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131. Shoichi Hirai : Angular Substituted Polycyclic Compounds. II.[*1] Reaction of Cholest-4-en-3-one with Metallic Cyano Complexes.

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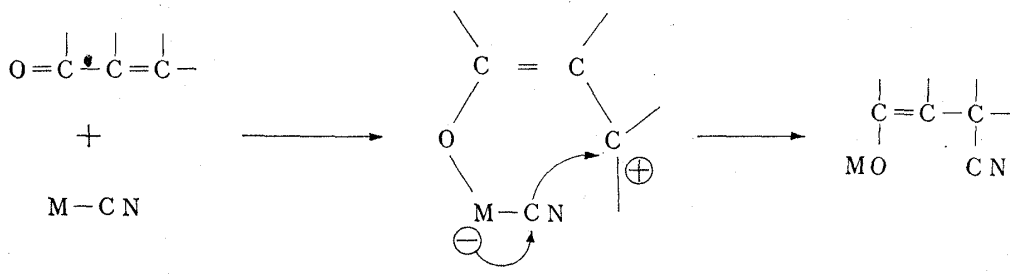
In the preceding paper,[*1] it was shown that the reactions of cholest-4-en-3-one (I) with potassium cyanide alone or in the presence of ammonium chloride in the polar solvents gave 3-oxo-5α-(II) and 3-oxo-5β-cholestane-5-carbonitrile (III), and in the former case the resulted cyano ketones were hydrolyzed simultaneously to form the corresponding acid amides.

In order to prevent this side reaction, it was conceived that the metallic cyano compounds, which are soluble in nonpolar solvents, should be employed. It is known that alkaline earth metal compounds of the type MXn (M=Mg or Al, etc. X=H or alkyl), which are widely employed as the reduction or alkylation agents, are all soluble in the nonpolar solvents such as ether, benzene and tetrahydrofuran. Now, in order to perform the cyanationreaction in the nonpolar medium, some cyano compounds of this type (M=Mg, Al,X=CN), such as CN-Mg-I,[*3] Li[Al $(CN)_4$],[*4] H[Al(*iso*-PrO)$_3$CN][*5] and H[Al (*tert*-BuO)$_3$CN][*5] were selected, which were all actually proved to be soluble at least in warm benzene.

It was also expected that at the same time these agents act as "Lewis acid" because



*1 Part I. W. Nagata, S. Hirai, H. Itazaki, K. Takeda : J. Org. Chem., **26**, 2413 (1961).

*2 Fukushima-ku, Osaka (平井章一).

*3 Addition of the dehyd. ether solution of hydrogen cyanide in the dehyd. ether solution of methyl magnesium iodide gave precipitates, which were assumed to be comprised essentially of CN-Mg-I. See Experimental part.

*4 This reagent was prepared by the method of Wittig and Bille (Z. Naturforsch., 6b, 226 (1951)).

*5 A solution of hydrogen cyanide in dry benzene was added to the benzene solution of aluminum isopropoxide. It should be considered that an equilibrium exists in this solution in the following way.

$$HCN + Al(iso\text{-}PrO)_3 \rightleftharpoons H[Al(iso\text{-}PrO)_3CN]$$

The addition of sodium isopropoxide to this solution gave massive crystalline precipitates, the infrared spectrum of which showed the bands for nitrile and isopropoxyl groups at 2250, 2160, 2060 cm^{-1} and at 1168, 1140, 1005 cm^{-1}. Therefore it was supposed that this compound consisted essentially of a sodium salt of this complex acid, Na[Al(*iso*-PrO)$_3$CN]; see Experimental part. Similarly, the mixture of aluminum *tert*-butoxide and hydrogen cyanide also forms the complex acid, H[Al(*tert*-BuO)$_3$CN]; see H. Meerwein, T. Bersin : Ann., **476**, 113 (1929).

of their electron attracting power, and consequently would facilitate the addition of the cyanide ion at the γ-carbon atom of the α,β-unsaturated ketone as follows:

Refluxing of cholest-4-en-3-one (I) in benzene solution with these cyanating agents actually gave the epimeric 5-cyano compounds and as was expected, none of the hydrolyzed products. As seen in the Table I, the yields were, however, not satisfactory. CN-Mg-I gave 3-oxo-5α-cholestane-5-carbonitrile only in 9.3% yield and the starting material

Table I. Cyanation of Cholest-4-en-3-one (I) with the Metallic Cyano Compounds

No.	Cholest-4-en-3-one (I)		Cyanating agents	dehyd. Benzene	Time (Refluxing)	Products (Yields, %)				
	(mg.)	(m*M*)	(m*M*)	(cc.)	H	(I)	(II)	(III)	(IV)	(V)
1	250	(0.655)	MgCNJ (1.96)	4	8	41.8	9.3	—	—	—
2	250	(0.655)	Li[Al(CN)$_4$] (6.6)	50 (*tert*-BuOH. 10)[a]	4	19.3	27.2	20.0	—	—
3	250	(0.655)	H[Al(*iso*-PrO)$_3$CN] (0.655×5)	28	6	—	—	—	30.8	21.3
4	500	(1.3)	H[Al(*tert*-BuO)$_3$CN] (1.3×5)	40	6	—	26.8	23.5	—	—

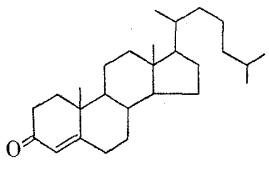
a) In this case, 10 cc. of *tert*-BuOH was employed as a solvent.

was mostly recovered (42%). The better results were obtained with the reagents, Li[Al(CN)$_4$] and H[Al(*tert*-BuO)$_3$CN]. In these cases, the greater part of the starting material was converted into the 3-oxo-5α- (II) and 3-oxo-5β-cholestane-5-carbonitrile (III) (see Table I). Although these results were not so much noticeable, an interesting change took place with H[Al(*iso*-PrO)$_3$CN].

