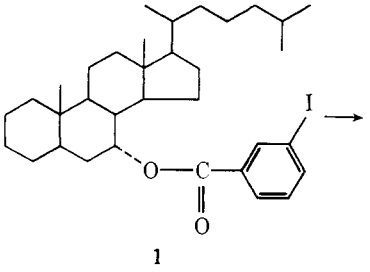
Removal of the Steroid Side Chain Using Remote Oxidation. Conversion of 3β-Cholestanol to Androsterone Acetate

Sir:

We have previously described the use of iodobenzene dichloride in the halogenation of steroids at C-5, -9, and -14.[1] Furthermore, with an attached *m*-iodobenzoate or *p*-iodophenylacetate at C-3, functionalization can be achieved specifically at C-9 or -14, respectively[2,3] in agreement with the calculated lengths of these reagents (see Table I). This can be done by converting these esters to the attached aryliodine dichlorides, followed by intramolecular radical chain halogenation.[2] In the more convenient radical relay process[3] the intermediate aryliodide-chlorine atom σ-complex in such a free radical process is generated by chlorine transfer from an external chlorinating radical. In either case the steroid halogenation is directed to produce a single chlorosteroid isomer; this is usually directly treated with base to generate the olefinic sterol, which is isolated as the acetate. We now describe a process which halogenates selectively at C-17, a position not attacked in intermolecular halogenation. This remote functionalization is the key step in an efficient conversion of 3β-cholestanol to androsterone acetate.

Initial experiments were designed to determine whether halogenation at C-17 could be achieved with attached iodobenzoates. Since a 3α *m*-iodobenzoate directs chlorination at C-9 in 75% yield and C-9 is almost the same distance from C-3 as C-17 is from C-7 (see Table I), we prepared 7α-cholestanyl *m*-iodobenzoate (**1**). Reaction of 7β-cholestanol[4] by inversion-esterification[5] with triphenylphosphine, diethyl azodicarboxylate, and *m*-iodobenzoic acid gave **1**[6] in 44% yield. Irradiation of **1** (618 mg, 1 mmol) and $PhICl_2$ (325 mg, 1.2 mmol) in 100 ml of CH_2Cl_2 for 30 min with a 275-W sunlamp (the free radical relay conditions previously described[3]) afforded after saponification, acetylation, and chromatography Δ^{16}-7α-cholestenyl acetate (**2**) in 54% yield as the only monoolefin.



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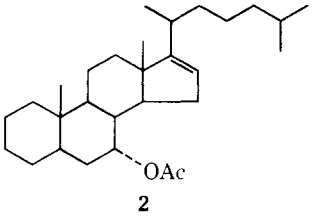


2

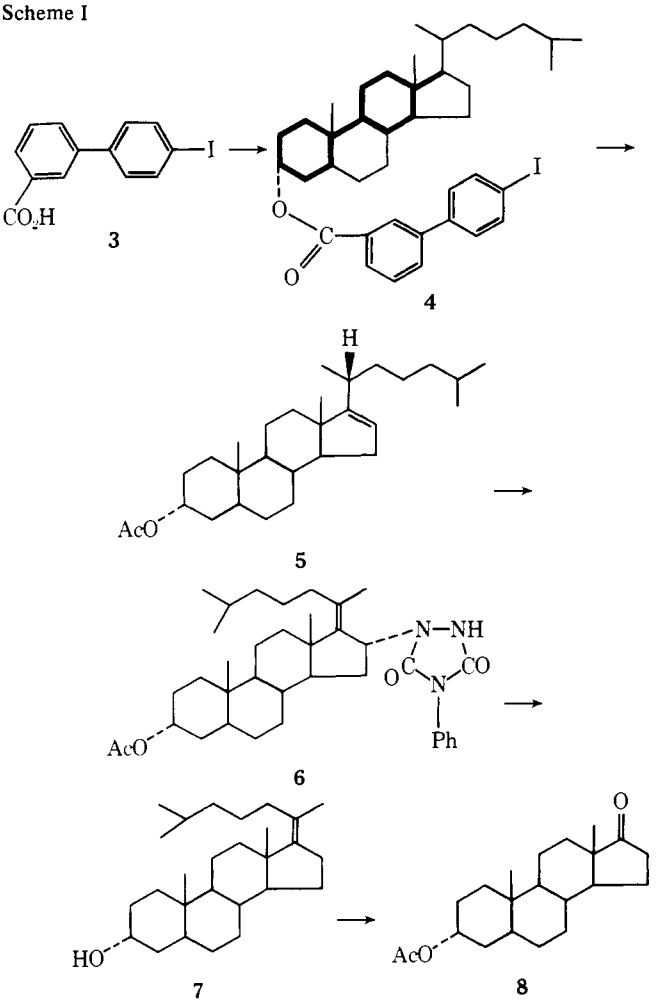
We were now interested in developing a reagent that would chlorinate efficiently at C-17 when attached at C-3. On examination of the steroid structure it is apparent that while C-9 is directly attached to ring A, C-17 is attached to ring A with the insertion of the six-membered ring C. Therefore inserting a phenylene into *m*-iodobenzoic acid to give **3** should provide a reagent capable of attacking C-17 from C-3 (see Table I for a comparison of the O-H distances in the substrate with the O-Cl distances in various attached reagent-chlorine atom complexes). Direct iodination of methyl 3-biphenylcarboxylate[7] with iodine, potassium iodate, and sulfuric acid in aqueous acetic acid[8] gave 4′-iodo-3-biphenylcarboxylic acid (**3**), mp 219-221°, in 75% yield (Scheme I). Inversion-esterification[5] of 3β-cholestanol with **3** furnished **4**, mp 117-118.5°, in 90% yield. Photolysis of **4** (3.7 g, 5.3 mmol) with $PhICl_2$ (1.61 g, 1.1 equiv) in 700 ml of carbon tetrachloride for 45 min at 25° gave, after processing,[2] 41% of Δ^{16}-3α-cholestenyl acetate

