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Studies on the Azasteroids and Related Compounds. II.[1] Reduction of 1,2,3,4,4a,5,7,8,9,10-Decahydro-6*H*-benzo[*c*]quinolizin-6-one and Related Compounds

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Reduction of 1,2,3,4,4a,5,7,8,9,10-decahydro-6*H*-benzo[*c*]quinolizin-6-one (I) under varying conditions were examined and afforded two aminoketones, *cis*- and *trans*-dodecahydro-6*H*-benzo[*c*]quinolizin-6-ones (IV and V), and three amino-alcohols, *cis*- and *trans*-6*α*-, and *trans*-6*β*-hydroxyperhydrobenzo[*c*]quinolizidines (VIa, VIIa and VIIIa), of which the unusual formation of VIa from *trans*-aminoketone (V) was discussed. B/C *trans*-perhydrobenzo[*c*]quinolizidine (III) was afforded in good yield from *trans*-aminoketone (V) *via* thioketalization followed by desulfurization with Raney nickel. Chemical evidences and NMR data made possible to establish the configurations of these amino-alcohols and their derivatives.

In the previous paper,[1] we reported the condensation and cyclization reactions of ethyl 2-piperidineacetate with cyclohexanone or 2-tetralone to give the quinolizine derivative (I or II), which would provide useful means for building up the skeleton of 14-azasteroids with an oxygen function at C_{11} position.

The present paper describes the reduction of 1,2,3,4,4a,5,7,8,9,10-decahydro-6*H*-benzo-[*c*]quinolizin-6-one (I) and the preparation of B/C *trans*-fused perhydrobenzo[*c*]quinolizidine (III), for preliminary studies of preparation of B/C *trans*-fused steroidal skeleton from the compound (II) analogs. The reduction of the compound (I) and its dihydro derivative (V) under varying conditions provided some stereochemically interesting informations in this field.

Table I. Product Ratios (IV:V) in Isomerization of Dodecahydro-6*H*-benzo[*c*]quinolizin-6-ones (IV $\rightleftarrows$ V)

No.	Starting material[a]	Reaction condition	Product ratio[b] IV : V
1	L	in *n*-hexane, R.T., 4 days	1 : 3
2	L	in MeOH, R.T., 4 days	1 : 6
3	L	in MeOH, R.T., 8 days	1 : 9
4	L	alumina in $CHCl_3$[c]	1 : 30
5	L	in 70% EtOH, reflux, 3 hr	1 : 7
6	L	KOH in 70% EtOH, reflux, 3 hr	1 : 30
7	B	in MeOH, R.T., 4 days	1 : 6
8	B	alumina in benzene[c]	1 : 20
9	B	in AcOH, 80—90°, 3 hr	1 : 30
10	B	KOH in 70% EtOH, reflux, 3 hr	1 : 30

a) L: The crude product (IV:V=1:3) obtained by reduction of I with $LiAlH_4$.
B: The crude product (IV:V=1:2) obtained by reduction of I with Li/NH_3.
b) Ratios were taken from VPC analysis of crude products in isomerization reactions.
c) column chromatography

1) Part I: *Chem. Pharm. Bull.* (Tokyo), **14**, 1399 (1966).
2) Location: *Toneyama, Toyonaka, Osaka-fu.*

Reduction of I with lithium in liquid ammonia gave 67% of a mixture of B/C *cis*–and *trans*–saturated aminoketones (IV) and (V), in the ratio of one to two in favor of V from vapor phase chromatographic (VPC) analysis. When I was reduced with lithium aluminum hydride, was also obtained in 41% yield a mixture of IV and V in the ratio of one to three, along with considerable amount of isomeric amino–alcohols (VIIa) and (VIIIa). And it was found from inspection of VPC data that the ratios of IV to V in the mixture obtained from the above reductions have gradually changed as standing the mixture in the polar solvents; the peak area of IV in VPC decreased as that of V increased. Change in the ratio was promoted simply by heating the mixture or adding acid or alkali to it, and the further conversion was hardly observed beyond the point that the ratio was reached to about one to thirty. These facts showed that the less stable *cis*–aminoketone (IV) underwent isomerization to the more stable *trans*–isomer (V), and that the isomerization might finally reach the equilibrium where the ratio would be around one to thirty in favor of V.

Reduction of I with sodium borohydride in methanol afforded three isomeric amino-alcohols (VIa), (VIIa) and (VIIIa) in 36%, 13% and 3% yields, respectively. When I was reduced with sodium borohydride in tetrahydrofuran in the presence of acetic acid, products were V in 11%, VIa in 24%, and VIIa in 29% yields, respectively, and it was failed to detect an amino–alcohol (VIIIa).