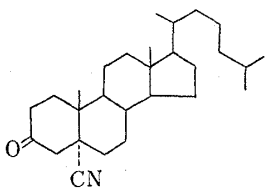
This reagent gave rise not only to cyanation at $C_{(5)}$ of cholest-4-en-3-one, but also to reduction of the 3-ketone, affording a mixture of stereoisomeric 5,3-cyanohydrins as follows.

Cholest-4-en-3-one (I) was treated with aluminum isopropoxide and hydrogen cyanide in boiling dehyd. benzene, and by chromatography on alumina of the crude products, two substances (V) and (IV), m.p. 80~87° and 135~137° were obtained in this order, both of which were proved to be a mixture of the 3-epimeric 5β-cyanohydrins for (V) and of the 3-epimeric 5α-cyanohydrins for (IV) in the following way. The analytical values of these substances were in good agreement with the formula $C_{28}H_{47}ON$ and the infrared spectra in Nujol showed bands corresponding to the nitrile and the hydroxyl groups, but no carbonyl band. Further, the oxidation of both (V) and (IV) with the chromium trioxide-pyridine complex afforded the pure 3-oxo-5β- (III) and 3-oxo-5α-cholestane-5-carbonitrile (II), m.p. 122~123° and 182~184° respectively. From these findings, it was established that (IV) and (V) belonged to the 5α- and 5β-cyano series respectively.

For comparison of (IV) and (V) with the reduction products of 3-oxo-5α- (II) and 3-oxo-5β-cholestane-5-carbonitrile (III), (II) and (III) were subjected to the Meerwein-Ponndorf and sodium borohydride reduction. Separation of the reduction products of the 5β-cyano compound (III) into the 3α- (X) and 3β-cyanohydrin (XI) by chromatography on alumina was successful, while separation of the 3-epimeric reduction products derived from the 3-oxo-5α-carbonitrile (II) failed. Moreover, the 3-epimeric reduction products did not form a digitonide. Thus, the mixture of the reduction products of 3-oxo-5α-cholestane-5-carbonitrile (II) with sodium borohydride was converted to the corresponding *p*-nitrobenzoate, which was then separated successfully by chromatography on alumina into each component, i.e. *p*-nitrobenzoate of (VIII) and (IX). These separated derivatives were returned then to their original alcohol (VIII) and (IX) by the method described below, and this fact furnished definite proof as to the determination of the steric configuration of both (VIII) and (IX) (see below).



(I)



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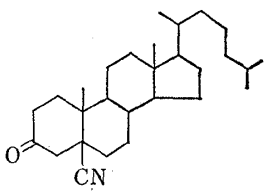

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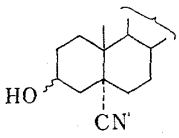
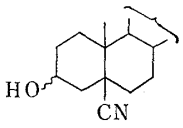
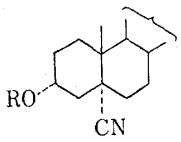


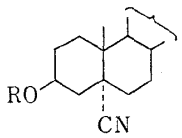
3α- and 3β-(IV)



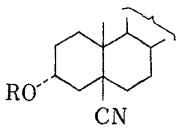
3α- and 3β-(V)



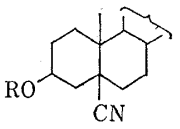
(VIII) R=H
(VI) R=*p*-NO_2-ϕ-CO-



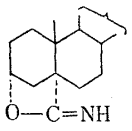
(IX) R=H
(VII) R=*p*-NO_2-ϕ-CO



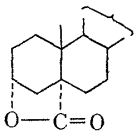
(X) R=H
(XII) R=*p*-NO_2-ϕ-CO-



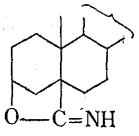
(XI) R=H
(XIII) R=*p*-NO_2-ϕ-CO-



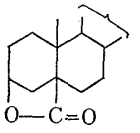
(XIV)



(XV)



(XVI)



(XVII)

An equivalent amount of 3α- (X) and 3β-hydroxy-5β-cholestane-5-carbonitrile (XI) were mixed and recrystallized from petr. ether. The mixed crystal thus obtained melted at 78~83° alone and on admixture with (V) and showed the identical infrared spectrum with that of (V). On the other hand, the mixture of 3α- (VIII) and 3β-hydroxy-5α-cholestane-5-carbonitrile (IX) in an equivalent amount was crystallized from alcohol and gave a mixed crystal of m.p. 134~139°, which showed no depression on admixture with the above-mentioned substance (IV) of m.p. 135~137° and almost the same infrared spectrum. In this way, it was demonstrated that the above-mentioned substances (IV) and (V) were actually the mixture of the 3-epimeric 3-hydroxy-5α- and -5β-cholestane-5-carbonitrile respectively.

For determination of the orientation of the 3-hydroxyl group in the four cyanohydrins, the following experiments were undertaken. The 3α- (X) and 3β-hydroxy-5β-cholestane-5-carbonitrile (XI) were converted into their *p*-nitrobenzoates and the four *p*-nitrobenzoates (VI), (VII), (XII), and (XIII) were treated with dehyd. methanolic hydrochloric acid. While (VII) and (XII) were both readily cleaved with this reagent and afforded the original cyanohydrins (IX) and (X), the other two *p*-nitrobenzoates resisted this ester exchange reaction.

The hydrolysis of the latter two esters, (VI) and (XIII), could be achieved without affecting the cyano group by refluxing with sodium bicarbonate in aqueous methanol. This suggested that the hydroxyl groups in (IX) and (X) had an equatorial character and on the contrary, those in (VIII) and (XI) an axial. The correctness of this assumption was proved by the transformation of (VIII) and (XI) to the γ-lactones (XV) and (XVII) as follows.

