On the Synthesis and the Stareochemical Study of Several α - Bromo - 6 - oxo - steroids Derived from Cholesterol.

On the Synthesis and the Stereochemical Study of Several α-Bromo-6-oxo-steroids Derived from Cholesterol.

Masayuki KUNIYOSHI*

Synopsis

3β-Acetoxy-5α-cholestan-6-one was prepared via several synthetic pathways from cholesterol. It was further converted into brmo-derivatives; 5α-bromo-, 5α,7α-dibromo-, and 5α,7β-dibromo-6-oxo compounds, in low yields by treatment with bromine in acetic acid containing a trace of hydrogen bromide at room temperature. It was found that the C_5-bromo atom of the 3β-acetoxy-5α-bromocholestan-6-one rearranges to the $C_7\alpha$ position, but not to the $C_7\beta$ position, by hydrogen bromide in acetic acid to give 7α-bromo-6-oxo compound. Stereochemical studies of these prepared α-bromo-6-oxo compounds were carried out by means of IR, NMR and ORD spectroscopic methods.

1. Introduction

It is well known that cholesterol is an important precursor of steroid hormons, and a constituent of all normal tissues of the animal organisms. In our laboratory, we have been studying the halogenation[1] and the reductive dehalogenation of 5α- and 5β-steroids which possess an oxo group on each position in ring A and B. In this paper, the conformations of some α-bromo-6-oxo steroids, which was derived from cholesterol, are discussed.

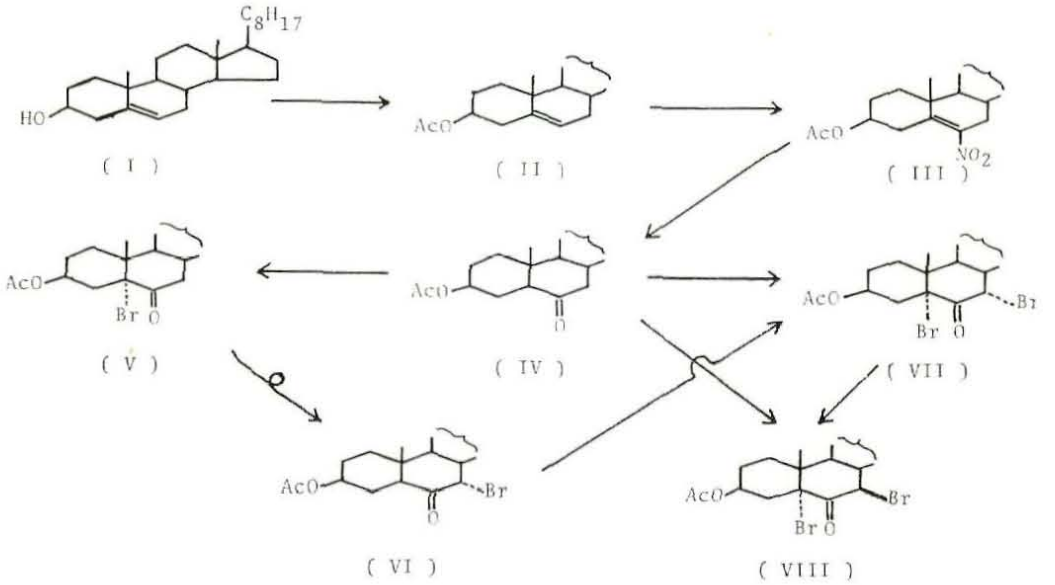
They are determined by signs of the Cotton effect in optical rotatory dispersion (ORD), the shifts of C=O stretching bands in infra-red (IR) spectra, and the pattern of the nuclear magnetic resonance (NMR) spectra. Furthermore, the author would like to describe a few reactions from the stereochemical viewpoint in order to clarify the properties of these produced α-bromo-6-oxo derivatives.

2. Results and Discussion

In the work described in this paper, the author found that the 3β-acetoxy-5α-bromocholestan-6-one (V); mp 158–160℃, IR: 1738, 1708cm^{-1} ($\nu_{c=o}$), was converted into 7α-bromoketone (VI); mp 140–142.5℃, IR: 1736, 1712cm^{-1} ($\nu_{c=o}$), by hydrogen bromide in acetic acid at room temperature (see Scheme 1. and experimental section). The ORD spectrum of this 7α-brmoketone (VI) showed a positive sign of the Cotton effect; $[\alpha]_{589}+15.9$, $[\alpha]_{336}+1750.0$ (peak), $[\alpha]_{290}-2195.5$ (trough) in dioxane at 22℃, in contrast with a negative Cotton curve of the 5α-bromoketone (V) (see Fig. 1.