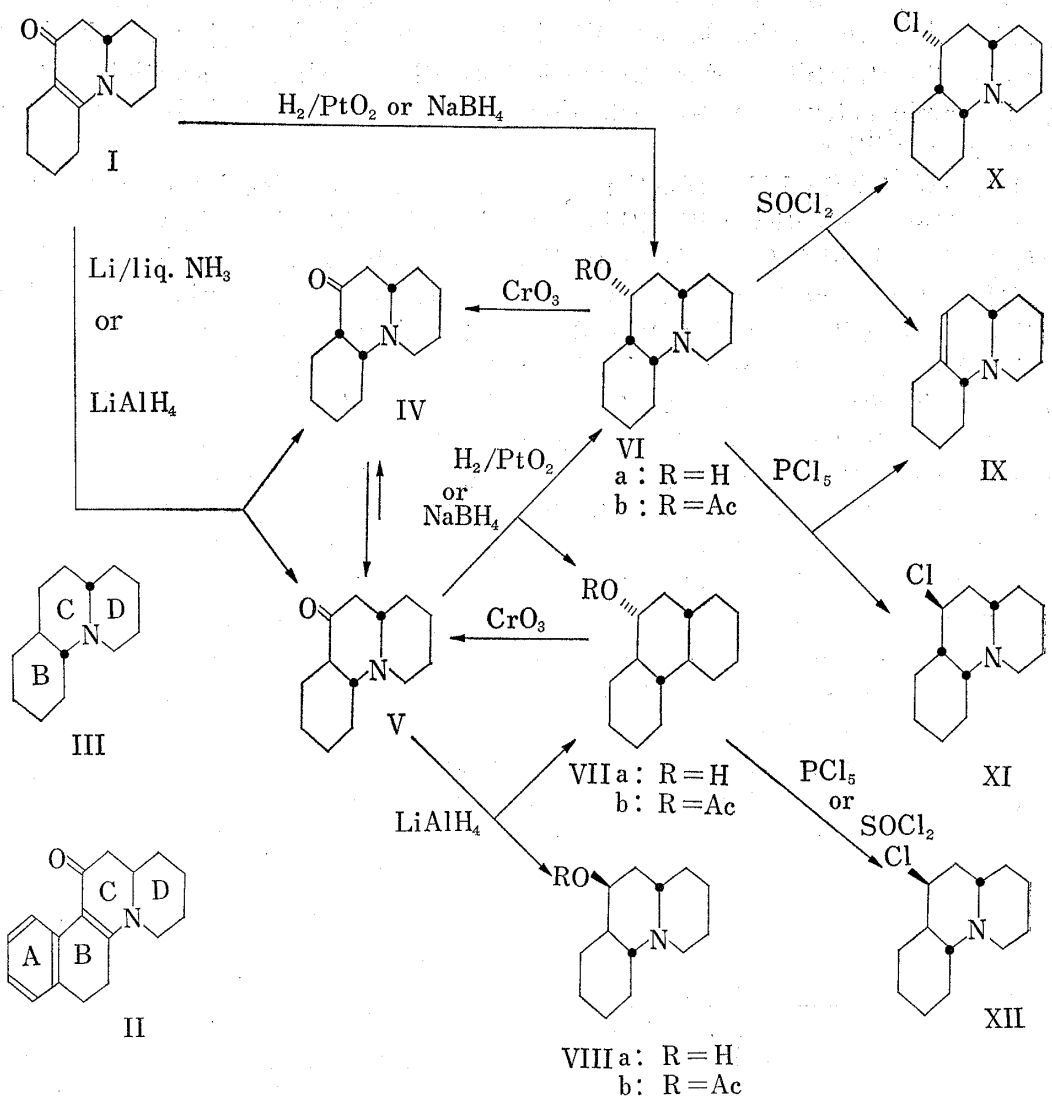


Chart 1

Table II. Product Ratios (VIa:VIIa:VIIIa) in Reductions of Dodecahydro-6*H*-benzo[*c*]quinolizin-6-ones (IV and V)

No.	Starting material	Reduction condition	Product ratio[a] VIa:VIIa:VIIIa
1	IV+V[b]	$NaBH_4$/MeOH, R.T., 1 hr	1 : 1 : 0
2	IV+V	$NaBH_4$/THF, AcOH, reflux, 3 hr	1 : 2 : 0
3	IV+V	H_2, PtO_2/AcOH–$HClO_4$, R.T.	1 : 1 : 0
4	IV+V	H_2, PtO_2/EtOH, R.T.	1 : 2 : 0
5	V	$NaBH_4$/THF, AcOH, reflux, 3 hr	1 : 9 : 0
6	V	H_2, PtO_2/AcOH–$HClO_4$, R.T.	1 : 2 : 0
7	V	$LiAlH_4$/ether, reflux, 3 hr	0 : 3 : 1[c]

a) The ratios were taken from VPC analyses, after trimethylsilylation of the reduction products.
b) The mixture obtained by Birch reduction of I (IV:V=1:2).
c) The ratio was taken from the amounts of VIIa and VIIIa isolated by alumina column chromatography of the reduction product.

As for catalytic hydrogenation of I, the aminoketone (V) in 18% yield and a mixture of two aminoalcohols (VIa and VIIa) in 27% yield with the starting material in 23% yield were among products when hydrogenation was halted at the point where one molar equivalent amount of hydrogen was consumed. After complete absorption of hydrogen in catalytic hydrogenation of I, two aminoalcohols (VIa in 63% and VIIa in 22%) were obtained.