3α-Hydroxy-5α-cholestane-5-carbonitrile (VIII) was heated under reflux with dehyd. methanolic hydrochloric acid for 4.5 hours and the crystalline product, m.p. 116~117°, showed in the infrared spectrum a strong imide band at 1671 cm^{-1}. This product was converted by the further treatment with conc. hydrochloric acid in alcohol to the A/B-*trans*-γ-lactone (XV), and moreover readily returned to the starting cyanohydrin (VIII) by the action of alkali or basic alumina. From these facts the formula (XIV) must be afforded to this compound of m.p. 116~117°. The analytical values were also in good agreement with this formula. An analogous reaction occurred with (VIII) by the action of conc. hydrochloric acid in boiling ethanol and chromatography of the product on basic alumina gave lactone (XV) and the starting cyanohydrin (VIII), which was derived apparently from the imidic γ-lactone (XIV) formed as the intermediate. 3β-Hydroxy-5β-cholestane-5-carbonitrile (XI) was then treated with methanolic hydrochloric acid in the same way and the infrared spectrum of the resulted crude product clearly showed the presence of the corresponding imidic γ-lactone (XVI) and A/B-*cis*-γ-lactone (XVII) (see Experimental part). Chromatography of this mixture on basic alumina analogously afforded the lactone and the starting cyanohydrin (XI), which was considered to be the converted product of (XVI).

On the contrary, the other two cyanohydrins (IX) and (X) remained perfectly unchanged by this treatment. These facts showed clearly that the cyano and hydroxyl groups in (VIII) and (XI) are situated in *cis*-relationship and those in (IX) and (X) in *trans*. Since (VIII) and (IX) were converted, as mentioned above, to 3-oxo-5α-cholestane-5-carbonitrile (II) and (X) and (XI) to 3-oxo-5β-cholestane-5-carbonitrile (III) by chromium trioxide oxidation, the configurations of the four cyanohydrins were designated as the formulae. The results of the reduction of both 3-oxo-5α- (II) and -5β-cholestane-5-carbonitrile (III) with sodium borohydride and aluminum isopropoxide are summarized in the Table II. The

Table II. Reduction of 3-Oxo-5α- and -5β-cholestane-5-carbonitrile (II) and (III) with Aluminum isopropoxide and Sodium borohydride

	$Al(iso\text{-}PrO)_3$	$NaBH_4$
A/B-*trans* 3-Oxo-5α-cholestane-5-carbonitrile (II)	——	(IX:VIII)/ca. 1:1.5
A/B-*cis* 3-Oxo-5α-cholestane-5-carbonitrile (III)	(X:XI)/3.4:1	(X:XI)/1:2.5

preponderating formation of *cis*-cyanohydrins (VIII) and (XI) in the former case suggested that the reagent attacked favourably from the other side of the cyano group.

Finally, it was noteworthy that in case of the reaction of cholest-4-en-3-one (I) with $H[Al(iso\text{-}PrO)_3CN]$, no cholest-4-en-ols were isolated, showing clearly that the cyanation at $C_{(5)}$ precedes to the reduction of 3-ketone.

Experimental*6

I. Cyanation of Cholest-4-en-3-one (I) with Metallic Cyano Compounds*7

*6 Melting points were measured on a Kofler-block "Monoscope" (Hans Bock Co., Frankfurt am Rhein, Germany) and are corrected. Unless otherwise stated, specific rotations were measured in $CHCl_3$ solution and ultraviolet spectra in 95% EtOH. For rotation measurement and elemental analysis, the samples having the melting points up to 120°, 180°, and over 180° were dried for 3 hr. over P_2O_5 *in vacuo* (1~2 mm. Hg) at room temperature to 60°, 70~90°, and 100~120° respectively. Chromatography was usually performed according to the method described by Reichstein and Shoppee (T. Reichstein, C. W. Shoppee: Discussions Trans. Faraday Soc., No. 7, 305 (1949)).

*7 In this experiment each substance was identified with the corresponding authentic sample by mixed melting point determination.

I-a) With Me-Mg-I and HCN——To a solution of the Me-Mg-I (prepared from 48 mg. of Mg and 300 mg. of MeI) in 7 cc. of dehyd. ether, a solution of 0.1 cc. of HCN in 5 cc. of dehyd. ether was added dropwise with stirring under cooling by ice-water, thereby white solid precipitates appeared, and the mixture was stirred further for 30 min. 20 cc. of dehyd. benzene was added and the ether was distilled off, where the solid precipitates dissolved in the solution. Then, a solution of 250 mg. of (I) in 4 cc. of dehyd. benzene was added and the mixture was refluxed with stirring for 8 hr. After cooling, 3 cc. of water and 4 cc. of 2*N* HCl were added and the resulted two layers were separated. The aqueous layer was extracted twice with ether and the organic layers were washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue (262.5 mg.) was chromatographed on 8 g. of alumina (Woelm neutral II) to give 104.3 mg. of the starting material, m.p. 78.5~79°, as needles from EtOH (from petr. ether-benzene (19:1~2:1) fraction) and 24.9 mg. of 3-oxo-5*α*-cholestane-5-carbonitrile (II), m.p. 182~184°, as needles from EtOH (from petr. ether-benzene (1:1) to benzene fraction).

I-b) With $LiAlH_4$ and HCN——To a solution of 250 mg. of $LiAlH_4$ in 50 cc. of dehyd. ether, a mixture of 1 cc. of HCN and 5 cc. of dehyd. ether was added dropwise with stirring under cooling by ice-water, thereby white solid precipitates appeared, and stirring was continued at room temperature for 30 min., 50 cc. of dehyd. benzene was added and the ether was distilled off. Then, a solution of 250 mg. of (I) in 5 cc. of dehyd. benzene was added, and the mixture was refluxed for 2 hr. After the addition of 10 cc. of *tert*-BuOH to dissolve the insoluble substance, it was refluxed further for 2 hr. After cooling, the reaction mixture was acidified with 10 cc. of water and 15 cc. of 2*N* HCl and the organic layer was separated. The aqueous layer was extracted twice with ether and the organic layers were washed twice with water, dried over Na_2SO_4 and evaporated *in vacuo*. The residue (299.6 mg.) was chromatographed on 8 g. of alumina (Woelm neutral II) and afforded 34.7 mg. of cholest-4-en-3-one (I), m.p. 81~82°, as needles from EtOH (petr. ether-benzene (9:1) fraction), 72.1 mg. of 3-oxo-5*α*-cholestane-5-carbonitrile (II), m.p. 179.5~182°, as needles from EtOH (from petr. ether-benzene (9:1~1:1) fraction) and 53.6 mg. of 3-oxo-5*β*-cholestane-5-carbonitrile (III), m.p. 119~120°, as needles from pentane (from benzene to benzene-$CHCl_3$ (4:1) fraction).