Received: April 30, 1975

* Dept. of General Education



Scheme 1. Synthetic pathways of 3β-Acetoxy-α,α'-bromocholestan-6-one

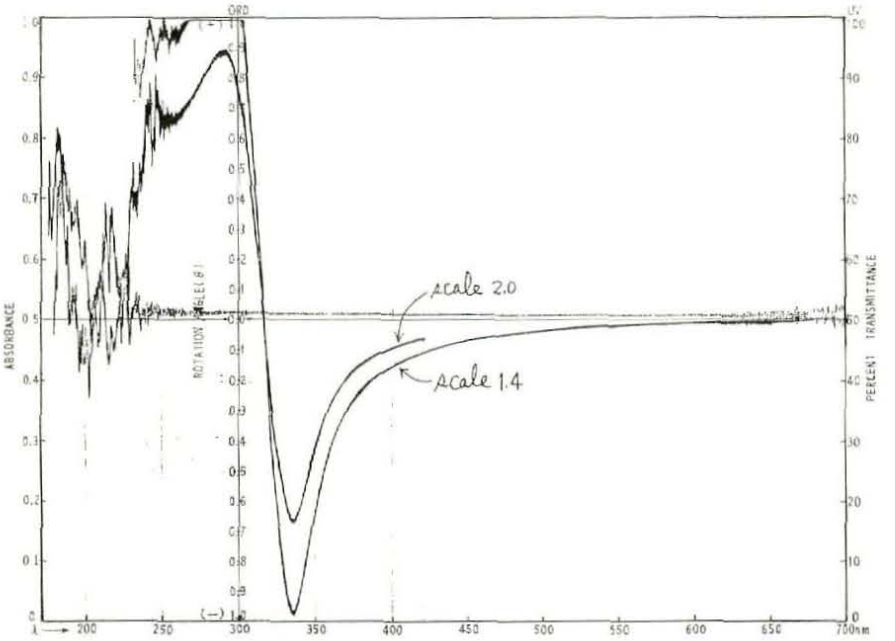


Fig. 1. ORD spectrum of 3β-Acetoxy-5α-bromocholestan-6-one
(C, 0.4110 in dioxane at 22℃)

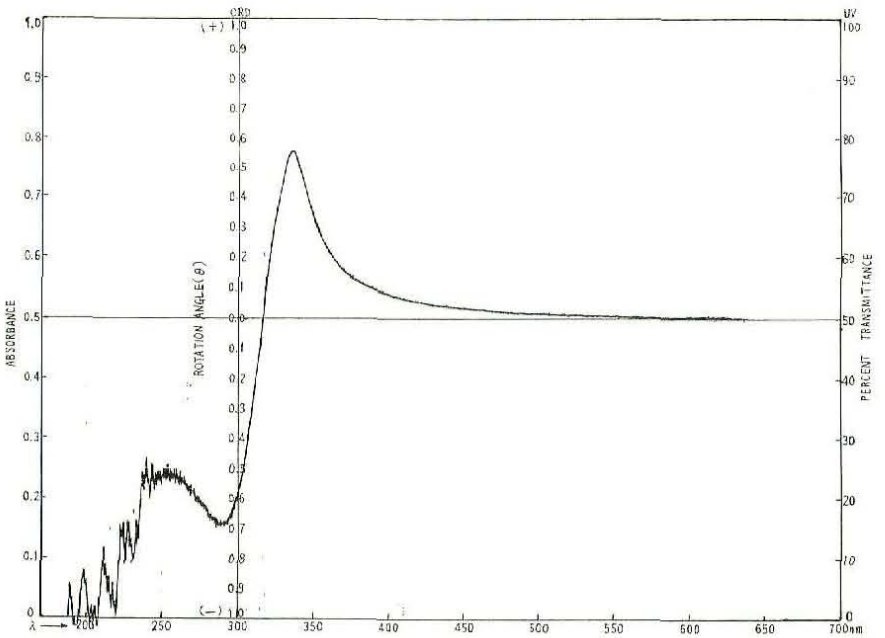


Fig. 2. ORD spectrum of 3β-Acetoxy-7α-bromocholestan-6-one.
(C, 0.5280 in dioxane at 22℃)

and Fig. 2.). The NMR spectrum of the 7α-bromoketone (VI) also appeared as a doublet at τ 5.82 with a small coupling constant (J=2.0Hz) assignable to the 7β-proton of equatorial character. Moreover, either V or VI gave the same dibromoketone derivatives, i.e., 3β-acetoxy-5α,7α-dibromocholestan-6-one (VII), by further monobromination.

