurred, while in carbon tetrachloride, extensive chlorination of the steroid was observed.

The mechanism of the photoreaction has not been established. A reasonable pathway is abstraction of a hydrogen atom by one of the oxygen atoms of the

nitro group, followed by transfer of the hydroxyl group thus formed to the radical center on carbon. The 14α alcohol would be predicted as the initial photoproduct by this mechanism. Indeed, in a reaction in which the dehydration step was omitted, some 5α-androstane-3α,14α-diol (**10**) was observed. Some 14 olefin **5** was also present, and it is not known whether this arose by dehydration of the 14α alcohol during the photoreaction or whether the 14 double bond can be formed directly. Although the photoreactions were carried out in a nitrogen atmosphere, the reaction does not seem to be strongly inhibited by oxygen.

As a synthetic method, remote oxidation with nitro compounds must be compared with the reaction effected with benzophenone derivatives. The nitro function appears to be somewhat less selective between secondary and tertiary positions than benzophenone is. A more serious disadvantage is the inability to stop the reaction cleanly at a single (two-electron) oxidation of the substrate. The yield of well-defined remote oxidation products is therefore lower in the nitro oxidation than in some of the reported benzophenone reactions.[1b-d] However, the present study serves to extend the generality of the principle of remote oxidation to a nonbenzophenone case. More importantly, nitro compounds oxidize by the direct introduction of oxygen or unsaturation into the substrate. Formation of a carbon–carbon bond requiring further degradation, as frequently occurs in benzophenone cases, is thus avoided.

Experimental Section

5α-Androstan-3α-yl β-(*p*-Nitrophenyl)propionate (2).—A mixture of 1.28 g (5 mmol) of 5α-androstan-3α-ol (**3**), 1.10 g (5.6 mmol) of β-(*p*-nitrophenyl)propionic acid, and 0.35 g of *p*-toluenesulfonic acid in 300 ml of benzene was heated for 24 hr, with the refluxing benzene passing through a Soxhlet extractor containing anhydrous Na_2SO_4. The solution was cooled, washed with two 50-ml portions of $NaHCO_3$ solution followed by three 50-ml portions of brine, and dried ($MgSO_4$), and the solvent was evaporated. Chromatography of the residue on 50 g of silica gel (ether–hexane) followed by recrystallization from aqueous CH_3CN afforded 1.45 g (64%) of compound **2**, mp 116–118°. (*Caution*—An acid chloride route to **2** was first employed, but reaction of the acid with $SOCl_2$ resulted in the formation of tarry by-products. Purification of the acid chloride by vacuum distillation resulted in explosions several times.)

Photochemical Oxidation.—Photooxidations employed a 450-W Hanovia lamp, a Corex or a Pyrex sleeve, a quartz immersion apparatus (all from Ace Glass Co.), and a 2-l. reaction vessel. A solution of 906 mg (2.0 mmol) of compound **2** in 1980 ml of CH_3CN was purged with nitrogen for 1 hr prior to and during irradiation.

The solvent was removed, and the residue was treated with 75 ml of HOAc containing a trace of iodine. After heating at reflux for 4 hr, the HOAc was removed and the residue was treated with 100 ml of 1.0 *M* KOH in MeOH at reflux for 4 hr. Removal of the MeOH, addition of 100 ml of water, extraction with three 50-ml portions of hexane, washing the combined extracts with three 50-ml portions of brine, drying ($MgSO_4$), and evaporating afforded the crude photoproduct referred to below.