I-c) With Al(*iso*-PrO)$_3$ and HCN——To a solution of 670 mg. of Al(*iso*-PrO)$_3$ in 13 cc. of dehyd. benzene, a mixture of 0.8 cc. of HCN and 5 cc. of dehyd. benzene was added dropwise under cooling by ice-water and stirring was continued at the same temperature for 30 min. A solution of 250 mg. of (I) in 10 cc. of dehyd. benzene was added and the mixture was refluxed for 6 hr. After cooling, it was worked up analogously to (I-b). The residue (290.3 mg.) was chromatographed on 8 g. of alumina (Woelm neutral II) to give the following products: 57.1 mg. of a mixed crystal (V), m.p. 80~87°, as needles from petr. ether (benzene fraction) and 82.2 mg. of a mixed crystal (IV), m.p. 135~137°, as needles from petr. ether (from benzene to benzene-$CHCl_3$ (1:1) fraction).

A mixed crystal of 3*α*-Hydroxy- and 3*β*-hydroxy-5*β*-cholestane-5-carbonitrile (V): Needles from petr. ether, m.p. 80~87°. IR ν_{max}^{Nujol} cm^{-1}: 2230 (C≡N), 3550, 3475, 3310, 1050 (C-OH). *Anal.* Calcd. for $C_{28}H_{47}ON$ (Mol. wt., 413.66): C, 81.29; H, 11.45; N, 3.39. Found: C, 80.89; H, 11.57; N, 2.96.

A mixed crystal of 3*α*-Hydroxy- and 3*β*-hydroxy-5*α*-cholestane-5-carbonitrile (IV): Needles from petr. ether, m.p. 135~137°. IR ν_{max}^{Nujol} cm^{-1}: 2230 (C≡N), 3570, 3250, 1043 (C-OH). *Anal.* Calcd. for $C_{28}H_{47}ON$ (Mol. wt., 413.66): C, 81.29; H, 11.45; N, 3.39. Found: C, 80.70; H, 11.39; N, 3.18.

Oxydation of (V) with Chromium trioxide-Pyridine Complex to 3-Oxo-5*β*-cholestane-5-carbonitrile (III)——To a solution of 30 mg. of (V) in 0.3 cc. of pyridine, a mixture of 30 mg. of CrO_3 and 0.5 cc. of pyridine was added and the mixture was allowed to stand overnight. The mixture was then poured onto 10 cc. of ice-water and extracted 3 times with ether. The ether extracts were washed with 2*N* H_2SO_4, water, 2*N* Na_2CO_3 and water successively, dried over Na_2SO_4 and evaporated *in vacuo*. The residue (26.1 mg.) was recrystallized from EtOH to afford 16.8 mg. of 3-oxo-5*β*-cholestane-5-carbonitril (III) of m.p. 122~123°.

Oxidation of (IV) with Chromium trioxide-Pyridine Complex to 3-Oxo-5*α*-cholestane-5-carbonitrile (II)——To a solution of 30 mg. of (IV) in 0.3 cc. of pyridine, a suspension of 30 mg. of CrO_3 and 0.5 cc. of pyridine was added and the mixture was allowed to stand overnight. Working up analogous to the case of (V) gave 26.3 mg. of the residue which afforded 20 mg. of 3-oxo-5*α*-cholestane-5-carbonitrile (II) of m.p. 182~183.5°, as needles from EtOH.

I-d) With Al(*tert*-BuO)$_3$ and HCN——To a solution of 1.62 g. of Al(*tert*-BuO)$_3$ in 25 cc. of dehyd. benzene, a cold solution of 1 cc. of HCN in 10 cc. of benzene was added dropwise with stirring under cooling by ice-water during 5 min. and the solution was stirred at room temperature for 30 min. A solution of 500 mg. of (I) in 5 cc. of dehyd. benzene was then added and the whole was refluxed for 6 hr. After cooling, the reaction mixture was worked up analogously to the case of (I-c). Evaporation of the ether *in vacuo* left 631 mg. of the residue, which was chromatographed on 15 g. of alumina (Woelm neutral II). It resulted in obtaining of 143.8 mg. of 3-oxo-5*α*-cholestane-5-carbonitrile (II), m.p. 181.5~184° (from petr. ether-benzene (4:1~1:1) fraction) and 125.5 mg. of 3-oxo-5*β*-cholestane-5-carbonitrile (III), m.p. 118~120° (from petr. ether-benzene (1:1) to benzene-$CHCl_3$ (9:1) fraction).

II. Reduction of 3-Oxo-5α-cholestane-5-carbonitrile (II)

II-a) Reduction with Al(*iso*-PrO)$_3$——282 mg. of (II) and 540 mg. of Al(*iso*-PrO)$_3$ were dissolved in 30 cc. of isopropyl alcohol. The solution was distilled slowly for 6 hr., until the Legal test[1] for Me_2CO in the distillate became almost negative. The reaction mixture was poured onto 10 cc. of ice-water, and 20 cc. of ether and 5 cc. of 50% KOH were added to produce two clear layers. The aqueous layer was extracted 3 times with ether and the ether extracts were washed twice with water, dried over Na_2SO_4 and evaporated *in vacuo*. 321.9 mg. of the residue was chromatographed on 8 g. of alumina (Woelm neutral II). The fractions 16～20 (148.8 mg., eluted with benzene) afforded 122.6 mg. of crystals, m.p. 133.5～136°(from petr. ether). The fractions 21～26 (39.4 mg., eluted with benzene and benzene-$CHCl_3$(9:1)) gave 36.4 mg. of crystals, m.p. 127～136°(from petr. ether). The fractions 27～31 (72.4 mg., eluted with benzene-$CHCl_3$(4:1)) afforded 61.4 mg. of crystals, m.p. 139～141°/158～160°(from petr. ether). The mixed melting points of these substances and (IV)(described at (I-c)) were not depressed.

