Tetrahedron Vol. 24, pp 845 to 857 Pergamon Press 1968 Printed in Great Britain

AZA STEROIDS—VII*

SYNTHESIS OF RING A-OXYGENATED 6-AZA STEROIDS

J. P. KUTNEY, G. EIGENDORF and J. E. HALL
Department of Chemistry, University of British Columbia, Vancouver 8, B.C.

(*Received in USA* 8 *April* 1967; *accepted for publication* 30 *May* 1967)

Abstract—Selective hydroboration of N-benzyl-6-aza-2,4-cholestadien-7-one (III) provided the two isomeric 3-hydroxy-6-aza steroids (V and VI) and the 2α-hydroxy derivative IV. This sequence provides a general entry into ring A-oxygenated 6-aza steroids and provides the first examples of this series which bear the Δ^4-3-keto chromophore.

PREVIOUS publications have demonstrated that the readily available Δ^5-7-one system in the steroids does provide a convenient entry into 6-aza steroids of the cholestane,[2–4] androstane[3,4] and pregnane[1] series. In all instances, the introduction of the hetero atom was achieved with the appropriate seco keto-ester, and served to exemplify the generality of this approach for the synthesis of ring B, as well as ring C aza steroids.[5,6] Unfortunately, this method could not be used for the synthesis of 6-aza steroids possessing oxygen functions at C_3, since the elimination of such functions was normally observed during the isolation of the desired keto-ester. Even in instances where such elimination was prevented by careful manipulation of the procedure, the subsequent reaction of the keto-ester with the amine resulted in loss of the C_3 function. It was, therefore, necessary to investigate a possible modification of the above sequence in order to achieve the synthesis of ring A-oxygenated 6-aza steroids. This publication reports some of our efforts in this direction.

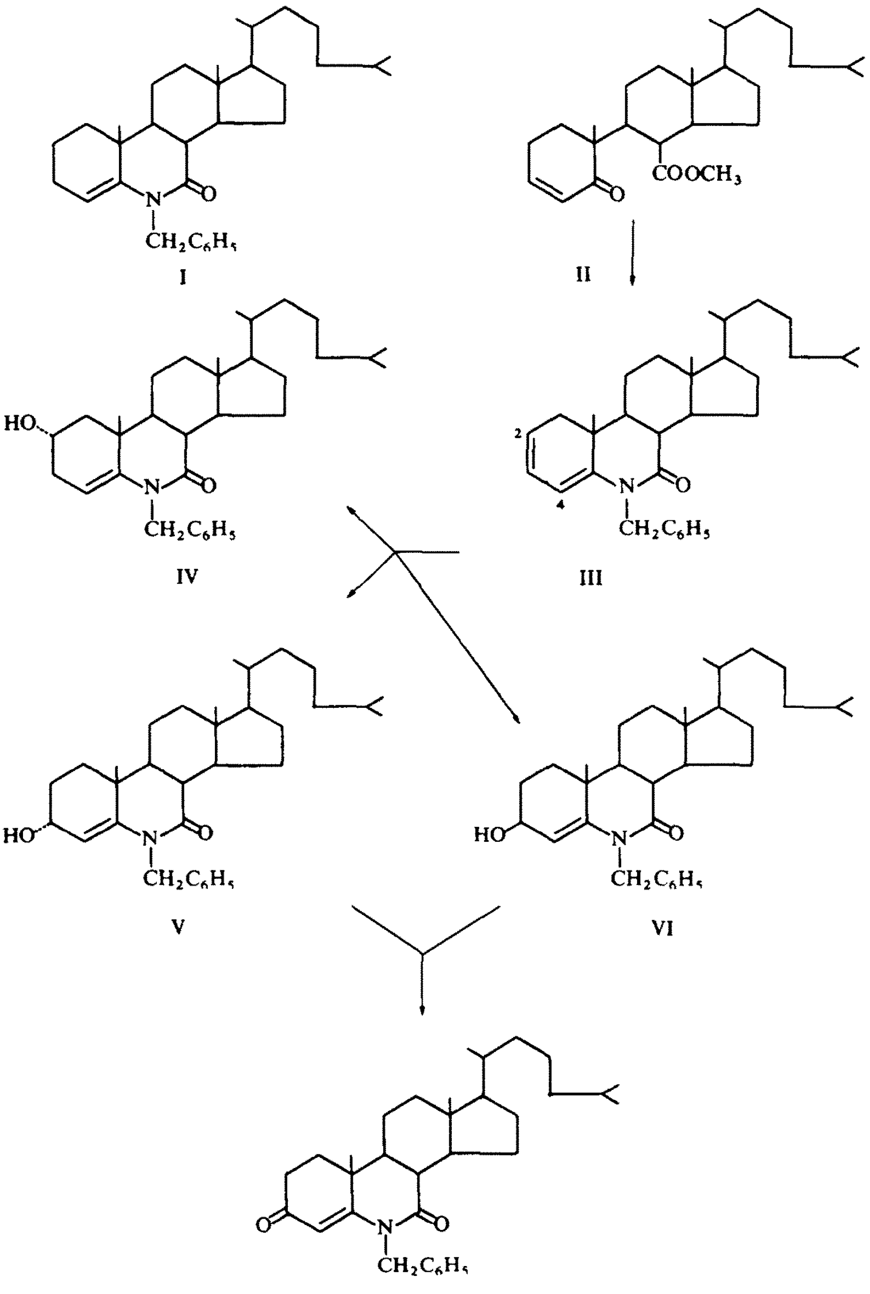
We turned our attention to the possibility of achieving selective reaction at the 2,3-double bond in the doubly unsaturated lactam III. Previous experiments in our laboratory with catalytic reduction indicated that this latter substance could be converted without difficulty to the enol lactam I, and it was, therefore, apparent that such a selective reaction could be feasible. In this regard, we chose to consider hydration of the olefinic linkage at the 2,3-position, and an attractive approach was available via the hydroboration technique originally developed by Brown *et al.*[7]

The doubly unsaturated lactam, N-benzyl-6-aza-2,4-cholestadien-7-one (III) was prepared in the usual manner[2–4] when methyl-5-oxo-5,7-seco-6-nor-3-cholesten-7-oate (II) was reacted with refluxing benzyl amine. The structure of III was readily apparent from its characteristic spectral data, in particular, the UV spectrum (λ_{max} 297 mμ), and conclusively established when catalytic reduction of this compound provided the known enol lactam I.