To assign the structure of these aminoalcohols (VIa—VIIIa), we scrutinized the behaviors of the aminoketones toward reduction and these amino-alcohols toward oxidation under varying conditions.

Catalytic and borohydride reductions of V afforded two aminoalcohols (VIa and VIIa), on the other hand, reduction with lithium aluminum hydride afforded aminoalcohols (VIIa) and (VIIIa) in 67% and 20% yields, respectively (see Table II). Chromium trioxide oxidations of VIIa, either in acetic acid or in pyridine as solvent, gave the amino ketone (V), whereas oxidation of VIa with chromium trioxide in acetic acid gave exclusively an isomeric aminoketone (V). However, VIa, upon oxidation with chromium trioxide in pyridine, gave a mixture of two isomeric aminoketones (IV and V), in the ratio of five to four in favor of IV.

From these reduction and oxidation experiments, it could be concluded that the B/C ring fusion of VIa is different from that of VIIa and that VIIIa has the same B/C ring junction as VIIa; *cis*–fused in VIa and *trans*–fused in VIIa and VIIIa. These conclusions were supported by the chlorination reactions of these aminoalcohols. Chlorination of VIa with thionyl chloride afforded the chloride (X) in poor yield, but VIa, when chlorinated in the presence of pyridine, gave IX. On the other hand, VIa was chlorinated with phosphorus pentachloride in chloroform at 5° to 10° to give mainly IX, along with small amount of XI. When the aminoalcohol (VIIa) was chlorinated with either thionyl chloride or phosphorus pentachloride, the chloride (XII) was secured as a sole product.

This unusual result that a mixture of isomeric *cis*– and *trans*–aminoalcohols were secured from reduction of *trans*–aminoketone could be explained as follows: Under this reduction condition, the *trans*–aminoketone (V) is partly isomerized to the less stable *cis*–isomer (IV), which is reduced faster than the *trans*–isomer (V), and in both IV and V, attack of the reducing reagent might occur preferably from β–side of the molecule than α–side (Fig. 1), because, as illustrated in the conformation (V'), β–side attack would be somewhat hindered by the presence of an axial hydrogen at C_7, while this hin-

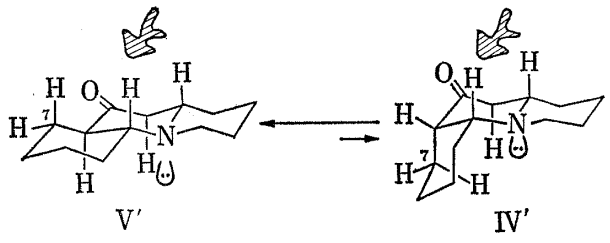


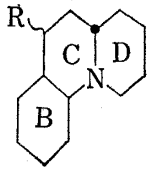
Fig. 1

drance was absent in the conformation (IV'). Therefore, the equilibrium between V and IV would proceed toward IV during the reduction to give more VIa in the reaction products and as a result, an equivalent mixture of VIa and VIIa was obtained.

When V was reduced with lithium aluminum hydride, the rate of reduction might be much faster than that of isomerization, and therefore, only a mixture of epimeric *trans*-amino-alcohols (VIIa) and (VIIIa) were obtained. Such an unusual result has been also observed on the sodium borohydride reduction of annofoline.[3)]

Configurations of substituents at C_6 were established by their nuclear magnetic resonance (NMR) spectra (Table III). In the compounds (VIIIa, VIIIb, XI and XII), signals corresponding to protons at C_6 appeared as multiplets with half-widths of about 7 cps. On the other hand, the NMR spectra of VIa, VIb and X showed signals corresponding to proton at C_6 as multiplets, whose half-widths were between 17 and 18 cps. In the NMR spectrum of VIIb, a proton at C_6 appeared as doublets of triplet at 5.60 τ (J=5 and 12 cps). However, in VIIa, a signal of proton at C_6 and that of an equatorial proton at C_1 were partly overlapped and therefore half-width of C_6-proton was obscure.

Table III. NMR Spectra of 6-Substituted Perhydrobenzo[*c*]quinolizidines



Compound No.	R	B/C Ring juncture	Signal for : τ	
			C_6-proton	C_1-eq. proton
VIa	α-OH	*cis*	6.30 (m., W½=17 cps)	6.90 (m.)
VIb	α-OAc	*cis*	5.30 (m., W½=18 cps)	6.87 (m.)
X	α-Cl	*cis*	5.37 (m., W½=17 cps)	6.75 (m.)
XI	β-Cl	*cis*	5.90 (m., W½=7 cps)	6.85 (m-d)
VIIa	α-OH	*trans*	6.80 (m., W½=*ca.* 22 cps)	6.68 (m.)
VIIb	α-OAc	*trans*	5.60 (d-t., J=5 and 12 cps)	6.76 (m.)
VIIIa	β-OH	*trans*	6.25 (m., W½=8 cps)	6.65 (m.)
VIIIb	β-OAc	*trans*	5.05 (m., W½=7 cps)	6.35 (m-d)
XII	β-Cl	*trans*	5.81 (m., W½=7 cps)	6.62 (m-d)
IX	Δ^6	—	4.60 (m., W½=8 cps)	6.65 (m-d)