II-b) Reduction with Sodium borohydride and Conversion of the Products to the *p*-Nitrobenzoates——To a solution of 1 g. of (II) in 50 cc. of EtOH and 5 cc. of tetrahydrofuran, a solution of 500 mg. of $NaBH_4$ in 5 cc. of water was added at room temperature and the mixture was stirred for 30 min. After refluxing for 2 hr., a solution of an additional 500 mg. of $NaBH_4$ in 5 cc. of water was added and the solution was refluxed for further 2 hr. 2 cc. of AcOH was added under cooling by ice-water and evaporation of EtOH gave the residue, which was extracted with ether. The ether solution was washed twice with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue (1.10 g.) was repeatedly chromatographed on 30 g. of alumina (Woelm neutral II), but the clear separation into components was not achieved. Therefore, the residue was treated with 550 mg. of *p*-nitrobenzoyl chloride and 6.5 cc. of pyridine for two days. After addition of 1 cc. of water, the reaction mixture was allowed to stand for 2 hr. and then poured onto 20 cc. of ice-water, extracted 3 times with ether, and the ether extracts were washed with 2*N* H_2SO_4, water, 2*N* Na_2CO_3 and twice with water successively, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was repeatedly chromatographed on alumina (Woelm neutral II), and the following products were obtained in a pure state. 263.2 mg. of 3α-hydroxy-5α-cholestane-5-carbonitrile *p*-nitrobenzoate (VI), m.p. 220～223°, as needles from Me_2CO (from petr. ether-benzene (4:1～2:1) fraction), 238.6 mg. of 3β-hydroxy-5α-cholestane-5-carbonitrile *p*-nitrobenzoate (VII), m.p. 238～240°, as rods from Me_2CO (from petr. ether-benzene (2:1～1:1) fraction), and 62.9 mg. of 3α-hydroxy-5α-cholestane-5-carbonitrile (VIII), m.p. 182～184°, as plates from EtOH (benzene-$CHCl_3$(2:1) fraction).

3α-Hydroxy-5α-cholestane-5-carbonitrile *p*-Nitrobenzoate (VI) : Needles from Me_2CO, m.p. 220～223°. IR ν_{max}^{Nujol} cm^{-1} : 2237(C≡N), 1711, 1609, 1527, 1347, 1286, 727(*p*-NO_2-C_6H_5-CO-O-). $[\alpha]_D^{24}$ −5.9°,(c=1.064). *Anal.* Calcd. for $C_{35}H_{50}O_4N_2$(Mol. wt., 562.77) : C, 74.69; H, 8.96; N, 4.98. Found : C, 74.92; H, 9.15; N, 5.17.

3β-Hydroxy-5α-cholestane-5-carbonitrile *p*-Nitrobenzoate (VII) : Rods from Me_2CO, m.p. 238～240°. IR ν_{max}^{Nujol} cm^{-1} : 2237(C≡N), 1713, 1610, 1532, 1294, 725(*p*-NO_2-C_6H_5-CO-O-). $[\alpha]_D^{24}$ +30.5°(c=1.052). *Anal.* Calcd. for $C_{35}H_{50}O_4N_2$(Mol. wt., 562.77) : C, 74.69; H, 8.96; N, 4.98. Found : C, 74.65; H, 8.90; N, 4.85.

II-c) Hydrolysis of 3β-Hydroxy-5α-cholestane-5-carbonitrile *p*-Nitrobenzoate (VII) with Dehyd. HCl-MeOH——To a solution of 100 mg. of (VII) in 16 cc. of $CHCl_3$, 25 cc. of 46.2% (W/W) HCl-MeOH was added and allowed to stand for four days. After evaporation of $CHCl_3$ and HCl-MeOH and addition of water, the residue was extracted 3 times with ether. The extracts were washed twice with water, dried over Na_2SO_4 and evaporated *in vacuo*. The residue (100.8 mg.) was chromatographed on 4 g. of alumina (Woelm neutral II) to give 16.5 mg. of *p*-nitrobenzoic acid methyl ester, m.p. 91.5～93°, as plates from ether (petr. ether-benzene (4:1) fraction), 8.9 mg. of the starting material (VII), m.p. 236.5～238°, as rods from ether and Me_2CO(from petr. ether-benzene (2:1) fraction) and 59.4 mg. of 3β-hydroxy-5α-cholestane-5-carbonitrile (IX), m.p. 158～160°, as fine needles from MeOH (from benzene-$CHCl_3$(9:1～4:1) fraction).

3β-Hydroxy-5α-cholestane-5-carbonitrile (IX) : Fine needles from MeOH, m.p. 158～160°. IR ν_{max}^{Nujol} cm^{-1} : 3240, 1042(C-OH), 2228(C≡N). $[\alpha]_D^{23}$ +14.5°(c=1.015). *Anal.* Calcd. for $C_{28}H_{47}ON$(Mol. wt., 413.66) : C, 81.29; H, 11.45; N, 3.39. Found : C, 80.72; H, 11.53; N, 3.24.

II-d) Hydrolysis of 3α-Hydroxy-5α-cholestane-5-carbonitrile *p*-Nitrobenzoate (VI)——i) With HCl-MeOH : To a solution of 100 mg. of (VI) in 22 cc. of $CHCl_3$, 25 cc. of 46.2% (W/W) HCl-MeOH was added and the mixture was allowed to stand for three days. The reaction mixture was worked up analogously to the case of (II-c).

Recrystallization of the residue (117 mg.) from Me_2CO afforded 70.2 mg. of the starting material, m.p. 220.5～223°, and from the filtrate an additional 11.0 mg. of the starting material of m.p. 219～222° was obtained.