Hydroboration of III with diborane in anhydrous diglyme at 0°, provided a white solid reaction product (m.p. 133–136°). This product was shown to be a mixture of

---

* Financial support for this work was provided by the B. C. Heart Foundation, the Medical Life Insurance Fund, and Smith, Kline and French Laboratories.



I II III IV V VI VII

three substances with similar R_f values, which could be separated either by careful preparative thin-layer or by extensive column chromatography.

The least polar compound, m.p. 151–153°, obtained crystalline after the above separation, was clearly of interest due to its spectral properties. The UV spectrum

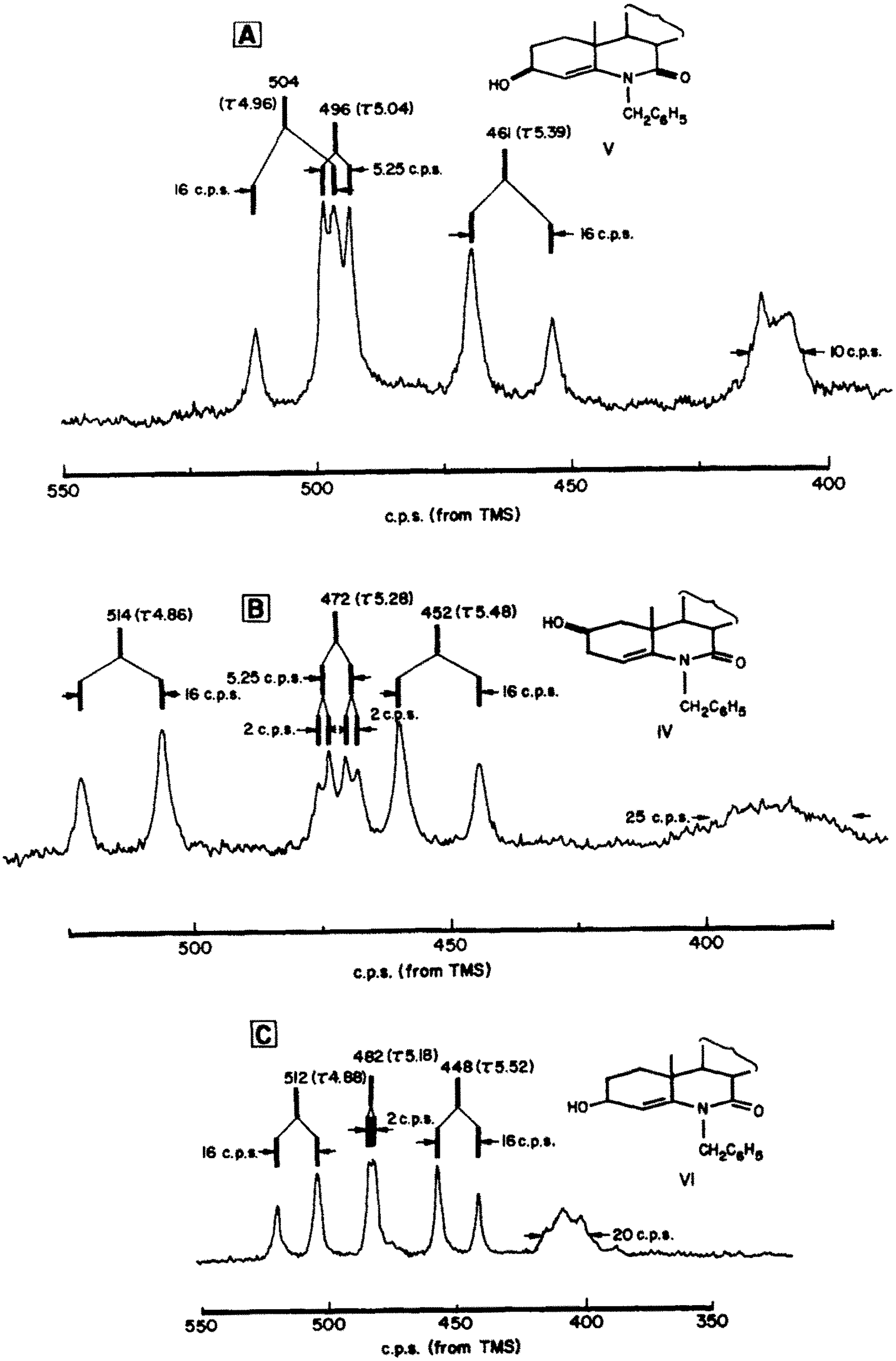


FIG. 1 Low Field Region of NMR Spectra of Hydroboration Products.

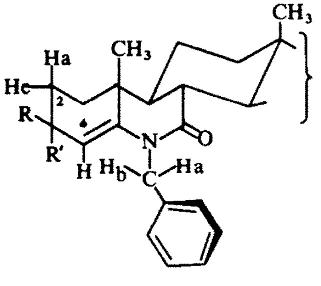
with the characteristic enol lactam absorption (λ_{max} 237 mμ) indicated that reaction at the 2,3-double bond had occurred. Confirmation of the enol lactam chromophore was provided by the IR absorption bands at 1635 and 1670 cm^{-1}. The expected hydration of the diene system in ring A of the starting material was then shown beyond doubt when a high resolution mass spectrometric determination established the molecular formula, $C_{33}H_{49}O_2N$, for this compound. The very informative NMR spectrum will be discussed below in conjunction with similar data obtained for the other hydroboration products.

The next product to be obtained in the chromatographic separation was also crystalline, m.p. 144–145·5°. As the above compound, it also exhibited the presence of an enol lactam system (λ_{max} 237 mμ; ν_{max} 1625 and 1670 cm^{-1}), and a simple hydration of the 2,3-double bond was again evident from its molecular formula, $C_{33}H_{49}O_2N$.

The third and most polar compound isolated from the hydroboration reaction was a crystalline substance, m.p. 176–178°, which again exhibited spectral characteristics in agreement with a hydroboration product.