From these data, we can draw the conclusion that in compounds (VIIIa, VIIIb, XI and XII), configurations of hydrogens at C_6 are equatorially oriented and that VIIIa, VIIIb and XII have the partial structure as shown in B, while XI has the partial structure as in D. On the other hand, in compounds (VIa, VIb, VIIa, VIIb and X), hydrogens at C_6 are axially oriented and therefore the configurations of VIa, VIb and X are shown by the partial structure (C), and VIIa and VIIb have the same structure (A).

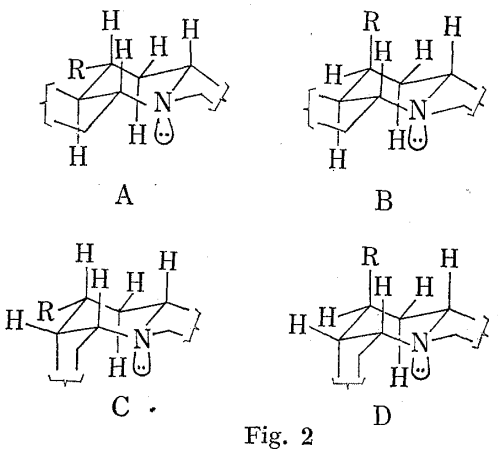


Fig. 2

3) F.A.L. Anet and N.H. Khan, *Chem. Ind.* (London), **1960**, 1238; F.A.L. Anet, *Tetrahedron Letters*, **1960**, 13.

Preparation of B/C *trans*-fused Perhydrobenzo[*c*]quinolizidine

For the preparation of B/C *trans*-fused perhydrobenzo[*c*]quinolizidine (III) from V, we examined four synthetic routes as shown in Chart 2.

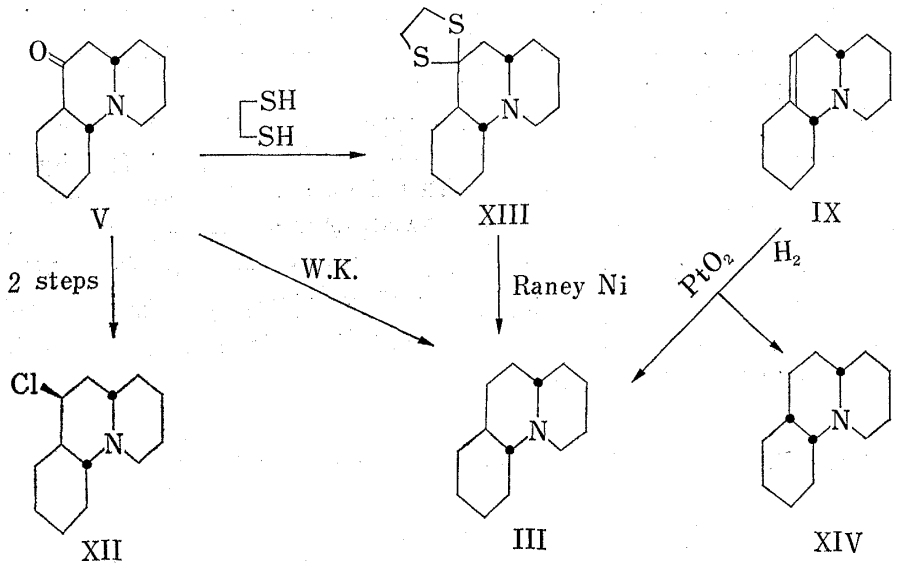


Chart 2

The chloride (XII), derived from VIIa, was found to be very stable and was subjected to hydrogenation under varying conditions, but we could not obtain III, and recovered the starting material unchanged. The compound (IX), derived from VIa by chlorination, was hydrogenated with platinum oxide in acetic acid to give a mixture of III and the *cis*-isomer (XIV). The aminoketone (V) was warmed with 1,2-ethanedithiol in glacial acetic acid containing boron trifluoride etherate to give the dithioketal (XIII) in 77% yield, which had no carbonyl absorption in the infrared spectrum and showed a signal at 6.79 τ as a singlet due to four protons of two methylene group neighbored by sulfur atoms in the NMR spectrum. Desulfurization of the dithioketal (XIII) with Raney nickel catalyst (W-2) afforded in 70% yield III as semi-solid, which showed the *trans*-quinolizidine bands at 2800 and 2755 cm^{-1} in the infrared spectrum. And further, Wolff-Kishner reduction of the aminoketone (V) also afforded III as semi-solid in poor yield, which was identified on the direct comparison with a sample obtained above. Thus, in view of its applicability to the steroid synthesis, the preferred method for the preparation of V from I and of III from V were the Birch reduction of I followed by treatment with alkaline or acidic medium, and thioketalization of V followed by desulfurization with Raney nickel catalyst.