From these results, two α-bromoketone V and VI can be confirmed to have the 5α and 7α-configuration, respectively. The 3β-acetoxy-5α,7α-dibromocholestan-6-one (VII) ; mp 151–152.5℃, IR : 1739, 1712cm^{-1} ($\nu_{c=o}$), was also prepared directly from the corresponding 5α-6-oxo compound (IV) by treatment with two equivalent of bromine in acetic acid. Whereas, the prolonged treatment over than 20 hrs. in this bromination condition led to the formation of 5α, 7β-dibromo-6-oxo compound(VIII) in low yield (20%) ; mp 129–131.5℃, IR : 1736, 1730cm^{-1} ($\nu_{c=o}$), which were seemed to be thermodynamically controlled product. Either these obtained dibromoketone VII or VIII showed, in accordance with expections, a simple negative Cotton curve in ORD spectrum (see Fig.3. and Fig.4.). The NMR spectrum of the 5α,7α-dibromoketone (VII) showed a doublet due to the 7β proton (1H, J=6Hz) at τ 5.76. While, that of VIII appeared as doublet due to the 7α proton (1H, J=13Hz) at τ 4.65.

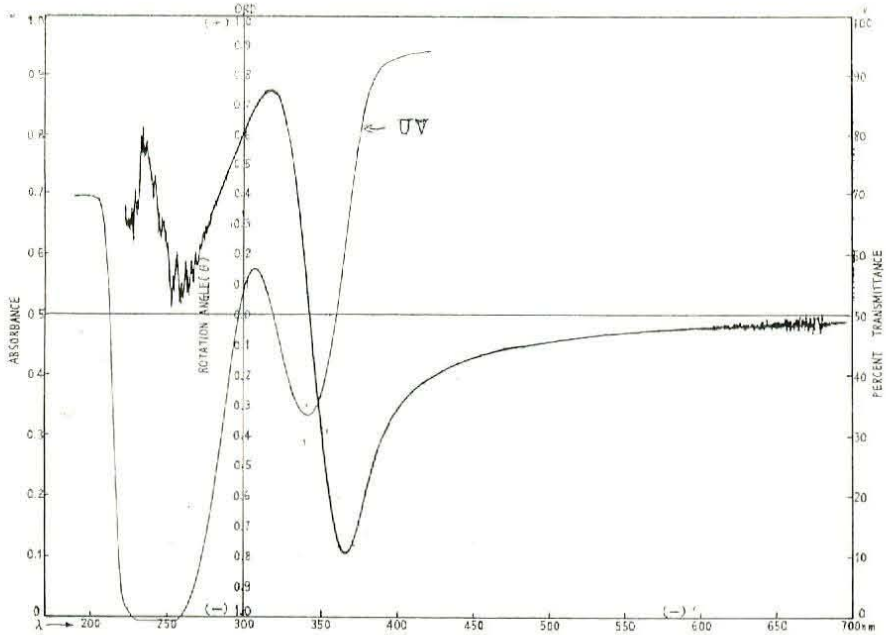


Fig. 3. ORD and UV spectra of 3β-Acetoxy-5α,7α-dibromcholestan-6-one
(C,0.2550 in dioxane at 22℃)