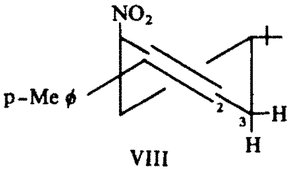
A discussion of the NMR spectra obtained for the above three compounds is now presented, since a comparative analysis of the data does allow structural assignments in all three instances. Fig. 1 shows a reproduction of the relevant low field regions of the spectra of these compounds determined at 100 Mc/s. Analysis of sections A, B and C in Fig. 1 can be made in terms of structures V, IV and VI, respectively.

If we first consider 3α-hydroxy-N-benzyl-6-aza-4-cholesten-7-one in terms of its conformational structure Va, it can be seen from molecular models that the 4,5-double bond transforms ring A into a half-chair conformation, and the dihedral angles involving substituents at C_2 and C_3 are not significantly altered from those encountered in the simple cyclohexene series. The coupling constants for the protons at these centers are, therefore, in reasonable agreement with the values normally quoted for the conventional half-chair conformations in cyclohexene systems.

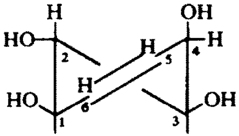


Ia: R = R' = H
Va: R = H; R' = OH

VIa: R = OH; R' = H
VIIa: R = R' = O



VIII

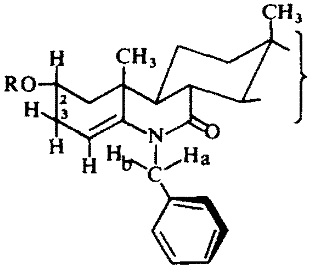


IX

Detailed studies on vinyl–allylic proton spin couplings are already available in the literature,[8–12] and provide data which is pertinent to the present discussion. We will utilize some of the data given on two typical examples, the cyclohexene derivative VIII,[8] and one of the conduritols IX,[11] as taken from two of these publications. These results are of relevance to the present situation.

If we now turn to section A in Fig. 1, it is seen that the olefinic proton signal (τ 5·04) is a doublet $J = 5{\cdot}25$ c/s. The multiplicity of the signal and the magnitude of the coupling constant indicate that the 3α-OH function is present in this hydroboration product ($J_{2,3e}$ and $J_{4,5}$ in VIII and IX are 5·0 and 5·3 c/s, respectively). Further confirmation of this assignment is available from the splitting of the C_3 proton signal in this compound. Since $J_{2a,3}$ and $J_{2e,3}$ in V are expected to be small (usually 2–5 c/s; for example, $J_{3,4} = 4{\cdot}4$ c/s in IX), and $J_{3,4}$ is shown to be approximately 5 c/s, it is seen that the width at half-height of the C_3 proton multiplet should be of the order, 9–15 c/s. In actual fact, the observed value is 10 c/s. On this basis, the least polar hydroboration product was assigned structure V.

Section B in Fig. 1 represents the low field proton region of the NMR spectrum of the second hydroboration product (m.p. 144–145·5). Analysis of this data allows an assignment of structure IV to this substance (IVa is the conformational structure).



IVa: R = H
IVb: R = Ac

From the previous work already mentioned above,[8] $J_{2,3a} = 2{\cdot}5$ and $J_{2,3e} = 5{\cdot}0$ c/s were the obtained values for the substituted cyclohexene VIII. In accord with these findings, it is clear that the C_4 olefinic proton in IV should appear as a quartet, and reference to section B reveals that such is the case ($J_{3e,4} = 2$ c/s and $J_{3a,4} = 5{\cdot}25$ c/s). The C_2 proton signal (half-height width, 25 c/s) is in agreement with its axial orientation.

Section C in Fig. 1 illustrates the low field region of the NMR spectrum for the most polar hydroboration product. One of the striking differences noted in this spectrum is the narrow doublet ($J = 2$ c/s) observed for the olefinic proton and establishes that the latter proton was coupled with an axial proton at C_3 ($J_{1,6}$ in IX is 1·9 c/s).

The above NMR discussion has provided evidence for the nature of the functionality in ring A of the three hydroboration products. We would like to complete our discussion of the NMR data in this series by returning to one of the characteristic features present in *all* the NMR spectra of the N-benzyl-6-aza-7-one steroid derivatives which we have synthesized in our laboratory. We refer now to the pair of doublets ($J = 16$ c/s) which are typically shown in Fig. 1, and which are due to the methylene protons of the benzyl group. The absorption pattern is typical of an AB system, and it is of some interest to comment on it briefly.

It has been recognized for some time that geminal protons adjacent to any dissymmetric moeity are magnetically non-equivalent and often couple with each other in the NMR spectrum. The earlier work[13, 14] suggested that this feature was characteristic of the methylene protons when this group was adjacent to an asymmetric center, although later studies revealed that this latter requirement was unnecessary. Recent publications from two laboratories[15, 16] have provided results on the magnetic non-equivalence of benzylic methylene protons in various heterocyclic bases, while two other groups have presented data in the phthalimidine[17] and imidazolidinone[18] series which are even more directly pertinent to the present discussion. In the two latter instances, the N-benzyl group is attached through the nitrogen atom to an asymmetric center. In the present investigation, we have available a somewhat different system in which the majority of the compounds do not contain an asymmetric center in the immediate vicinity of the benzylic protons. Table 1 summarizes the data for a variety of N-benzyl-6-aza-7-one steroid analogues, and illustrates the relative effect of the functionality in ring A on the chemical shifts of these protons.

TABLE 1. NMR DATA (100 Mc/s) ON BENZYLIC PROTONS

Compound	Protons	Line positions (c/s separation from TMS)	Chemical shift τ-scale	Chemical shift difference, ppm
I (see Ia)	a, b	528, 512	4·80	0·68
		460, 444	5·48	
IV (see IVa)	a, b	522, 506	4·86	0·62
		460, 444	5·48	
IVb	a, b	522, 506	4·86	0·57
		465, 449	5·43	
V (see Va)	a, b	512, 496	4·96	0·43
		469, 453	5·39	
VI (see VIa)	a, b	520, 504	4·88	0·64
		456, 440	5·52	
VII (see VIIa)	a, b	516, 500	4·92	0·32
		484, 468	5·24	

The difference between the chemical shifts of these two protons is possibly rationalized on the basis of preferred conformations in these compounds. Molecular models reveal that minimum interactions between the phenyl group and the neighboring atoms occur when this group lies in a plane approximately perpendicular to the plane of the lactam system which represents ring B in the 6-aza steroids. As the conformational structures IVa, Va and VIa indicate, this situation places the two geminal protons (H_a and H_b) in different environments. Clearly, H_a would be influenced by the lactam CO group, while H_b is in close proximity to the C_4 olefinic linkage in the ring A unsaturated 6-aza compounds. Since the relative effects on these two protons is difficult to ascertain, it is not possible to make definite predictions as to which proton is deshielded.