Experimental

Melting points were uncorrected. Vapor phase chromatographic works were done with an Perkin-Elmer gas chromatograph model 800 with nitrogen at a flow rate of 40 ml/min as the carrier gas on a 10-ft. 1.5% SE-30 column. The NMR spectra were taken on a Hitachi Perkin-Elmer H-60 type Spectrometer at 60 Mc in $CDCl_3$ with tetramethylsilane as internal reference.

Reduction of 1,2,3,4,4a,5,7,8,9,10-Decahydro-6*H*-benzo[*c*]quinolizin-6-one (I)——a) With lithium in liq. ammonia: To a well stirred suspension of 1.5 g of Li cut in small pieces in 500 ml of liq. ammonia was added a solution of 2.3 g of I dissolved in 30 ml of anhydrous ether as soon as possible, and stirring was continued for 30 min before halting the reaction by adding an excessive amount of NH_4Cl and ammonia was evaporated. To the residue thus obtained was added 50 ml of H_2O and extracted with $CHCl_3$. The combined extract was washed with saturated brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave 1.8 g (67%) of pale yellow oil, which was purified either by chromatography on alumina with benzene or by distillation *in vacuo* to give *trans*-1,2,3,4,4a,5,6a,7,8,9,10,10a-dodecahydro-6*H*-benzo[*c*]quinolizin-6-one (V), bp 160—180° (0.1 mmHg) (bath temp.). Picrate: mp 209—211°, recrystallized from

EtOH. *Anal.* Calcd. for $C_{19}H_{24}O_8N_4$: C, 52.29; H, 5.55; N, 12.84. Found: C, 52.39; H, 5.88; N, 13.13. Perchlorate: mp 174—175°, recrystallized from EtOH–ether. *Anal.* Calcd. for $C_{13}H_{22}O_5NCl$: C, 50.73; H, 7.21; N, 4.55. Found: C, 50.94; H, 7.18; N, 4.79. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2800, 2750 and 1710.

b) With lithium aluminum hydride: To a solution of 1.10 g of I in 40 ml of anhydrous tetrahydrofuran was added 500 mg of $LiAlH_4$ and the mixture was refluxed for 20 min. After adding 20 ml of AcOEt followed by 60 ml of H_2O under ice cooling, the organic layer was separated, and the aqueous layer was extracted with 30 ml of AcOEt. The combined organic extract was washed with saturated brine and dried over anhydrous K_2CO_3. Evaporation of the solvent gave 750 mg of brown pasty residue, which was chromatographed over 30 g of alumina. The first elution with 240 ml of benzene gave 450 mg (41%) of viscous oil, which was identical with V by comparison of their infrared (IR) spectra. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2800, 2750 and 1710. The picrate had mp 208—210°. The second elution with 300 ml of a 1:1 mixture of benzene—$CHCl_3$ gave 20 mg of colorless solid. The third elution with 200 ml of $CHCl_3$ also gave 150 mg of colorless solid. The combined product of the second and the third elutions (15%) was found to consist of a mixture of aminoalcohols (VIIa and VIIIa) from IR inspection. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550, 3350—3100, 2780, and 2740.