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ii) With $NaHCO_3$ in aqueous methanol : To a solution of 100 mg. of (VI) in 60 cc. of MeOH, 3 cc. of satud. $NaHCO_3$ solution was added and the mixture was refluxed for 3 hr. After cooling, 1 cc. of AcOH was added to neutralize the mixture and the MeOH was evaporated *in vacuo*. 20 cc. of water and 5 cc. of $2N$ Na_2CO_3 were added to the residue and were extracted 3 times with ether. The ether layers were washed twice with water, dried over Na_2SO_4 and evaporated *in vacuo*. The residue (87.7 mg.) was chromatographed on 4 g. of alumina (Woelm neutral II) to afford 4.0 mg. of the starting material, m.p. 219~221°, as needles from Me_2CO(petr. ether-benzene (2:1) fraction), and 55.7 mg. of 3α-hydroxy-5α-cholestane-5-carbonitrile (VIII), m.p. 182~184°, as plates from MeOH (from benzene to benzene-$CHCl_3$(4:1) fraction).

3α-Hydroxy-5α-cholestane-5-carbonitrile (VIII) : Plates from MeOH, m.p. 182~184°. IR ν_{max}^{Nujol} cm^{-1}: 3567, 1046(C-OH), 2241(C≡N). $[\alpha]_D^{24}$ +14.6°(c=1.083). *Anal.* Calcd. for $C_{28}H_{47}ON$(Mol. wt., 413.66): C, 81.29; H, 11.45; N, 3.39. Found : C, 80.87; H, 11.50; N, 3.26.

III. Reduction of 3-Oxo-5β-cholestane-5-carbonitrile (III)

III-a) With Al(*iso*-PrO)$_3$——To a solution of 169.5 mg. of (III) in 10 cc. of dehyd. isopropyl alcohol was added a solution of 339 mg. of Al(*iso*-PrO)$_3$, in 7 cc. of dehyd. isopropyl alcohol. The solution was refluxed at such a rate that slow distillation occurred, the reaction being continued until the Legal test[1] for Me_2CO in the distillate became negative (6 hr.). The reaction mixture was poured onto 10 cc. of ice-water, and 20 cc. of ether and 6 cc. of 50% KOH were added to produce two clear layers. The aqueous layer was extracted 3 times with ether and the ether layers were washed twice with water, dried over Na_2SO_4, and was evaporated *in vacuo*. The residue (173.3 mg.) was chromatographed on 8 g. of alumina (Woelm neutral II) from which 91.3 mg. of 3α-hydroxy-5β-cholestane-5-carbonitrile (X), m.p. 72~77°, as needles from petr. ether (from benzene to benzene-$CHCl_3$ (9:1) fraction) and 26.9 mg. of 3β-hydroxy-5β-cholestane-5-carbonitrile (XI), m.p. 96~99°/118~120°, as needles from MeOH (from benzene-$CHCl_3$(2:1~1:1) fraction).

III-b) Reduction with Sodium borohydride and Conversion of the Products to the *p*-Nitrobenzoates——To a solution of 600 mg. of (III) in 30 cc. of EtOH, a solution of 300 mg. of $NaBH_4$ in 3 cc. of water was added at room temperature and stirred at the same temp. for 30 min. After refluxing for 2 hr., a solution of an additional 300 mg. of $NaBH_4$ in 3 cc. of water was added and refluxed for further 2 hr. After cooling, the reaction mixture was worked up analogously to the case of (II-b). The residue (664 mg.) was chromatographed on 20 g. of alumina (Woelm neutral II) and afforded the following results.

12.3 mg. of 3-oxo-5β-cholestane-5-carbonitrile (III), m.p. 124~126°, as needles from EtOH (petr. ether-benzene (1:1) fraction), 136.0 mg. of 3α-hydroxy-5β-cholestane-5-carbonitrile (X), m.p. 71~75°, as needles from petr. ether (from petr. ether-benzene (2:3~1:2) fraction) and 346.5 mg. of 3β-hydroxy-5β-cholestane-5-carbonitrile (XI), m.p. 93~97°/116~120°, as plates from EtOH (from benzene to benzene-$CHCl_3$(4:1) fraction).

136.0 mg. of (X) was treated with 110 mg. of *p*-nitrobenzoyl chloride in 2 cc. of pyridine for two days. 2 cc. of water was added and allowed to stand for 2 hr., and then the reaction mixture was poured onto 20 cc. of ice-water and extracted 3 times with a mixture of ether and $CHCl_3$. The organic extracts were washed with $2N$ H_2SO_4, water, $2N$ Na_2CO_3 and twice with water, dried over Na_2SO_4 and evaporated *in vacuo*. The chromatography of the residue (192.8 mg.) on 8 g. of alumina (Woelm neutral II) afforded 9.7 mg. of a mixture of (XII) and (XIII), m.p. 195~205°(petr. ether-benzene (2:1) fraction), and 113.0 mg. of 3α-hydroxy-5β-cholestane-5-carbonitrile-*p*-nitrobenzoate (XII), m.p. 209~210°, as rods from Me_2CO (from petr. ether-benzene (2:1~1:1) fraction).

3α-Hydroxy-5β-cholestane-5-carbonitrile *p*-Nitrobenzoate (XII) : Rods from Me_2CO, m.p. 210~212°. IR ν_{max}^{Nujol} cm^{-1} : 2229(C≡N), 1723, 1510, 1285, 725(*p*-NO_2-C_6H_5-CO-O-). $[\alpha]_D^{26}$ +16.6°(c=1.069). *Anal.* Calcd. for $C_{35}H_{50}O_4N_2$(Mol. wt., 562.77) : C, 74.69; H, 8.96; N, 4.98. Found : C, 74.78; H, 9.02; N, 4.84.

346.5 mg. of (XI) was also esterified with 300 mg. of *p*-nitrobenzoyl chloride in 5 cc. of pyridine for two days. After reaction, it was worked up analogously to the case above. The residue (506.1 mg.) was also chromatographed on 15 g. of alumina (Woelm neutral II) and there was obtained 316 mg. of 3β-hydroxy-5β-cholestane-5-carbonitrile *p*-nitrobenzoate (XIII), m.p. 243~244°, as plates from Me_2CO (from petr. ether-benzene (4:1~1:1) fraction).