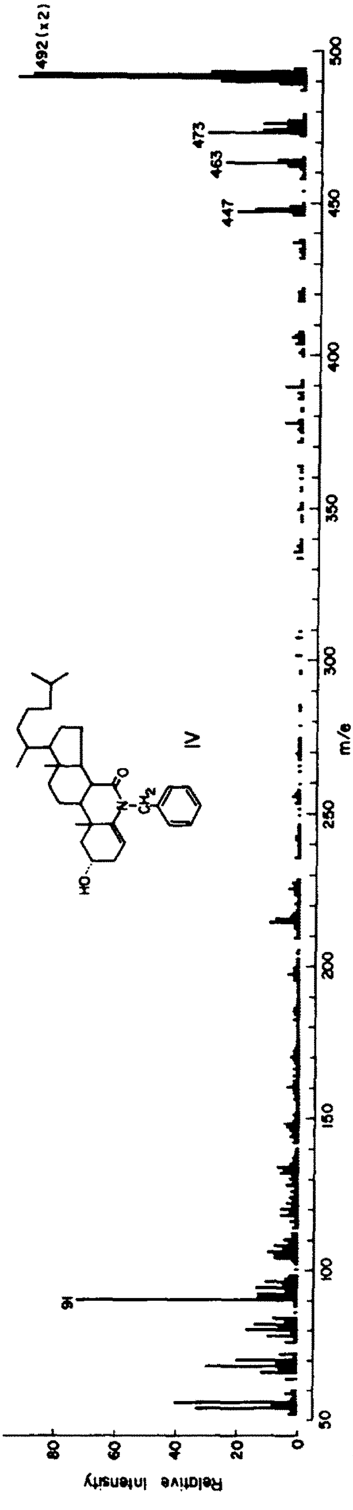
Although the NMR data mentioned above provided good support for the structures of the three hydroboration products, we felt that it would be desirable to obtain some chemical evidence to substantiate the proposed formulations. It was clear that the most direct confirmation of the suggested structures would involve simple dehydration to the parent diene III.

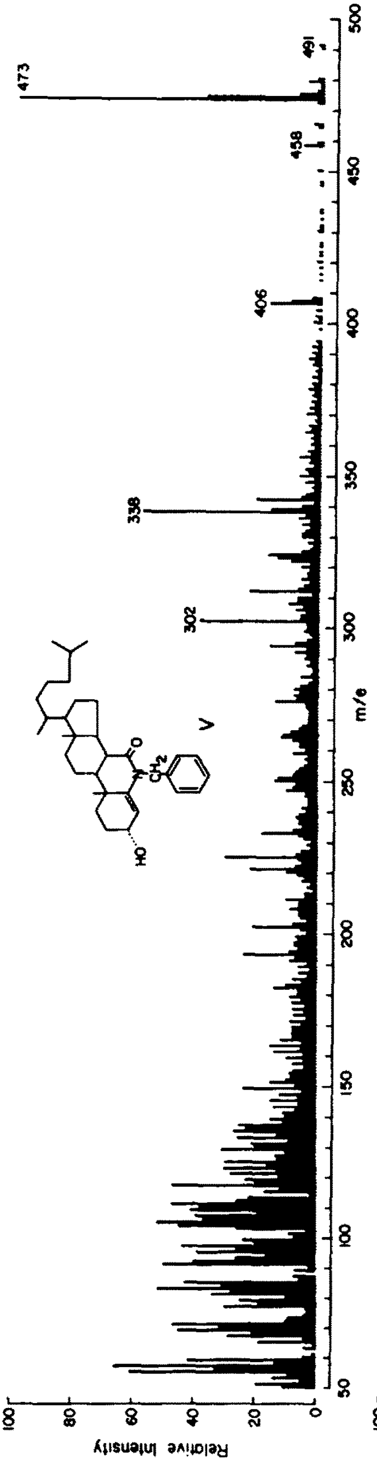
The elimination of water from V and VI to yield the starting diene III was readily demonstrated in several ways. The instability of the axial isomer, 3α-hydroxy-N-benzyl-6-aza-cholest-4-ene-7-one (V), was immediately apparent during its attempted purification. Column or thin-layer chromatography of this compound on alumina immediately led to a partial conversion to the diene III. In fact, it was only possible to obtain pure V by very rapid manipulations during the purification procedure. Even on standing, this substance has a tendency to dehydrate in part to the starting diene. On the other hand, the equatorial 3β-hydroxy derivative VI was considerably more stable, and its purification was not quite so difficult. Dehydration occurs to a lesser extent, and it was possible to purify this compound by chromatographic procedures with only a small loss by conversion to the diene.