c) With sodium borohydride in MeOH: To a solution of 4.50 g of I in 50 ml of MeOH was added 4.40 g of $NaBH_4$. The resulting mixture was refluxed for 3 hr. After evaporation of MeOH, the syrupy residue was treated with 150 ml of H_2O, and shaken with five 50 ml portions of $CHCl_3$. The $CHCl_3$ extract was washed with saturated brine and dried over anhydrous K_2CO_3. Evaporation of $CHCl_3$ gave 5.02 g of pale brown paste, which was chromatographed on 150 g of alumina. The first elution with 1.8 liter of benzene recovered 1.10 g (24%) of the starting material (I) (Fr. A). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1620 and 1550. The second elution with 2.5 liter of a 1:1 mixture of benzene—$CHCl_3$ gave 1.80 g of a mixture of aminoalcohols (Fr. B). The third elution with 1.2 liter of $CHCl_3$ afforded 0.61 g (13%) of *trans*–6*α*–hydroxyperhydrobenzo[*c*]quinolizidine (VIIa) as colorless solid, which was recrystallized from *n*–hexane to give fine prisms, mp 138—140°. Repeated recrystallizations gave a sample for analysis, mp 141—142°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3584, 3390, 3100, 2801, 2755, 1050 and 1002. NMR τ: 6.80 (m, C_6–proton) and 6.68 (m, C_1–equatorial proton). *Anal.* Calcd. for $C_{13}H_{23}ON$: C, 74.59; H, 11.08; N, 6.69. Found: C, 74.63; H, 11.13; N, 6.58. VIIa was acetylated with Ac_2O in pyridine in usual way, giving the acetate (VIIb). IR $\tau_{max}^{CHCl_3}$ cm^{-1}: 2800, 2755 and 1740. NMR τ: 5.60 (d–t, C_6–proton) and 6.76 (m, C_1–equatorial proton). The above fraction (B) was rechromatographed on alumina. The first elution with 3.0 liter of a 1:1 mixture of benzene—$CHCl_3$ gave 1.61 g (36%) of *cis*–6*α*–hydroxyperhydrobenzo[*c*]quinolizidine (VIa), which was recrystallized from *n*–hexane to give colorless needles, mp 130—131°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3584, 3413, 2798, 2752, 1054, 1033, and 1016. NMR τ: 6.30 (m, C_6–proton) and 6.90 (m, C_1–equatorial proton). *Anal.* Calcd. for $C_{13}H_{23}ON$: C, 74.59; H, 11.08; N, 6.69. Found: C, 74.58; H, 11.00; N. 6.82. VIa was acetylated with Ac_2O in pyridine in usual way giving the acetate (VIb). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2798, 2752, and 1740. NMR τ: 5.30 (m, C_6–proton) and 6.87 (m, C_1–equatorial proton). The second elution with 1.0 liter of $CHCl_3$ gave 0.15 g (3%) of *trans*–6*β*–hydroxyperhydrobenzo[*c*]quinolizidine (VIIIa), recrystallized from *n*–hexane to give colorless leaflets, mp 133—135° IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3597, 3413, 3145, 2797, 2758, 1053, 1044 and 1017. NMR τ: 6.25 (m, C_6–proton) and 6.65 (m, C_1–equatorial proton). *Anal.* Calcd. for $C_{13}H_{23}ON$: C, 74.59; H, 11.08; N, 6.69. Found: C, 75.00; H, 11.22; N, 6.25. Acetylation of VIIIa with Ac_2O in pyridine afforded the acetate (VIIIb) as viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2795, 2755, 1730 and 1720 (sh). NMR τ: 5.05 (m, C_6–proton) and 6.35 (m–d C_1–equatorial proton).

d) With sodium borohydride—AcOH in tetrahydrofuran: i) At room temperature: To a solution of 420 mg of I in 20 ml of anhydrous tetrahydrofuran was added 400 mg of $NaBH_4$, followed by 8 ml of AcOH. After standing at R.T. for 5 min, to the reaction mixture was added 10% NaOH. The organic layer was separated and the aqueous layer was extracted with two 20 ml portions of tetrahydrofuran. The combined extract was washed with saturated brine and dried over anhydrous K_2CO_3. Evaporation of tetrahydrofuran gave 380 mg of pale brown paste, which was chromatographed on 20 g of alumina. The first elution with 250 ml of a (1:1) mixture of benzene—$CHCl_3$ gave 130 mg (31%) of the starting material (I) recovered. The second elution with 150 ml of a 1:1 mixture of benzene—$CHCl_3$ gave 37 mg (9%) of colorless solid, which was identical with a sample of VIa obtained from the above reaction (c) on comparison of their IR spectra. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3584, 3413, 2798, 2752, 1054, 1033 and 1016. The third elution with 200 ml of $CHCl_3$ afforded 125 mg (30%) of VIIa, which was identical with the authentic sample obtained from the reaction (c) on comparison of their IR spectra. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3584, 3390—3100, 2801, 2755, 1050 and 1002.

ii) At refluxing temperature: To a solution of 410 mg of I in 20 ml of tetrahydrofuran was added 400 mg of $NaBH_4$, followed by 8 ml of AcOH, and the reaction mixture was refluxed for 3 hr. After adding 30 ml of 10% NaOH, the organic layer was separated, and the aqueous layer was extracted with two 20 ml portions of tetrahydrofuran. The combined extract was washed with saturated brine and dried over anhydrous K_2CO_3. Evaporation of the solvent gave 430 mg of pale brown semi–solid, which was chromatographed on 20 g of alumina. The first elution with 300 ml of benzene gave 45 mg (11%) of viscous oil, which wsa identical with V on comparison of their IR spectra. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2800, 2755 and 1710. The second elution with 170 ml of a 1:1 mixture of benzene—$CHCl_3$ gave 125 mg of a mixture of VIa and VIIa. The third elution with 200 lm of $CHCl_3$ gave 100 mg (24%) of colorless crystal, which was identical with VIIa on comparison of their IR spectra. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3584, 3390—3100, 2801, 2755, 1050 and 1002. The above mixture

of VIa and VIIa was chromatographed on 10 g of alumina to give 100 mg (24%) of VIa and 20 mg (5%) of VIIa. The total yield of VIIa was 29%.