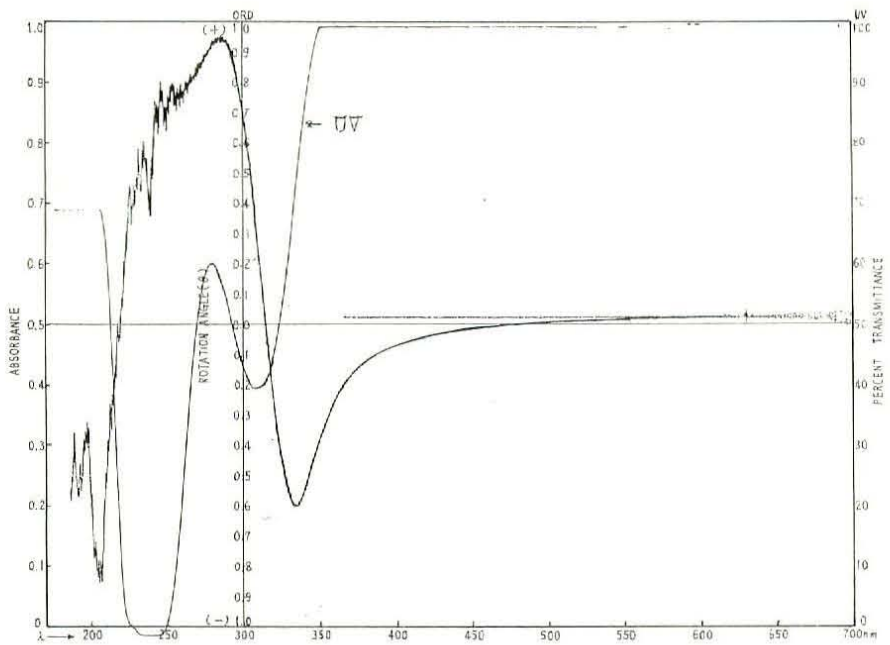


Fig. 4. ORD and UV spectra of 3β-Acetoxy-5α,7β-dibromocholestan-6-one
(C, 0.2550 in dioxane at 22℃)

In order to make evidence whether these interpretations of the NMR spectra were right or not, the dihedral angles (θ) between C_7-and C_8-proton were calculated with the Abraham's equation[2] based on the values of coupling constant (J) from NMR data.

$$J = 12.4\ \mathrm{Cos}^2\theta : \quad 0^\circ \leqq \theta \leqq 90^\circ$$
$$= 14.3\ \mathrm{Cos}^2\theta : \quad 90^\circ \leqq \theta \leqq 180^\circ$$

As shown in Fig.5, the calculated values of θ for VII and VIII were 46° and 168°, respectively.

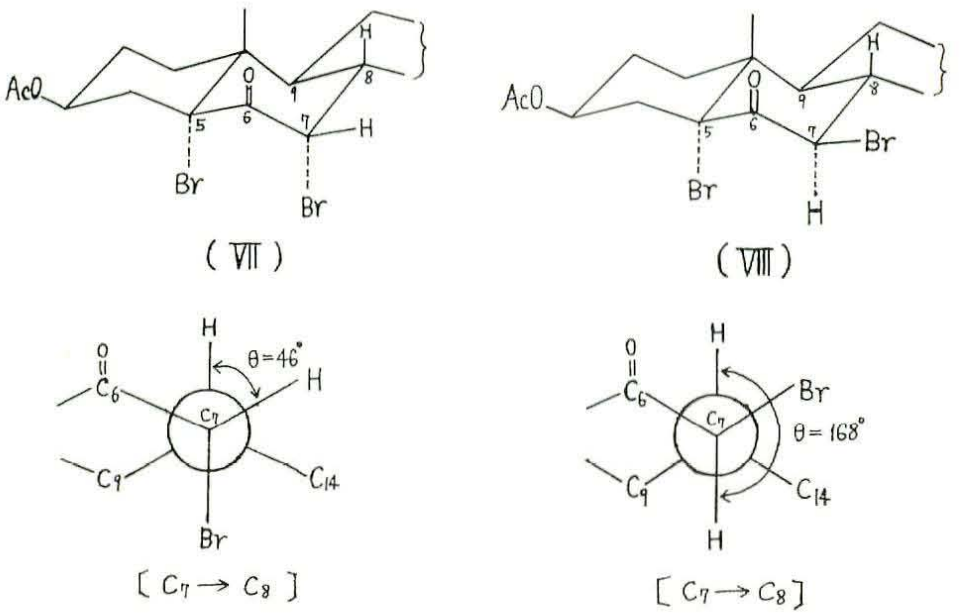


Fig. 5. Dihedral angle between the C_7-and C_8-proton

Table 1. The c=o stretching absorption bands for 6-oxo group of the 5α-cholestan-6-one and its bromo-derivatives in IR spectra.

Bromoketone	$\nu_{c=o}$ (cm^{-1})	$\Delta\nu$*
3β-acetoxy-5α-cholestan-6-one (IV)	1711	—
3β-acetoxy-5α-bromocholestan-6-one (V)	1708	-3
3β-acetoxy-7α-bromocholestan-6-one (VI)	1712	1
3β-acetoxy-5α,7α-dibromocholestan-6-one (VII)	1712	1
3β-acetoxy-5α,7β-dibromocholestan-6-one (VIII)	1730	19

*$\Delta\nu$ is the difference of carbonyl absorption band between the bromoketones and its parent ketone.