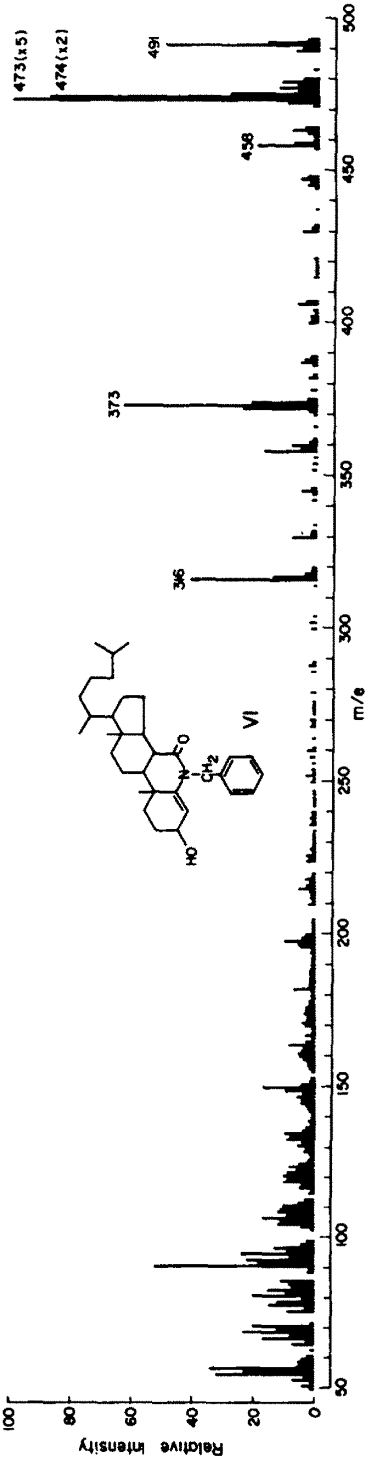
The relative ease of dehydration was again evident in the attempted acetylation of V and VI. In both instances, reaction with acetic anhydride and pyridine provided, as one of the major components, the diene III. In each case, some acetylation had occurred as indicated by the appropriate CO absorption in the IR spectrum of the crude reaction mixture, but isolation of the pure compounds was rendered impossible by their consistent tendency to convert to the diene.

A rather dramatic difference in the ease of dehydration was also noted in the mass spectra of the isomeric 3-hydroxy compounds V and VI (Fig. 2). It will be seen that the molecular ion peak (*m/e* 491) is very weak in the mass spectrum of V, whereas the M-18 fragment (*m/e* 473) forms the base peak. A relative comparison of the intensities of the corresponding peaks in the spectrum of VI reveals immediately the difference in the ease in which water is lost from these two compounds.

Turning now to the 2-OH derivative IV, the experimental results indicated that this compound was considerably more stable than the above mentioned hydroboration products. Chromatographic purification could be achieved without difficulty, and reaction of this material with acetic anhydride and pyridine provided the acetate derivative. This latter compound exhibited the expected spectral features in the IR and UV spectra (1740 cm^{-1}, λ_{max} 237 mμ), and when subjected to high resolution mass spectrometry, the molecular formula, $C_{35}H_{51}O_3N$, was established. Saponification of the latter regenerated, in part, the starting material IV, but provided


492 (x2)
473
463
447
91
HO
N
CH2
O
IV
Relative Intensity
0
20
40
60
80
m/e
50
100
150
200
250
300
350
400
450
500


473
491
458
406
338
302
HO
N
CH2
O
V
Relative Intensity
0
20
40
60
80
100
m/e
50
100
150
200
250
300
350
400
450
500


473 (x5)
474 (x2)
491
458
373
316
HO
N
CH2
O
VI
Relative Intensity
0
20
40
60
80
100
m/e
50
100
150
200
250
300
350
400
450
500

in addition a small amount of the diene III. The isolation of this latter substance demonstrated that dehydration is also feasible in this system, but somewhat more forcing conditions are necessary than in the two previous compounds mentioned above.

The final step in the synthetic sequence involved oxidation of the alcoholic functions. These results would not only provide further evidence in support of the proposed structures, but they would hopefully yield the desired Δ^4-3-keto chromophore in ring A. Several different experiments were conducted, and these are discussed in succession.

Oxidation of VI with chromium trioxide in acetone (Jones reagent) or pyridine (Sarett reagent) provided a smooth conversion to a new crystalline compound, m.p. 173–174·5°, $C_{33}H_{47}O_2N$, which exhibited spectral properties in accord with the 3-keto structure VII. Of particular note was the UV spectrum which revealed rather dramatic changes in the absorption maxima on the addition of alkali to the alcohol solution of this compound (λ_{max}^{EtOH} 284 mμ; λ_{max} 287 mμ, after addition of a few drops of 0·1N NaOH and allowing it to stand for 5 min; λ_{max} 292 mμ, after 30 min and

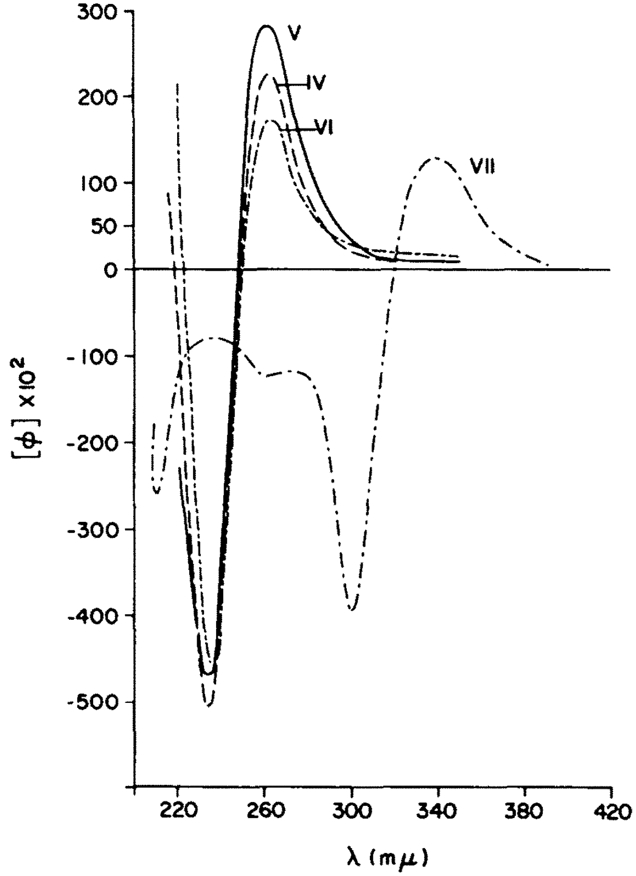


Fig.3. ORD Curves

λ_{max} 294 mμ, after 3 hr in presence of 0·1N NaOH). The bathochromic shift (237 mμ → 284 mμ) observed in neutral solution and the spectral changes in alkali are in excellent agreement with those reported by Ban *et al.*,[20] for an identical chromophore. In similar fashion, there was also a marked alteration in the ORD curve of the oxidation product when compared to the typical Cotton effect already known in the enol lactam systems[21] and observed in VI and the other two hydroboration products (Fig. 3). These results were sufficient to establish the structure of the oxidation product, although other spectral results are given in the experimental section.