e) With hydrogen–platinum oxide: A solution of 560 mg of I in 20 ml of AcOH in the presence of a few drops of $HClO_4$ was shaken with 50 mg of PtO_2 under H_2 atmosphere at R.T. Hydrogenation was stopped when 75 ml of H_2, one molar equivalent, was absorbed. The catalyst was filtered off, and washed with AcOH. The filtrate and the washings were combined, and AcOH was evaporated *in vacuo*. The residue was dissolved in 40 ml of $CHCl_3$ and to the resulting solution was added a paste, prepared from 1 g of anhydrous K_2CO_3 and 0.5 ml of H_2O, with vigorous agitation. The organic layer was decanted and dried over anhydrous K_2CO_3. Evaporation of $CHCl_3$ gave 490 mg of brown pasty residue, which was chromatographed on 15 g of alumina. The first elution with 50 ml of benzene gave 100 mg (18%) of viscous oil, which was identical with V on comparison of their IR spectra. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2800, 2755 and 1710. The second elution with 140 ml of benzene gave 130 mg (23%) of pale yellow semi-solid, which was identical with the starting material on comparison of their IR spectra. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1620 and 1550. The third elution with 90 ml of $CHCl_3$ afforded 150 mg (27%) of a mixture of VIa and VIIa.

f) With hydrogen (2 moles)–platinum oxide: Nine hundred mg of I was hydrogenated with 100 mg of PtO_2 in 20 ml of AcOH in the presence of a few drops of $HClO_4$ under an atmospheric pressure of H_2 at R.T. After uptake of 2 molar equivalent amount of H_2 (207 ml at 17°), the catalyst was removed and the solvent was evaporated *in vacuo*, giving the dark brown residue which was dissolved in 60 ml of $CHCl_3$ and added a paste, prepared from 5 g of anhydrous K_2CO_3 and 2.5 ml of H_2O, with vigorous agitation. Treatment as described above gave 860 mg of brown pasty residue, which was chromatographed on 40 g of alumina. The first elution with 400 ml of a 1:1 mixture of benzene—$CHCl_3$ gave 370 mg of VIa which was identical with the authentic sample of VIa on comparison of their IR spectra. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3584, 3413, 2798, 2752, 1054, 1033 and 1016. The second elution with 100 ml of $CHCl_3$ gave 70 mg of VIIa, as colorless crystal, which was identical with the authentic sample of VIIa on comparison of their IR spectra. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3584, 3390—3100, 2801, 2755, 1050 and 1002. The above mixture of VIa and VIIa was rechromatographed on 10 g of alumina to give 200 mg of VIa and 130 mg of VIIa. Total yields of VIa and VIIa were 570 mg (63%) and 200 mg (22%), respectively.

Isomerization of *cis*-and *trans*-Dodecahydro-6*H*-benzo[*c*]quinolizin-6-one (IV and V)——Upon treatment of crude mixtures of IV and V obtained from reductions of I with Li in liq. ammonia or $LiAlH_4$ under varying conditions, ratios of IV to V were taken from VPC analyses, with respect to isomerization, data were summarized in Table I.

Reduction of *trans*-Dodecahydro-6*H*-benzo[*c*]quinolizin-6-one (V)[4]——a) With $NaBH_4$: To a mixture of 310 mg of V and 310 mg of $NaBH_4$ in 20 ml of anhydrous tetrahydrofuran was added 6 ml of AcOH dropwise under ice cooling, and the resulting mixture was refluxed for 2 hr. After adding 40 ml of 10% NaOH, the organic layer was separated and the aqueous layer was extracted with 30 ml of $CHCl_3$. The combined extract was washed with saturated brine and dried over anhydrous K_2CO_3. Evaporation of the solvent afforded 270 mg of a mixture of VIa and VIIa as colorless solid in the ratio described in Table II, both identified on comparison of their IR spectra with those of the authentic samples.

b) With hydrogen–platinum oxide: Two hundred and forty mg of V was hydrogenated with 20 mg of PtO_2 in 20 ml of AcOH containing a few drops of $HClO_4$ at R.T., until further absorption of H_2 was hardly observed. Treatment as described in reduction of I gave 220 mg of pale brown solid, which was identified as a mixture of VIa and VIIa from VPC analysis (see Table II).

c) With $LiAlH_4$: To a solution of 450 mg of V in 50 ml of anhydrous ether was added 230 mg of $LiAlH_4$ and the mixture was refluxed with stirring for 3 hr. After adding 10 ml of AcOEt with ice cooling, then 50 ml of H_2O was added, and the organic layer was separated. The aqueous layer was extracted with 100 ml of AcOEt. The combined extract was washed with saturated brine and dried over anhydrous K_2CO_3. Evaporation of the solvent gave 400 mg of pale brown semi-solid, which was chromatographed on 15 g of alumina. The first elution with 200 ml of $CHCl_3$ gave 90 mg (20%) of colorless solid, mp 132—134°, which was identified as VIIIa on comparison of their IR spectra. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3597, 3413, 3145, 2797, 2758, 1053, 1044 and 1017.

The second elution with 170 ml of a 1:1 mixture of $CHCl_3$–EtOH gave 300 mg (67%) of colorless solid, mp 138—140°, which was identifical with VIIa on comparison of their IR spectra. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3584, 3390—3100, 2801, 2755, 1050 and 1002.