These stereochemical assignments mentioned above, were also completely supported by the observation of the IR spectra. The infra-red absorption bands ($\nu_{c=o}$) of prepared bromoketones are summarised in Table 1. In α-haloketone[3], it is well known that the difference ($\triangle\nu$) of frequency in carbonyl absorption between the equatorial-halogenated ketone and its parent keton is greater than that in the case of the axial-halogenated ketone. Therefore, the $\triangle\nu$ value for the compound VII ; $\triangle\nu$= 1, indicates that both bromines are axial (α-oriented) and the $\triangle\nu$ value for the compound VIII ; $\triangle\nu$=19, indicates that one bromine is axial (α-oriented) and another bromine is equatorial (β-oriented).

In the next paper, the author would like to report for the reductive dehalogenation of these α-bromo-6-oxo derivatives prepared in this work.

3 Experimental

Measurements. All melting points are uncorrected. The IR spectra and ORD spectra were measured using a Hitachi EPI-S-2 spectrophotometer and a JASCO model ORD/UV-5 spectrometer, respectively. The NMR spectra were measured in deutero-chloroform and carbon tetrachloride, with TMS as internal standard, using a Hitachi R-24 spectrometer. The mass spectra were obtained using Hitachi RMU-6L spectrometer.

Cholesteryl acetate. According to the method of J.O. Ralls[4], it was prepared by refluxing a solution of cholesterol (I) (10g) in acetic acid anhydride (75ml) for 2 hrs. Cooling, filtering, washing and crystallization from ethanol gave needles (9g), mp 114–115℃, IR (KBr) : 1738cm^{-1} ($\nu_{c=o}$) ; NMR ($CDCl_3$) τ: 5.40 (m, 1H), 4.61 (m, 1H), 7.98 (s, 3H).

6-Nitrocholesteryl acetate[5]. A solution of cholesteryl acetate (2.5g) in absolute ether (35ml) was stirred under cooling at −10℃ by a salt-ice-bath, and then 95% fuming nitric acid (15ml) was added dropwise during one hour. The end point of the reaction was confirmed by tlc. After sterring for 1 hr. more at 0℃, the reaction mixture was poured into water and washed with 5% sodium hydroxide solution. The solution was next washed with saturated sodium chloride solution until the water layer was neutral to litmus. The ethereal solution was the dried and evaporated under reduced pressure. Crystallization of the residue from ethanol gave needles of (III) (2.0g), mp 103–104℃, IR (KBr) : 1519 (ν_{No_2}) and 1745cm^{-1} ($\nu_{c=o}$) ; NMR ($CHCl_3$) τ: 5.35 (m, $W_{1/2}$ =18Hz, C_3-H, 1H), 7.96 (s, 3H).

Found : C, 73.46 ; H, 9.96 ; N, 2.95%. Calcd. for $C_{29}H_{47}O_4N$: C, 73.55 ; H, 9.95 ; N, 2.96%.

3β-Acetoxy-5α-cholestan-6-one. Reduction of III (6.5g) with zinc and acetic acid according to Dodson and Riegel[6] and crystallization from ethanol gave needles of IV (4.0g, 62%), mp 127–129℃, IR (KBr) : 1730, 1711cm^{-1} ($\nu_{c=o}$) ; NMR ($CDCl_3$) τ: 5.45 (m, C_3-H, 1H), 8.05 (s, 3H) ; ORD (C, 0.7680, di.) at 22℃ : $[\alpha]_{317}$−708.3

(trough), $[\alpha]_{310}$ −472 (peak), $[\alpha]_{307}$ −473 (trough), $[\alpha]_{275}$ +723(peak); MS: 444 (M^+), 385 (M−AcO).

Bromination of 3β-acetoxy-5α-cholestan-6-one. For general directions see reference no.7.

(a) 3β-acetoxy-5α-bromocholestan-6-one: (IV) (1.40g), in acetic acid (200ml) containing a trace of hydrogen bromide, was treated at 20℃ with bromine (640mg, 1.05mol) in acetic acid. After 10 min., water was added, and the reaction mixture was extracted with ether. The ethereal solution was washed with sodium bicarbonate solution, dried, and evaporated under reduced pressure. Crystallization from ethanol-acetone gave plates of V (1.2g), mp 158−160℃, IR (KBr): 1738, 1708cm^{-1} ($\nu_{c=o}$), NMR ($CHCl_3$): τ 7.68 (d, J=13Hz, C_4-H, 1H), 7.98 (s, 3H); ORD (C, 0.4100, di.) at 22℃: $[\alpha]_{589}$ −40.9, $[\alpha]_{335}$ −3243.9 (trough), $[\alpha]_{290}$ +4292.6 (peak); MS: 522 (M^+), 524 (M−2).