In a similar manner, compound V was oxidized to VII. This latter experiment provided conclusive evidence that the only difference in the structures of V and VI was one of stereochemistry at C_3, as had been previously suggested from the NMR data. Furthermore, the above arguments, when considered collectively, now establish that the structure IV, previously assigned to the third hydroboration product, was correct.

In subsequent experiments, it was advantageous to merely subject the total hydroboration mixture to oxidation and isolate the desired Δ^4-3-keto-6-aza steroid VII. In this way, considerably better yields of the latter compound could be obtained.

In conclusion, the hydroboration of N-benzyl-6-aza-2,4-cholestadien-7-one provides 2α- and the two C_3 isomeric hydroxy derivatives. The observed selectivity of diborane in forming a predominance of C_2 hydroboration products over C_3 may be due to the ability of the enol lactam system to stabilize the transition state which would give IV over that which leads to V and VI.

This work now completes a synthetic entry into the ring A-oxygenated 6-aza steroids of the cholestane series. Since the appropriate unsaturated lactam system required for hydroboration is also available in the pregnane and androstane series, the extension to these novel compounds is also obvious.

EXPERIMENTAL

M.ps were determined on a Koffler block and are uncorrected. UV spectra were measured in MeOH soln on a Cary 11 spectrophotometer, and IR spectra were taken as KBr pellets on a Perkin-Elmer Model 21 spectrophotometer. NMR spectra were recorded at 60 megacycles/s on a Varian A-60 instrument and at 100 megacycles/s on a Varian HA-100 instrument, using $CDCl_3$ as solvent; the line positions or centres of multiplets are given in the Tiers τ scale with reference to TMS as the internal standard; the multiplicity, integrated areas and type of protons are indicated in parentheses. Only the values obtained at 100 megacycles/s are recorded below. The mass spectra were taken on an Atlas CH4 mass spectrometer, using the direct insertion technique, the electron energy being maintained at 70 eV. The high resolution mass spectra for the determination of molecular formulae were obtained on an AEI MS9 mass spectrometer. The ORD curves were taken in MeOH soln on a JASCO UV/ORD/CD-5 spectropolarimeter.

In all experiments, the TLC plates were prepared from neutral alumina (Woelm), to which 1% by wt of a fluorescent indicator (Electronic phosphor, General Electric Co.) was added. Antimony trichloride in glacial AcOH or 50% aqueous orthophosphoric acid were used as the spray reagents. In general, the plates were heated for 10 min at 100° after spraying, during which time, the compounds were recognized as blue spots on the chromatoplates. The solvent systems utilized benzene and $CHCl_3$, and these are indicated below in parentheses.

For column chromatography, neutral alumina (Woelm) was used in all cases, and deactivation was done by the addition of water. The approximate activity of the adsorbent utilized in specific experiments is indicated below.

N-*Benzyl-6-aza-2,4-cholestadien-7-one* (III)

Compound II (2.2 g) was taken up in benzylamine (5 ml), and the mixture refluxed for 15 hr under an atm of N. The cooled reaction mixture was treated with ether, and the latter was washed with dil HCl aq to remove excess benzylamine. The separated ether soln was washed with 5% NaOH aq and water, and finally, dried over $MgSO_4$. Removal of the solvent *in vacuo*, initially on a steam bath, and finally, at 200–220°/0·1 mm, provided a yellow-brown glass (2·0 g). Chromatography of this reaction product on alumina (200 g, activity IV) yielded III (1·2 g) as a colorless viscous oil. All attempts to obtain the product in crystalline form failed, although its purity was established by TLC (benzene), λ_{max} (log ε): 297 mμ (3·73); ν_{max}: 1670, 1638 and 1575 cm^{-1} (diene lactam); NMR: 2·88 (multiplet, 5H, aromatic), 4·24, 4·60, 4·95, 5·09 (multiplets, 5H, olefinic H and $—NC\underline{H}_2C_6H_5$). (Found: 473·365. Calc. for $C_{33}H_{40}NO$: 473·365).

Catalytic reduction of N-*benzyl-6-aza-2,4-cholestadien-7-one*

The lactam III (50 mg) was dissolved in EtOH (10 ml), and to this soln, 10% Pd–C (30 mg) was added. The reduction was allowed to proceed for 30 min, during which time, one mole H_2 had been absorbed. Removal of the catalyst and evaporation of the solvent yielded the reduction product (45 mg), which was identical in every respect (IR, mixed m.p., UV, TLC) with the known enol lactam I.[3,4]

Hydroboration of N-*benzyl-6-aza-2,4-cholestadien-7-one*

The lactam III (1·2 g) was dissolved in anhyd diglyme (24 ml) and placed in a small 3-necked flask. Diborane gas generated in another vessel was then slowly passed into this mixture kept at 0° over a period of 2 hr. The reagent was prepared from $NaBH_4$ (630 mg) in diglyme (17 ml) to which a soln of BF_3–Et_2O (2·8 ml) in diglyme (12 ml) was slowly added over a period of 2 hr.

The reaction mixture was immediately treated with 5% NaOH aq (45 ml) and 30% H_2O_2 aq (12 ml), and after allowing to stand for 5 min, it was extracted with ether. The ether extract was thoroughly washed with water and 5% $FeSO_4$ aq soln. After drying over $MgSO_4$, and evaporation of the solvent, a slightly yellow amorphous material (1·1 g) was obtained. Trituration of the latter with pet. ether caused some separation of a white solid (m.p. 133–136°), However, for the chromatographic separations mentioned below, the total crude product was always used.

The crude reaction product was initially shown by TLC to be a mixture of 3 components ($CHCl_3$, R_f values of 0·49, 0·50 and 0·60). A detailed investigation on the possibility of utilizing preparative TLC as a method of separation was carried out, and a typical experiment is described.

The crude hydroboration mixture (120 mg) was placed on an air-dried chromatoplate (60 × 20 cm, 65 g of adsorbent, 0·4 mm approximate thickness), and the plate was developed in $CHCl_3$. Removal of the zones and extraction with MeOH–ether (1:1) provided a fraction (10 mg) subsequently shown to be VI, another fraction (69 mg, IV), and a third fraction (22 mg, V). The recovery (101 mg, 80%) was consistently good in this separation.

