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SYNTHETIC STUDIES IN STEROIDAL SAPOGENINS AND ALKALOIDS—IV

STEREOCHEMISTRY OF MICHAEL ADDITION TO 5,17(20)-PREGNADIEN-3β-OL-16-ONES

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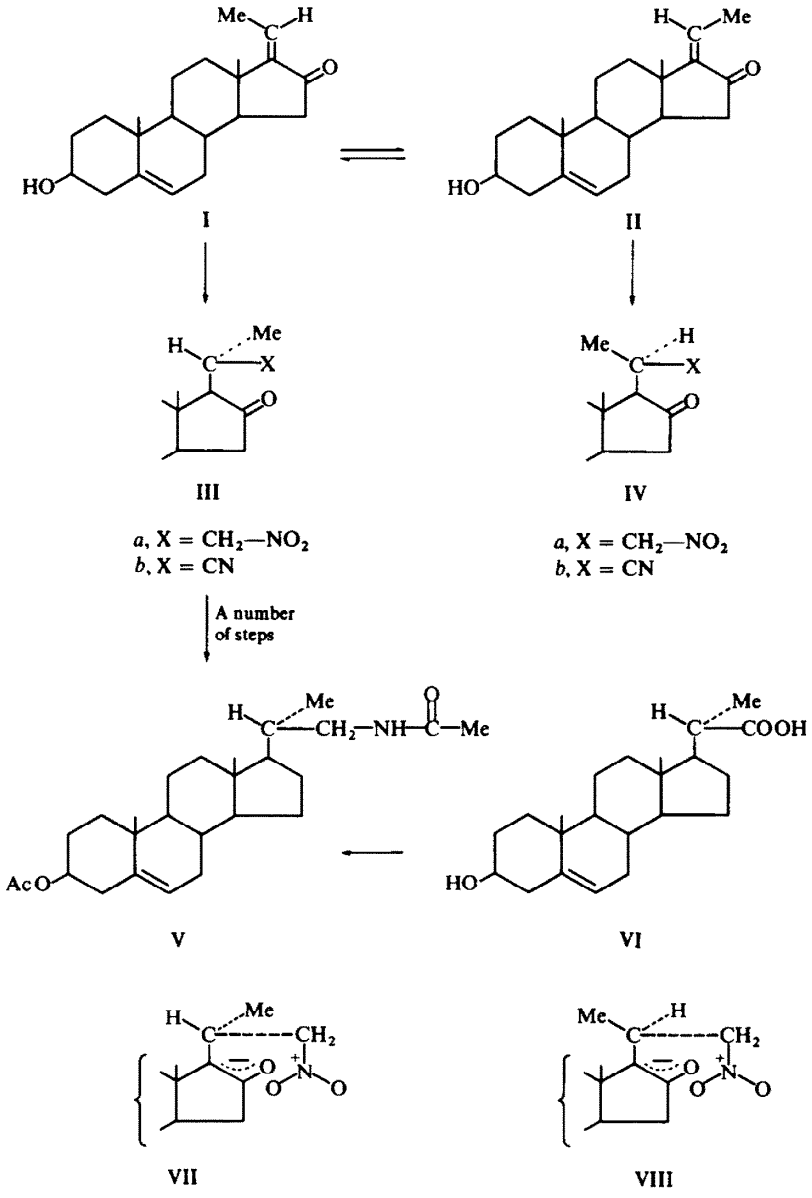
Abstract—Addition of nitromethane and sodium cyanide to *cis*- and *trans*-5,17(20)-pregnadien-3β-ol-16-one has been investigated. The stereochemistry of the nitroadducts has been established by correlation with bisnorcholenic acid.

IN OUR proposed scheme[1] for the synthesis of steroidal sapogenins and alkaloids, a number of new asymmetric centres arise on Michael addition to 5,17(20)-pragnadien-3β-ol-16-one. The present study was initiated to explore, with the help of less complicated addenda, conditions for control of the stereochemistry at C-17 and C-20.

Addition of nitromethane to *cis*-ketone I proceeds readily in t-butyl alcohol containing one equivalent of potassium t-butoxide. At 35° the reaction is complete in less than two hr. When addition is carried out with a large excess of nitromethane no substantial *cis-trans* isomerization of the substrate is detected by periodic TLC examination of the reaction mixture. Apparently, the rate of isomerization by weakly basic nitromethyl anion is considerably lower than the rate of its addition to ketone I.