(b) 3β-acetoxy-7α-bromocholestan-6-one: V (200mg) in acetic acid (50ml) containing a trace of hydrogen bromide was stirred at room temperature for 16hr. The usual procedure gave prismes of VI (from methanol–acetone) (80mg), mp 140−142℃, IR (KBr): 1736, 1712cm^{-1} ($\nu_{c=o}$); NMR ($CHCl_3$): τ 5.82 (d, J=2Hz, $C_7\beta$-H, 1H), 6.72 (dd, $J_{5,4}$=4 and $J_{5,4}$=12Hz, 1H); ORD (C, 0.5280, di.) at 22℃: $[\alpha]_{589}$ +159.1, $[\alpha]_{336}$ +1750.0 (peak), $[\alpha]_{290}$ −2195.5 (trough); MS: 522 (M^+), 524 (M−2).

(c) 3β-Acetoxy-5α,7α-dibromocholestan-6-one and 3β-Acetoxy-5α,7β-dibromocholeslan-6-one: The mixture of 5α-ketone (IV) (1g) and acetic acid (20ml) with a trace of hydrogen bromide was treated with 14.7ml of 5% bromine–acetic acid solution at room temperature for 14hrs. After removal of excess of bromine with aqueous sodium hydrogen sulfite, the reaction mixture was extracted with ether. The ethereal solution was washed with water, dried, and evaporated under reduced pressure. The resultant oil (800mg) was chromatographed on silica gel (50g). Elution with benzen–n-hexane (1:10) (500ml) gave a colorless oil (35mg) of VII. After recrystallization from methanol, mp 151−152℃ (needle), IR (KBr): 1739, 1712cm^{-1} ($\nu_{c=o}$); NMR($CDCl_3$): τ 5.76 (d, $J_{7\beta,8}$=6Hz, 1H); ORD (C, 0,255, di.) at 22℃: $[\alpha]_{589}$ −30.0, $[\alpha]_{365}$ −1510.0 (trough), $[\alpha]_{316}$ +1550.0 (peak).

Found: C, 57.82; H, 7.59%. Calcd. for $C_{29}H_{44}O_4Br_2$: C, 57.83, H, 7.66%. Further elution with benzene–n-hexane (1:5) (900ml) gave a product VIII (20mg), mp 129−131.5℃, IR (KBr): 1736, 1730cm^{-1} ($\nu_{c=o}$); NMR($CHCl_3$): τ 4.65 (d, $J_{7\alpha,8}$ =13Hz, 1H); ORD (C, 0.255, di.) at 22℃: $[\alpha]_{589}$ 0, $[\alpha]_{332}$ −1902.2 (trough), $[\alpha]_{284}$ +2800.0 (peak), after recrystallization from methanol.

Found: C, 57.84; H, 7.66%. Calcd for $C_{29}H_{44}O_4Br_2$: C, 57.83; H, 7.66%.

Acknowledgement

The author wishes to express his deep thanks to Professor J.Y. Satoh of Rikkyo University and Professor Kyoichi Suga of Chiba University for their helpful suggestions and guidance throughout this work. Thanks are also due to Professor Iwao Mori of the University of the Ryukyus for his kind advice.

References

1) E.W. Warnhoff, J.Org.Chem., *28*, 887 (1963) ; F.Sonheimer, G.Rosenkranz, O.Mancera and C.Jerassi, J.Amer.Chem.Soc., *75*, 2601 (1953).
2) R.F.Zurcher, Helv. Chim.Acta., *46*, 2054 (1963) ; A.I.Cohen and S.Rock, Steroids, *3*, 243 (1964).
3) R.C.Cookson, J.Cem.Soc., 282 (1954) ; R.C.Cookson, S.H. Dangegaonker, ibid., 352 (1955).
4) Org.Syn., coll. vol.2, 191 (1950).
5) Constantine, E.A.Nagnostostopoulos and L.F.Fieser, J.Amer. Chem.Soc., 76, 532 (1954).
6) R.M.Dodson and B.Riegel, J.Org.Chem., *13*, 424 (1948).
7) C.W.Shoppee, A.B.Devine, and R.E.Lack, J.Chem.Soc., 6458 (1965) ; C.W.P. Crowne, R.M.Evans, G.F.U.Green and A.G. Aong, J.Chem.Soc., 4351 (1956).