3β-Hydroxy-5β-cholestane-5-carbonitrile *p*-Nitrobenzoate (XIII) : Plates from Me_2CO, m.p. 243~244°. IR ν_{max}^{Nujol} cm^{-1} : 2236(CN), 1720, 1613, 1534, 1282, 728(*p*-NO_2-C_6H_5-CO-O-). $[\alpha]_D^{28}$ +49.0°(c=1.066). *Anal.* Calcd. for $C_{35}H_{50}O_4N_2$(Mol. wt., 562.77) : C, 74.69; H, 8.96; N, 4.98. Found : C, 74.81; H, 9.00; N, 4.79.

III-c) Hydrolysis of 3α-Hydroxy-5β-cholestane-5-carbonitrile *p*-Nitrobenzoate (XII) with Dehyd. HCl-MeOH——To a solution of 60 mg. of (XII) in 10 cc. of $CHCl_3$, 15 cc. of 33% (W/W) HCl-MeOH was added and the solution was allowed to stand for three days. The reaction mixture was worked up analogously to the case of (II-c). The residue (88.9 mg.) was chromatographed on 4 g. of alumina (Woelm neutral II) and gave 5.8 mg. of *p*-nitrobenzoic acid methyl ester, m.p. 94~95°, as plates from

ether (pert. ether-benzene (9:1) fraction), 5.9 mg. of (XII) of the starting material, m.p. 208~208.5°, as rods from Me_2CO, (petr. ether-benzene (1:1) fraction), and 32.2 mg. of (X), m.p. 74~78°, as silky needles from petr. ether (from benzene-$CHCl_3$ (9:1~4:1) fraction).

3α-Hydroxy-5β-cholestane-5-carbonitrile (X) : Silky needles from, petr. ether, m.p. 74~77°. IR ν_{max}^{Nujol} cm^{-1} : 2243(C≡N), 3555, 3310, 1047(C-OH). $[\alpha]_D^{25}$ +28.5°(c=0.643). *Anal.* Calcd. for $C_{28}H_{47}ON$ (Mol. wt., 413.66) : C, 81.29; H, 11.45; N, 3.39. Found : C, 80.74; H, 11.53; N, 3.20.

III-d) Hydrolysis of 3β-Hydroxy-5β-cholestane-5-carbonitrile *p*-Nitrobenzoate (XIII)——i) With HCl-MeOH : A solution of 100 mg. of (XIII) in 20 cc. of $CHCl_3$ was treated with 25 cc. of 33% (W/W) HCl-MeOH for three days. The reaction mixture was worked up similarly to the case of (II-d-i). Recrystallization of the residue (126.0 mg.) from Me_2CO afforded 88.0 mg. of the starting material, m.p. 243~244°, as plates.

ii) With $NaHCO_3$ in aqueous Me_2CO and MeOH : To a solution of 100 mg. of (XIII) in a mixture of 10 cc. of Me_2CO and 50 cc. of MeOH, 2 cc. of satud. $NaHCO_3$ solution was added and refluxed for 7 hr. After cooling, it was worked up analogously to the case of (II-d-ii). The residue (150.2 mg.) was chromatographed on 8 g. of alumina (Woelm neutral II) and afforded 1.3 mg. of the starting material (XIII), m.p. 242~243°, as plates from EtOH (petr. ether-benzene (2:1) fraction) and 54.5 mg. of (XI), m.p. 95~87°/118~120°(double melting point), as needles from EtOH (from benzene-$CHCl_3$ (4:1~2:1) fraction).

3β-Hydroxy-5β-cholestane-5-carbonitrile (XI) : Needles from EtOH, m.p. 95~97°/118~120°. IR ν_{max}^{Nujol} cm^{-1} : 3445, 1056(C-OH), 2240(C≡N). $[\alpha]_D^{25}$ +22.2°(c=1.034). *Anal.* Calcd. for $C_{28}H_{47}ON$ (Mol. wt., 413.66) : C, 81.29; H, 11.45; N, 3.39. Found : C, 80.95; H, 11.55; N, 3.35.

IV. Lactonization of 3α-Hydroxy-5α-cholestane-5-carbonitrile (VIII)

IV-a) With conc. HCl in EtOH——A solution of 93.0 mg. of (VIII) in a mixture of 15 cc. of EtOH and 3 cc. of 36% HCl was refluxed under a N_2 gas stream for 3 hr. After cooling, EtOH was evaporated *in vacuo*, water was added and the mixture was extracted 3 times with ether. The ether extracts were washed twice with water, dried over Na_2SO_4 and evaporated *in vacuo*. The infrared spectrum of the residue (96.0 mg.) showed an absorption bands at 1755 cm^{-1} corresponding to lactone and at 1660 cm^{-1} corresponding to imide. By the alumina chromatography (Woelm neutral II, 4 g.), 3α-hydroxy-5α-cholestane-5-carboxylic acid γ-lactone (XV) and 3α-hydroxy-5α-cholestane-5-carbonitrile (VIII) were obtained but 3α-hydroxy-5α-cholestane-5-carbonimidic acid γ-lactone (XIV) was not found as follows : 9.4 mg. of 3α-hydroxy-5α-cholestane-5-carboxylic acid γ-lactone (XV), m.p. 176~177.5°, as plates from EtOH (from petr. ether-benzene (14.5:1~9:1) fraction) and 48.2 mg. of (VIII), m.p. 183.5~185°, as needles from EtOH (from benzene to benzene-$CHCl_3$ (4:1) fraction).

3α-Hydroxy-5α-cholestane-5-carboxylic acid γ-Lactone (XV) : Plates from EtOH, m.p. 176~177.5°. $[\alpha]_D^{24}$ +22.3°(c=0.780). IR ν_{max}^{Nujol} cm^{-1} : 1756(γ-lactone). *Anal.* Calcd. for $C_{28}H_{46}O_2$ (Mol. wt., 414.62) : C, 81.10; H, 11.18. Found : C, 80.69; H, 11.26.