On the grounds of rear-side attack, generally observed in steroid reactions,[2] the 20*S* configuration was expected in IIIa. Further, both on the basis of back-side protonation of the adduct anion and equilibration to a more stable arrangement, β-orientation is favoured for the C-17 side-chain. The predicted stereochemistry for IIIa was established by correlation with bisnorcholenic acid (VI). The thioketal from the acetate of IIIa was reduced with LAH. The resulting amine was acetylated and desulphurized to obtain a product which was shown to be identical with amide V obtained from bisnorcholenic acid (VI). All the reactions in this series are expected to preserve the stereochemical integrity at C-20 and C-17.

Under identical conditions nitromethane addition to ketone II is much slower than the addition to I. Even after 24 hr considerable quantities of unreacted II were found in the reaction mixture. From early small scale runs it was erroneously concluded[3] that the adduct from *trans*-ketone was identical with IIIa as it had the same R_f value in a number of solvent systems. Preparative scale reaction, however, gave a nitroketone IVa which differed from IIIa in details of IR spectrum, m.p. and rotation. IR spectra of the crude products obtained from ketones I and II revealed that predominantly one product is formed in each case, showing that the addition is stereospecific. In comparison, Beard *et al.*[4] observed a degree of randomness in 1,4-Grignard addition to a similar system.



Next the possibility of obtaining adduct IIIa from a mixture of ketones I and III was investigated. This seemed feasible if the reaction was carried out under conditions of rapid substrate equilibration, provided the addition to *cis*-ketone I is sufficiently fast as compared to the addition to the *trans*-ketone. Reaction of an equimolar mixture of I and II with nitromethane in presence of excess base was complete in less than 3 hr, as expected, and furnished an impure adduct (more than 80% of IIIa) which on crystallization afforded IIIa. It seems, therefore, that it is not essential to start with pure *cis*-ketone in the aforementioned synthetic scheme.

The reason for considerable difference in the rate of nitromethane addition to *cis*- and *trans*-ketones I and II is not clear. From models, C-20 seems equally accessible to an addendum from the rear side in both the isomers. Further, these unsaturated ketones have comparable stabilities[5] and the observed rate variation is not likely to arise from differential relief of steric strain.

This difference in rates of addition can, however, be rationalized in terms of a stabilizing field interaction in the transition state for the addition to the *cis*-ketone, as shown in VII. Such stabilization may not be available in the case of addition to the *trans*-ketone, as the necessary orientation of the side chain forces the C-18 and C-21 Me groups too close to each other. An alternate explanation can be that, on purely steric grounds, the most favourable orientations for the bulkiest group (nitromethyl) attached to C-20 are the ones shown in VII and VIII. Again, in the transition state for addition to the *trans*-ketone such an arrangement would be opposed by interaction between C-21 and C-18 Me groups.

To clarify the situation, the addition of the smaller cyanide ion to these two α,β-unsaturated ketones was studied. Here again two different adducts (IIIb and IVb) were obtained and the reaction with the *cis*-ketone was considerably faster. As the linear cyanide group is not expected to have greater steric requirements than the Me group,* it seems that the size may not be responsible for the observed effect.

Sondheimer and Mazur[7] have demonstrated a field interaction in C-16, C-22 dicarbonyl steroids with 20*S* orientation by IR spectroscopy. In the IR spectrum of nitro ketone IIIa, both the carbonyl and nitro absorptions are slightly shifted as compared to those in IVa. This difference persists in their acetates. In the nitriles IIIb and IVb, on the other hand, no significant shifting of cyano or carbonyl frequencies is observed. It may be pointed out that conclusions about interactions, drawn from products, may not be applicable to the respective transition states because of the differences in geometry, bond length and charge distribution.

Additions of dimethylamine and *p*-tolyl mercaptan to ketones I and II were also attempted. No charge stabilization of the above type can be visualised in the transition state for these reactions. It was, therefore, thought that such an effect would be definitely established in the earlier cases if the rates of amine and thiol addition to the *cis*-ketone were not found to be appreciably higher than the rates for the addition to the *trans*-ketone. Under the conditions tried, however, extensive *cis-trans* isomerization of the substrate occurred prior to addition and no conclusion could be drawn. It is interesting to note that *p*-tolyl mercaptan brings about rapid *cis-trans* isomerization even in absence of base, conceivably by free radical addition-expulsion mechanism.[7]

EXPERIMENTAL

The general experimental procedures are the same as given in Part III. Amounts of unreacted *cis*- and *trans*-ketones in the reaction mixture were approximately estimated from aliquots by TLC and UV absorption at 243 mμ. For these reactions the temp was maintained within ±2° of the given value by immersing the reaction flask in a constant temp bath. Each quantitative estimate is based on at least two runs. To detect small displacements in IR peaks, the spectra to be compared were recorded without displacement on the same chart of a Perkin–Elmer-237 instrument.