Table I. Calculated Distances in Steroids and Reagents

Steroids (A/B trans)		
Oxygen	Hydrogen	Distance (Å)[a]
3α	9α	4.41
3α	14α	6.52
3α	17α	8.49
7α	17α	5.04[b]
Reagent–Chlorine Atom σ-Complex[c]		O–Cl Distance (Å)[d]
m-Iodobenzoate		4.27
p-Iodophenylacetate		6.84
m-Iodophenylacetate		5.24
4′-Iodo-3-biphenylcarboxylate (**3**)		8.68
4-(*p*-Iodophenyl)butyrate		8.11

[a] Calculated from X-ray crystal diffraction data for 5α-androstan-3α,17β-diol.[16] [b] Calculated from average values of steroidal molecular dimensions.[17] [c] Standard bond lengths and angles appropriate to straight-chain alkanes in their most stable conformation were assumed. Ph–I and I–Cl bond lengths and the Ph–I–Cl bond angle were taken from X-ray data for $PhICl_2$.[18] Reasonable conformations for the reagents were assumed. [d] The distances between the ester oxygen and a chlorine atom attached to the iodine were calculated from the Cartesian coordinates of the atoms involved.[20] The ester group was assumed to be in the nonlactone conformation.[21]

Scheme I



(5), 40% of recovered 3α-cholestanyl acetate, and 19% of polar impurities. Increasing the amount of $PhICl_2$ used to 2.5 equiv afforded 54% of Δ^{16}-3α-cholestenol, mp 119–120°, 7% 3α-cholestanol and 39% of polar impurities.[9,10]

In order to obtain 17-keto steroids, a procedure was needed to convert the Δ^{16} steroids into their $\Delta^{17(20)}$ isomers. This was accomplished by treatment of **5** with *N*-phenyltriazolinedione in methylene chloride (25°, 24 hr) to provide the ene adduct **6** in 65% yield. The stereochemistry of the double bond would result from α attack on the steroid and intramolecular hydrogen transfer. Saponification of **6** followed by reduction with lithium in ethylamine[11] gave *Z*-$\Delta^{17(20)}$-3α-cholestenol (**7**),[12] mp 133–135°, in 74% yield. Acetylation of **7** followed by ozonolysis (ethyl acetate, −20°) afforded androsterone acetate (**8**) in 78% yield,[15] completing a rational conversion of 3β-cholestanol to androsterone acetate. The remote oxidation procedure described may prove useful in converting abundant steroids into the valuable steroidal hormones.