5α,14β-Androstane-3,15-dione (7).—A Corex filter had been used in a 24-hr protoreaction. The crude photoproduct was dissolved in 50 ml of dry tetrahydrofuran, and 0.600 g of finely powdered sodium borohydride was added, followed by 2.0 ml of boron trifluoride etherate. After 1 hr, water was added, followed by dilute sulfuric acid. Excess chromic acid reagent (prepared from 2.3 ml of concentrated H_2SO_4 and 2.7 g of CrO_3, diluted to 10 ml) was then added. After 15 min, 2-propanol was added, followed by brine and hexane. The organic layer was separated, washed with brine until neutral, and dried ($MgSO_4$), and the solvent was evaporated. The residue was chromatographed on 10 g of silica gel (ether–hexane) to afford 97 mg of 5α-androstan-3-one (**4**) (18%), 64 mg of 5α,14β-androstane-3,15-dione (**7**) (11%), and 40 mg of more polar material.

Compound **7**, homogeneous by vpc (3% SE-30, 220°) and by tlc, exhibited mp 182–183.5°, unchanged upon recrystallization from aqueous acetone and from hexane; mass spectrum *m/e* 288.2085 ($C_{19}H_{28}O_2$ requires 288.2089), base peak *m/e* 97 (characteristic of 15-keto steroids[7]); nmr ($CDCl_3$) δ 0.983 (19-CH_3) and 1.200 (18-CH_3) (assigned structure requires δ 0.967 and 1.226[8]); ir 1742 and 1712 cm^{-1} (five- and six-membered cyclic ketones, respectively). The 14β stereochemistry is known to be preferred in 15-keto steroids lacking substitution at C-17.[9]

5α-Androst-14-en-3-one (6).—A Pyrex filter had been used in a 12-hr photoreaction. The crude photoproduct (488 mg) was chromatographed on 12 g of silica gel using gradient elution in which a flask of 250 ml of hexane fed the column and was in turn fed by a second flask containing 40% ether–60% hexane. A mixture of 358 mg of 5α-androstan-3α-ol (**3**) and 5α-androst-14-en-3α-ol (**5**) was eluted, followed by 123 mg of more polar material. The mixture of **3** and **5**, dissolved in 30 ml of acetone and cooled to 0°, was treated with 15% excess of the chromic acid reagent described above. The excess oxidant was destroyed with 2-propanol after 4 min. The low temperature and short contact time were essential to prevent degradation of the double bond. Hexane and brine were added, the organic layer was separated, washed with brine until neutral, and dried ($MgSO_4$), and the solvent was evaporated to give 354 mg of a mixture of 5α-androstan-3-one (**4**) and 5α-androstan-14-en-3-one (**6**). This mixture was chromatographed on 20 g of 20% silver nitrate on silica gel, again using gradient elution with hexane and 20% ether–80% hexane, affording 213 mg of compound **4** (39%) and 140 mg of compound **6** (26%). Compound **6**, recrystallized from aqueous CH_3CN, exhibited mp 117–118.5° (lit.[5] mp 118–119°); nmr ($CDCl_3$) δ 1.033 (18- and 19-CH_3's) (lit.[5] δ 1.033 for both CH_3's); ir 1715 cm^{-1} (six-membered cyclic ketone).

Analysis of the More Polar Neutral Fraction.—The more polar fraction (123 mg) obtained from chromatography of the crude photoproduct (12 hr photoreaction) presumably consisted of diols and polymer. Oxidation with excess Jones reagent (25° for 30 min), work-up with hexane and brine as described above, and vacuum sublimation afforded 60 mg of yellow material. The nmr spectra of this material exhibited several sharp singlets for angular methyl groups. The two largest singlets were found at δ 1.050 and 1.108 when the solvent was deuteriochloroform and at δ 0.733 and 0.533 when the solvent was benzene. The calculated peak positions for the 18- and 19-CH_3's of 5α-androstane-3,12-dione (**9**) are, respectively, δ 1.108 and 1.133 in deuteriochloroform and δ 0.748 and 0.523 in benzene.[8,10]

Registry No.—**2**, 39949-94-5; **3**, 7657-50-3; **6**, 17305-51-0; **7**, 39949-97-8; β-(*p*-nitrophenyl)propionic acid, 16642-79-8.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, to the Texas A & M University Chemistry Department, and to the Texas A & M University Research Council for support of this work.

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