For larger scale separations, careful column chromatography could be utilized. For this purpose, alumina (activity IV) was the most desirable adsorbent, and benzene was the eluting solvent. In a typical separation, the crude hydroboration mixture (2·4 g obtained in another experiment) was chromatographed on alumina (200 g). Careful elution with benzene yielded a total of 46 fractions (50 ml each), which were then examined on TLC. Fractions 13–17 (230 mg) were combined and contained mainly V and a trace of IV. Fractions 18–24 (630 mg) were combined and contained mainly VI and traces of IV.

Each of these combined portions were rechromatographed (ratio of adsorbent:material of 100:1) to finally yield pure V (210 mg, R_f 0·60), IV (570 mg, R_f 0·50), and VI (110 mg, R_f 0·49).

In each instance, the column chromatographic separation was complicated by decomposition of the compounds. It will be noted that considerably less than half (only 890 mg from 2·2 g) of the desired hydroboration products were recovered. Appreciable dehydration of both V and VI to the lactam III was always observed, whereas IV was stable and could be purified without difficulty.

In general, the TLC technique was superior in overall separation and recovery, although obviously more tedious in its application.

The data obtained for the three hydroboration products is as follows:

3β-*Hydroxy*-N-*benzyl-6-aza-4-cholesten-7-one* (VI). M.p. 176–178° (crystallized in ether–hexane); λ_{max} (log ε): 237 mμ (4·03); ν_{max}: 3460 (OH), 1667 and 1630 cm^{-1} (enol lactam); NMR: 2·90 (multiplet, 5H, aromatic), 4·88 (doublet, $J = 16$ c/s, 1H, H_a of $—NC\underline{H}_2C_6H_5$ group, see VIa), 5·52 (doublet, $J = 16$ c/s, 1H, H_b of $—NC\underline{H}_2C_6H_5$ group, see VIa), 5·18 (doublet, $J = 2$ c/s, 1H, olefinic), 5·93 (broad multiplet, 1H, $>C\underline{H}OH$); ORD: (Fig. 3, C, 0·0999 mg/ml), $[\phi]_{350}$ +1472, $[\phi]_{300}$ +2945; $[\phi]_{263}$ +17,700 (peak), $[\phi]_{250}$ 0, $[\phi]_{236}$ −46,300 (trough), $[\phi]_{218}$ +21,600. (Found: 491·371. Calc. for $C_{33}H_{49}NO_2$: 491·376)

3α-*Hydroxy*-N-*benzyl-6-aza-4-cholesten-7-one* (V). M.p. 151–153° (crystallized from ether–hexane). λ_{max} (log ε): 237 mμ (4·01); ν_{max}: 3510 (OH), 1670 and 1635 cm^{-1} (enol lactam); NMR: 2·90 (multiplet, 5H, aromatic), 4·96 (doublet, J = 16 c/s, 1H, H_a of $—N\underline{CH}_2C_6H_5$ group, see Va), 5·39 (doublet, J = 16 c/s, 1H, H_b of $—N\underline{CH}_2C_6H_5$ group, see Va), 5·04 (doublet, J = 5·25 c/s, 1H, olefinic), 5·89 (broad multiplet, 1H, $\rangle C\underline{H}OH$); ORD: (Fig. 3, C, 0·0948 mg/ml), $[\phi]_{350}$ +1037, $[\phi]_{300}$ +3630, $[\phi]_{261}$ +28,500 (peak), $[\phi]_{248}$ 0, $[\phi]_{235}$ −47,700 (trough), $[\phi]_{220}$ −23,300. (Found: 491·371. Calc. for $C_{33}H_{49}NO_2$: 491·376.)

2α-*Hydroxy*-N-*benzyl-6-aza-4-cholesten-7-one* (IV). M.p. 144–145·5° (crystallized from aqueous MeOH), λ_{max} (log ε): 237 mμ (4·01); ν_{max}: 3460 (OH), 1670 and 1630 cm^{-1} (enol lactam); NMR: 2·90 (multiplet, 5H, aromatic), 4·86 (doublet, J = 16 c/s, 1H, H_a of $—N\underline{CH}_2C_6H_5$ group· see IVa), 5·48 (doublet, J = 16 c/s, 1H, H_b of $—N\underline{CH}_2C_6H_5$ group, see IVa), 5·28 (quartet, $J_{3e,4}$ = 2 c/s, $J_{3a,4}$ = 5·25 c/s, 1H, olefinic), 6·17 (broad multiplet, 1H, $\rangle C\underline{H}OH$); ORD: (Fig. 3, C, 0·0973 mg/ml), $[\phi]_{330}$ +1010, $[\phi]_{300}$ +2020, $[\phi]_{262}$ +22,950 (peak), $[\phi]_{248}$ 0, $[\phi]_{234}$ −51,000 (trough), $[\phi]_{216}$ +8080. (Found: 491·373. Calc. for $C_{33}H_{49}NO_2$: 491·376.)

Acetylation of hydroboration products

Attempts to obtain the acetate derivatives of IV, V and VI were only partially successful. The isomeric C_3-hydroxy compounds (V and VI) could not be successfully acetylated (Ac_2O, pyridine), since both compounds led to a mixture of the desired acetates (IR data only) and the lactam III. Further chromatographic purification of the acetylation mixture merely provided for further conversion of the acetate to the lactam III.

The experiment was more successful in the conversion of IV and is described.

The 2α-hydroxy-6-aza steroid IV (25 mg) was treated with pyridine (0·5 ml) and Ac_2O (0·5 ml), and the mixture was heated for 25 min at 70°. The cooled mixture was poured onto ice water, and the white ppt which formed was separated and dried (22 mg). This material was recrystallized from ether–MeOH to yield the pure acetate (10 mg), m.p. 156–157·5°; λ_{max} (log ε): 237 mμ (4·08); ν_{max}: 1740 and 1245 (OAc), 1670 and 1643 cm^{-1} (enol lactam); NMR: 2·90 (multiplet, 5H, aromatic), 4·86 (doublet, J = 16 c/s, 1H, H_a of $—N\underline{CH}_2C_6H_5$ group, see IVb), 5·43 (doublet, J = 16 c/s, 1H, H_b of $—N\underline{CH}_2C_6H_5$ group, see IVb), 5·26 (quartet, $J_{3e,4}$ = 2·4 c/s, $J_{3a,4}$ = 5·8 c/s, 1H, olefinic), 5·03 (broad multiplet, 1H, CHOAc), 8·05 (singlet, 3H, CH_3CO). (Found: 533·383. Calc. for $C_{35}H_{51}NO_3$: 533·387.)