Addition of nitromethane to cis-5,17(20)-*pregnadien*-3β-ol-16-one (I). A soln of *cis*-ketone[5] I (100 mg) in t-butyl alcohol (10 ml) was added to the potassium salt of nitromethane (from K metal, 10 mg, nitromethane, 0·1 ml and t-butyl alcohol, 5 ml) and the mixture was allowed to stand at 35°. Small lots of the mixture

* This inference will, however, be invalid if the cyanide group is highly solvated in the transition state.

were withdrawn at intervals, neutralized with dil AcOH and diluted with water. The ppt was collected, washed with water, dried and examined.

Time	*cis*-ketone %	*trans*-ketone %
15 min	40	not detected
30 min	20	traces
1·5 hr	traces	not detected
3 hr	not detected	not detected

After 3 hr the remaining mixture was processed, as above, to get the crude adduct in quantitative yield. Two crystallizations from EtOH afforded pure IIIa, m.p. 184–185°, $[\alpha]_D^{27}$ −200°, ν_{max} 5·75, 6·45, 9·8 μ. (Found: C, 70·73; H, 9·10; N, 3·75. $C_{22}H_{33}NO_4$ requires: C, 70·37; H, 8·86; N, 3·73%.). The acetate was crystallized from EtOH, m.p. 183–184°, $[\alpha]_D^{25}$ −161°, ν_{max} 5·75, 6·46, 8·0 μ. (Found: C, 68·60; H, 8·14. $C_{24}H_{35}NO_5$ requires: C, 69·03; H, 8·45%.)

Addition of nitromethane to trans-5,17(20)-*pregnadien*-3β-ol-16-one (II). A reaction of *trans*-ketone II (100 mg) was kept, at 35°, under exactly the same conditions as above. Analysis of aliquots gave the following results:

Time	*cis*-ketone %	*trans*-ketone %
15 min	not detected	100
24 hr	traces	30
3 days	not detected	not detected

At the end of 3 days the remaining mixture was processed to obtain the crude product in almost quantitative yield. Two crystallizations from aqueous EtOH furnished pure IVa, m.p. 161–162°, ν_{max} 5·8, 6·4, 9·58, 9·8 μ. (Found: C, 70·65; H, 9·09. $C_{22}H_{23}NO_4$ requires: C, 70·37; H, 8·80%.) The acetate was crystallized from MeOH, m.p. 193–194°, ν_{max} 5·75, 5·8, 6·46, 8·06 μ. (Found: C, 68·9; H, 8·87. $C_{24}H_{35}NO_5$ requires: C, 69·03; H, 8·45%.)

Addition of nitromethane to cis- *and* trans-*ketone mixture in presence of excess base.* A soln of *cis*- and *trans*-ketone mixture (1:1, 100 mg) in t-butyl alcohol (10 ml) was added to the potassium salt of nitromethane (from K metal 80 mg, nitromethane, 0·1 ml and t-butyl alcohol 5 ml), and the mixture was allowed to stand at 35°. Examination of an aliquot after 3 hr revealed the absence of unsaturated ketones. The remaining mixture was then worked up as before yielding a solid the IR of which was similar to a 4:1 mixture of nitro ketones IIIa and IVa. Two crystallizations from EtOH afforded pure IIIa, m.p. 182–183·5°.

Treatment of IVa *with excess nitromethyl anion.* To a soln of IVa (10 mg) in t-butyl alcohol (1 ml) was added in potassium salt of nitromethane (from k metal, 1 mg, nitromethane, 0·1 ml and t-butyl alcohol, 1 ml). The mixture was worked up, as before, after 6 days. The IR spectrum of the product (9 mg) was identical with that of IVa.

Conversion of 3β-*acetoxy*-20S-*nitromethyl*-5-*pregnen*-16-*one* (IIIa) *to* 20S-*aminomethyl*-5-*pregnen*-3β-*ol* O,N-*diacetate* (V). Dry HCl was passed through a soln of acetate of IIIa in ethane-1,2-dithiol (3 ml) at 0° for 3 hr. The reaction mixture was kept overnight at 0–5°. It was poured with stirring into a suspension of anhyd K_2CO_3 in distilled $CHCl_3$. Water was added with stirring for 3 min and the $CHCl_3$ layer separated, washed and dried. Evaporation of the solvent left a dark residue which was triturated with EtOH to obtain a dirty white solid which showed no IR absorption in the CO region.

A solution of the above thioketal in THF (50 ml) was added, dropwise with stirring, to a slurry of LAH (0·5 g) in THF. Stirring and heating was continued for 6 hr. Excess reagent was decomposed with water (1·5 ml) and 50% KOH aq (2 ml). The mixture was filtered and the residue was washed with hot THF. Distillation of the filtrate left a solid which was acetylated as such.