IV-b) With 25% (W/W) HCl-MeOH——A solution of 48.2 mg. of (VIII) in 17 cc. of 25% (W/W) HCl-MeOH was refluxed for 4.5 hr. After cooling, the excess HCl-MeOH was evaporated *in vacuo*, water was added and the mixture was extracted 3 times with ether. Ether extracts were washed twice with water, dried over Na_2SO_4, and evaporated *in vacuo*. Recrystallization of the residue (53.8 mg.) from MeOH and ether afforded 29.2 mg. of (XIV) of m.p. 116~117°. 15.3 mg. of above obtained (XIV) was chromatographed on 4 g. of alumina (Woelm neutral II) and gave 0.2 mg. of (XV), m.p. 172~174°, as plates from EtOH (petr. ether-benzene (9:1) fraction) and 12.8 mg. of (VIII), m.p. 176~179°, as fine needles from EtOH (from benzene to benzene-$CHCl_3$ (9:1) fraction).

3α-Hydroxy-5α-cholestane-5-carbonimidic acid γ-Lactone (XIV) : Prisms from MeOH and ether, m.p. 116~117°. $[\alpha]_D^{21}$ +21.3°(c=0.802). IR ν_{max}^{Nujol} cm^{-1} : 1763 (week lactone), 1671 (strong imide). *Anal.* Calcd. for $C_{28}H_{47}ON$ (Mol. wt., 413.66) : C, 81.29; H, 11.45; N, 3.39. Found : C, 81.86; H, 11.60; N, 2.88.

As mentioned above (chromatography and IR-spectrum), this substance (XIV) contains some of (XV).

V. Lactonization of 3β-Hydroxy-5β-cholestane-5-carbonitrile (XI)

V-a) With 25% (W/W) HCl-MeOH——A solution of 100 mg. of (XI) in 20 g. of 25% (W/W) HCl-MeOH was refluxed for 4.5 hr. The HCl-MeOH was evaporated *in vacuo*, and worked up as usually. Infrared spectrum of the residue (120.8 mg.) showed the absorption bands corresponding to imide. Chromatography of the residue on 4 g. of alumina (Woelm neutral II) gave 73.0 mg. of (XI), m.p. 93~98°/112~116°, as needles from MeOH (from benzene-$CHCl_3$ (9:1~2:1) fraction).

V-b) With 33.3% (W/W) HCl-MeOH at 160°——A solution of 110 mg. of (XI) in 15 cc. of 33.3% (W/W) HCl-MeOH in an autoclave (made from steel) at 160° for 5 hr. After cooling, the reaction mixture was poured onto water and extracted 3 times with $CHCl_3$. The $CHCl_3$ extracts were washed twice with water, dried over Na_2SO_4 and evaporated *in vacuo*. The residue (104 mg.) was chromatographed on 4 g. of alumina (Woelm neutral II) to give 10.8 mg. of 3β-hydroxy-5β-cholestane-

5-carboxylic acid γ-lactone (XVII), m.p. 133～134.5°, as needles from EtOH (from petr. ether-benzene (4:1～2:1) fraction) and 21.9 mg. of the starting material (XI), m.p. 95～97°/116～120°(from benzene to benzene-$CHCl_3$(9:1) fraction).
3β-Hydroxy-5β-cholestane-5-carboxylic acid γ-Lactone (XVII) : Needles from EtOH, m.p. 133～134.5°. $[\alpha]_D^{20}$ +21.7°(c=1.050). IR ν_{max}^{Nujol} cm^{-1} : 1760, 1187, 959(γ-lactone). *Anal.* Calcd. for $C_{28}H_{46}O_2$(Mol. wt., 414.65) : C, 81.10; H, 11.18. Found : C, 80.93; H, 11.23.

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Summary

Cyanation of cholest-4-en-3-one (I) was attempted with CN-Mg-I, Li[Al(CN)$_4$], H[Al-(*tert*-BuO)$_3$CN], and H[Al(*iso*-PrO)$_3$CN] respectively to give the cyano ketone compounds, but in the case of H[Al(*iso*-PrO)$_3$CN], 1,3-cyanohydrins were obtained. The reduction of epimeric 3-oxo-cholestane-5-carbonitrile with aluminum isopropoxide and with sodium borohydride afforded the four cyanohydrins which were designated as the formulae (VIII), (VII), (XII), and (XIII).

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132. Wataru Nagata, Shoichi Hirai, Tsutomu Aoki und Ken'ichi Takeda : Über angular substituierte polycyclische Verbindungen. III.*1 Alkalische Degradation von 3α-Alkoxy-3β-amino-5β-cholestan-5-carbonsäure-γ-laktam.

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In der vorhergehenden Mitteilung[1] berichteten wir über die Einführung der Nitril- sowie Säureamid-Gruppe an die 5-Stellung von Cholest-4-en-3-on (I), die in der Einwirkung von Kaliumcyanid auf (I) sowohl in Abwesenheit als auch in Gegenwart von Ammoniumchlorid besteht, wobei im ersteren Fall durch die zugleich stattfindende Verseifung neben den anderen Produkten 5β- sowie 5α-Säureamid (II bzw. III) in vorwiegender Menge entstanden.[1,2] Es wurde ferner gezeigt, daß die Säureamid-Körper in ihrem Gleichgewicht bevorzugt in einer gebrückten Form, d.h. Hemiketalform vorliegen und somit konnten sie leicht in die entsprechenden 3α-Alkyläther, z.B. (IV), (V) und (VI) übergeführt werden.

Es ist nun weit bekannt, daß die tertiären Säureamide, besonders die angularen, gegen die alkalische Verseifung stark widerstehen.*3 Die Schwierigkeit der Verseifung

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*2 Fukushima-ku, Osaka (永田 亘, 平井章一, 青木 務, 武田健一).
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