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References and Notes

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(9) The intermediate chlorosteroids were rather unstable, as expected for tertiary 17-chloro compounds, so they were directly converted to the olefins with base. The polar impurities consisted of 56% of very polar unidentified materials and 44% of a compound which is probably 16-chloro-Δ^{16}-3α-cholestenyl acetate.
(10) An alternative approach to 17 functionalization is based on inserting two methylenes into *p*-iodophenylacetic acid to extend it from C-14 to C-17. Chlorination of 3α-cholestanyl 4-(*p*-iodophenyl)butyrate in carbon tetrachloride gave 17% of Δ^{16}-3α-cholestenyl acetate, 19% of Δ^{14}-3α-cholestenyl acetate, and 16% polar impurities. Similar chlorination of the 3-(*p*-iodophenyl)propionate of 5-(*p*-iodophenyl)valerate gave less than 10% of steroidal olefins. If the methylene chain is in the lowest energy extended conformation, the iodophenyl is pointed toward the steroid with an odd number of methylenes and away from the steroid with an even number of methylenes.
(11) Cf. A. S. Hallsworth, H. B. Henbest, and T. I. Wrigley, *J. Chem. Soc.*, 1969 (1957).
(12) The NMR signal of the 21-CH_3 of **7** occurs at 93 Hz. In the *E* isomer the corresponding absorption occurs at 101 Hz.[13] This dependence of the chemical shift of the methyl group has been previously observed in $\Delta^{17(20)}$ pregnenes.[14]
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Nuclear Magnetic Resonance of Rare Spins. Determination of ^{15}N Parameters from Proton Fourier Transform Nuclear Magnetic Resonance by Elimination of Signals Due to Abundant Isotope

Sir:

Previously we have proposed[1] a method which leads to the abundant isotope signals elimination by Fourier transform NMR (we shall call this method AISEFT). At this time, it was applied to the measurement of ^{13}C-^{1}H couplings. We wish to describe here an extension of this procedure to the determination of ^{15}N parameters. It consists in collecting a first proton interferogram while irradiating ^{15}N transitions and a second one without irradiation. These two data collections are then subtracted, and this sequence is repeated until a suitable S/N ratio is obtained. In this way strong resonances due to molecules containing ^{14}N would in principle disappear and only ^{15}N satellites together with these satellites decoupled from ^{15}N would remain, these latter signals being shifted in phase by an angle of 180°. This procedure is an adaptation to Fourier transform of a method applied by Freeman[2] to CW NMR.

In principle, this method should yield all nitrogen parameters. Unfortunately, due to small instrumental instabilities, the strong peaks do not entirely disappear. This prevents the measurements of small couplings, except when resonances due to molecules containing ^{14}N are broad. This opportunity occurs for formamide (Figure 1). In this case, it has been possible to detect all the couplings between protons and ^{15}N, ^{15}N being in natural abundance: J_{14} = 88.3 Hz, J_{24} = 90.7 Hz, J_{34} = 14.6 Hz. In fact it is always possible to observe splittings larger or equal to 5 Hz, but for the other molecules under investigation (always with ^{15}N in natural abundance), we could only measure the one bond coupling $^{1}J_{NH}$, the other couplings being too small. (A typical AISEFT is shown in Figure 2.) Results are gathered in Table

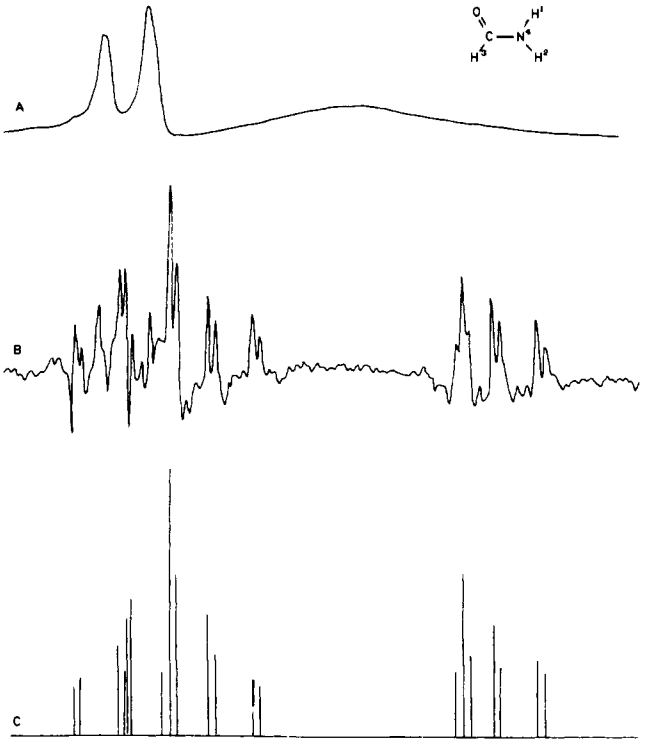

Figure 1. (A) Normal 90-MHz proton spectrum of formamide. (B) AISEFT spectrum. Lines down arising from ^{15}N satellites decoupled of ^{15}N. (C) Theoretical spectrum of $HCO^{15}NH_2$. All spectra were recorded with a Bruker HX 90 spectrometer interfaced with a Nicolet 1080 computer.