A mixture of the acetylated product, EtOH (10 ml), dioxan (10 ml) and Raney Ni was refluxed for 3–5 hr. The catalyst was removed by filtration and washed with hot dioxan. The residue obtained on evaporation of the combined filtrates was crystallized from dil AcOH to obtain a colourless solid, m.p. 250–251°, $[\alpha]_D^{38}$ −45°. It has the same R_f value as authentic 20S-aminomethyl-5-pregnen-3β-ol-O,N-diacetate

in a number of solvent systems, and showed no depression in m.p. on admixture. (Found: C, 75·13; H, 9·82; N, 3·43. $C_{26}H_{41}NO_3$ requires: C, 75·18, H, 9·88; N, 3·37%.)

Preparation of 20S-*aminomethyl*-5-*pregnen*-3β-*ol*-O,N-*diacetate* (V) *from bisnorcholenic acid.* The method of Chaplin *et al.*[8] was used to obtain 3β-acetoxy-20S-carboxamido-5-pregnene, m.p. 223–225°, from 3β-acetoxy-Δ^5-bisnorcholenic acid.*

The above amide (0·5 g) in dioxan (30 ml) was refluxed with a suspension of LAH (0·5 g) for 16 hr. Excess reagent was decomposed with water (1 ml) and 50% KOH aq. The reaction mixture was filtered and the residue washed with hot dioxan. The solvent was distilled off from the combined filtrates and the residue washed with hot water, dried and acetylated. Crystallization from dil AcOH furnished pure V, m.p. 251–253°, $[\alpha]_D$ −44°. (Found: C, 75·15; H, 10·00. $C_{26}H_{41}NO_3$ requires: C, 75·18; H, 9·88%.)

Addition of sodium cyanide to cis-5,17(20)-*pregnadien*-3β-*ol*-16-*one* (I). To a soln of *cis*-ketone (40 mg) in freshly distilled DMF (1·2 ml) was added a soln of NaCN (100 mg), NH_4Cl (40 mg), water (0·8 ml) and DMF (1·6 ml). The reaction mixture was allowed to stand at 20°. Small lots of the mixture were withdrawn at intervals and diluted with water. The ppt was collected, thoroughly washed with hot water, dried and examined.

Time	*cis*-ketone %	*trans*-ketone %
0·5 hr	90	not detected
1·5 hr	60	not detected
3·0 hr	10	not detected
24 hr	not detected	not detected

After 24 hr the reaction mixture yielded a crude material which was crystallized from EtOH to obtain pure IIIb, m.p. 179–180°, ν_{max} 4·95, 5·75 μ, $[\alpha]_D^{30}$ −166°. (Found: C, 77·78; H, 9·25. $C_{22}H_{31}O_2N$ requires: C, 77·41; H, 9·09%.)

Addition of sodium cyanide to trans-5,17(20)-*pregnadiene*-3β-*ol*-16-*one* (II). Addition of NaCN to *trans*-ketone (40 mg) was carried out under exactly the same conditions as above. The progress of the reaction is given below:

Time	*trans*-ketone %	*cis*-ketone %
0·5 hr	100	not detected
2 hr	90	not detected
4 hr	80	traces
24 hr	20	not detected
3 days	not detected	not detected

At the end of 3 days the reaction mixture yielded a crude adduct which on crystallization from EtOH afforded pure IVb, m.p. 209–210°, ν_{max} 4·95, 5·75 μ, $[\alpha]_D^{30}$ −185°. (Found: C, 76·91; H, 9·48. $C_{22}H_{31}O_2N$ requires: C, 77·41; H, 9·09%.)

Attempted addition of dimethylamine to cis-5,17(20)-*pregnadiene*-3β-*ol*-16-*one* (I). Dry Me_2NH was passed through a soln of *cis*-ketone I (5 mg) in t-butyl alcohol (2 ml) for 5 min. The reaction mixture was allowed to stand at room temp. After 1 hr examination of an aliquot by TLC showed substantial isomerization but no addition.

Addition of p-*tolyl mercaptan to* cis-5,17(20)-*pregnadiene*-3β-*ol*-16-*one* (I). A mixture of the *cis*-ketone (50 mg), *p*-tolyl mercaptan (25 mg) and EtOH (1 ml) was allowed to stand at room temp. After 3 hr an aliquot was withdrawn, diluted with water and the ppt washed with water, dried and examined by TLC Extensive isomerization of the starting ketone was observed. The addition was complete in 3 days when the reaction mixture was processed in the usual manner. The crude adduct crystallized from EtOH, m.p. 179–180°, ν_{max} 5·8 μ.

Prior isomerization was observed even when the reaction was carried out in dark in presence of hydroquinone.

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