Saponification of 2α-*acetoxy*-N-*benzyl-6-aza-4-cholesten-7-one*

The above acetate (5 mg) was taken up in a mixture of EtOH (1 ml) and 1N KOH (0·3 ml), and the mixture allowed to stand for 10 min at 20°. The reaction mixture was made acidic by the addition of 1M AcOH in EtOH, and then evaporated to dryness. The residue was extracted with $CHCl_3$, and this extract was placed on a chromatoplate ($CHCl_3$). Two zones were eluted from the plate (MeOH–ether 1:1)—one of these was shown to be IV (2 mg), and the other was the lactam III (1 mg).

Oxidation of hydroboration products

A series of experiments were performed on the isolated pure products, as well as on the crude hydroboration mixture. CrO_3 in acetone (Jones reagent) and in pyridine (Sarett reagent) gave identical results. Several typical experiments are described.

The derivative IV (22 mg) was treated for 12 hr at room temp with CrO_3 (30 mg) in pyridine (1 ml). After this time, MeOH (0·5 ml) was added and the reaction mixture was evaporated to dryness. The residue was taken up in $CHCl_3$, and the concentrated $CHCl_3$ extract was placed directly on a thin-layer chromatoplate and separated (benzene–$CHCl_3$ 1:1). The material which was eluted from the plate with ether–MeOH was recrystallized from ether–hexane to provide a pure sample of VII (5 mg), m.p. 173–174·5°; λ_{max} (log ε): 284 mμ in neutral MeOH soln (4·39): 287 mμ, after 5 min in the presence of 0·1N NaOH (4·33); 292 mμ, after 30 min in the presence of 0·1N NaOH (4·06); 294 mμ, after 3 hr in contact with alkali (4·32); 296 mμ, after 20 hr in contact with alkali (4·31); ν_{max}: 1680, 1665 and 1590 cm^{-1} (ketone and lactam CO); NMR: 2·88 (multiplet, 5H, aromatic), 4·92 (doublet, J = 16 c/s, 1H, H_a of $—N\underline{CH}_2C_6H_5$ group, see VIIa), 5·24 (doublet, J = 16 c/s, 1H, H_b of $—N\underline{CH}_2C_6H_5$ group, see VIIa), 4·60 (singlet, 1H, olefinic); ORD: (Fig. 3, C, 0·103 mg/ml), $[\phi]_{400}$ +950, $[\phi]_{340}$ +13,070 (peak), $[\phi]_{320}$ 0, $[\phi]_{300}$ −29,400 (trough), $[\phi]_{270}$ −11,880, $[\phi]_{260}$ −12,360, $[\phi]_{230}$ −8070, $[\phi]_{208}$ −18,040. (Found: 489·362. Calc. for $C_{33}H_{47}NO_2$: 489·361.)

A similar oxidation of V (20 mg) provided VII (4 mg). The latter compound was shown to be identical in every respect (mixed m.p., IR, TLC) with the above oxidation product.

The crude mixture (53 mg) taken directly from the hydroboration reaction was oxidized with CrO_3 (85 mg) in pyridine (2·2 ml) for 12 hr at room temp. Addition of MeOH (2 ml), and workup of the reaction mixture as described above provided the crude oxidation product. The latter was again subjected to TLC separation, and the eluted material (13 mg) was crystallized from ether–hexane to provide pure VII (11 mg).

REFERENCES

[1] Part VI. J. P. Kutney and C. Gletsos, *Steroids* **7**, 67 (1966).
[2] T. L. Jacobs and R. B. Brownfield, *J. Am. Chem. Soc.* **82**, 4033 (1960).
[3] J. P. Kutney and R. A. Johnson, *Chem. & Ind.*, 1713 (1961).
[4] J. P. Kutney, R. A. Johnson and I. Vlattas, *Canad. J. Chem.* **41**, 613 (1963).
[5] J. P. Kutney, I. Vlattas and G. V. Rao, *Ibid.* **41**, 958 (1963).
[6] J. P. Kutney and I. J. Vlattas, *Steroids* **4**, 595 (1964).
[7] H. C. Brown, *Hydroboration*. Benjamin, New York (1962).
[8] E. W. Garbisch, *J. Am. Chem. Soc.* **86**, 5561 (1964).
[9] L. D. Hall and L. F. Johnson, *Tetrahedron* **20**, 883 (1964).
[10] L. D. Hall, *J. Org. Chem.* **29**, 297 (1964).
[11] R. J. Abraham, H. Gottschalck, H. Paulsen and W. A. Thomas, *J. Chem. Soc.* 6268 (1965).
[12] R. D. Haugwitz, P. W. Jeffs and E. Wenkert, *Ibid.* 2001 (1965).
[13] J. J. Drysdale and W. D. Phillips, *J. Am. Chem. Soc.* **79**, 319 (1957).
[14] P. M. Nair and J. D. Roberts, *Ibid.* **79**, 4565 (1957).
[15] R. K. Hill and Tak-Hang Chen, *Tetrahedron* **21**, 2015 (1965).
[16] R. W. Horobin, J. McKenna and J. M. McKenna, *Ibid.* Supplement No. 7, 35 (1966).
[17] A. H. Lewin, J. Lipowitz and T. Cohen, *Tetrahedron Letters* 1241 (1965).
[18] P. L. Southwick, J. A. Fitzgerald and G. E. Milliman, *Ibid.* 1247 (1965).
[20] Y. Ban, Y. Sato, I. Inoue, M. Nagai (née Seo), T. Oishi, M. Terashima, O. Yonemitsu and Y. Kanaoka, *Tetrahedron Letters* 2261 (1965).
[21] J. P. Kutney, G. Eigendorf and J. E. May, *Chem. Commun.* 59 (1966).