Reduction of a Mixture of Dodecahydro-6*H*-benzo[*c*]quinolizin-6-one (IV and V)——A crude mixture of IV and V obtained from the Birch reduction of I, of which the ratio was 1:2 in favor of V, was employed for reductions with $NaBH_4$ or PtO_2 under the conditions as shown in Table II to give mixtures of VIa and VIIa in varying ratios (see Table II).

Oxidation of *cis*-6*α*-Hydroxyperhydrobenzo[*c*]quinolizidine (VIa)——a) With chromium trioxide in AcOH: To a solution of 125 mg of VIa in 2 ml of AcOH was added 90 mg of CrO_3, and the resulting mixture was warmed on a steam-bath (80—90°) for 3 hr. After cool, thirty ml of H_2O followed by solid Na_2CO_3 were added to make the solution alkaline and then extracted with three 20 ml portions of $CHCl_3$. The combin-

4) The equilibrium mixture of V and IV in a 30: 1 ratio was used as V.

ed extract was washed with H_2O, and dried over anhydrous K_2CO_3. Evaporation of the solvent afforded 30 mg of dark brown pasty residue. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2800, 2750 and 1710, which was assigned mostly as V contaminated with a trace of IV from VPC analysis.

b) With chromium trioxide in pyridine: To a complex from 150 mg of CrO_3 and 1.5 ml of pyridine was added a solution of 100 mg of VIa dissolved in 2.5 ml of pyridine. The resulting mixture was allowed to stand R.T. for 24 hr. After adding 50 ml of H_2O, the mixture was shaken with three 20 ml portions of $CHCl_3$. The combined extract was washed with H_2O and dried over anhydrous K_2CO_3. Evaporation of $CHCl_3$ gave 40 mg of dark brown pasty residue, which was characterized as a mixture of IV and V in the ratio of 5:4 from VPC analysis.

Oxidation of *trans*-6*α*-Hydroxyperhydrobenzo[*c*]quinolizidine (VIIa)——a) With chromium trioxide in AcOH: Treatment of 125 mg of VIIa as described in the oxidation of VIa with 85 mg of CrO_3 in 2 ml of AcOH afforded 40 mg of dark brown pasty residue, which was assigned as V contaminated with a trace of IV from VPC analysis. IR $\nu_{max}^{CHCl_3}$ cm^{-1}:2780, 2750 and 1710.

b) With chromium trioxide in pyridine: One hundred and five mg of VIIa was treated with CrO_3–pyridine complex as described in the oxidation of VIa to give 50 mg of dark brown pasty residue which was assigned mostly as V contaminated with a trace of IV from VPC analysis.

Chlorination of *cis*-6*α*-Hydroxyperhydrobenzo[*c*]quinolizidine (VIa)——a) With phosphorus pentachloride: To a solution of 880 mg of VIa dissolved in 20 ml of anhydrous $CHCl_3$ was added 900 mg of anhydrous $CaCO_3$, and followed by portionwise addition of 1.0 g of PCl_5 at R.T. with stirring. Stirring was continued for further 80 min and after adding 50 ml of saturated $NaHCO_3$ solution, the organic layer was separated. The aqueous layer was extracted with two 20 ml portions of $CHCl_3$ and the combined extract was washed with H_2O, and dried over anhydrous K_2CO_3. Evaporation of the solvent gave 550 mg of reddish brown pasty residue, which was chromatographed on 20 g of silica–gel. The first elution with 350 ml of $CHCl_3$ afforded 110 mg (12%) of pale brown oil, *cis*–6*β*–chloroperhydrobenzo[*c*]quinolizidine (XI), which was positive to the Beilstein test. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2800 and 2755. NMR τ: 5.90 (m, C_6–proton) and 6.85 (m–d, C_1–equatorial proton). Picrate: mp 193—196°, recrystallized from iso–PrOH–EtOH. *Anal.* Calcd. for $C_{19}H_{25}O_7N_4Cl$: C, 49.94; H, 5.51; N, 12.26. Found: C, 50.36; H, 5.56; N, 12.24. The second elution with 550 ml of a 10:1 mixture of $CHCl_3$–EtOH gave 320 mg (42%) of pale brown oil, Δ^6–perhydrobenzo[*c*]quinolizidine (IX).

IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2800, 2760, and 835. NMR τ: 4.60 (m, $>C=\overset{H}{\overset{|}{C}}-CH_2-$) and 6.65 (m–d, C_1–equatorial proton). Picrate: mp 159—161.5°, recrystallized from iso–PrOH. *Anal.* Calcd. for $C_{19}H_{24}O_7N_4$: C, 54.30; H, 5.67; N, 13.16. Found C, 54.28; H, 5.75; N, 13.33.

b) With thionyl chloride at room temperature: To a solution of 400 mg of VIa in 10 ml of anhydrous benzene was added a solution of 0.5 ml of $SOCl_2$ in 5 ml of anhydrous benzene dropwise at R.T. over a period of 30 min with stirring, and stirring was continued for another 1 hr. The reaction mixture was treated with H_2O followed by 10% NaOH to make the solution alkaline, and the benzene layer was separated. The aqueous layer was extracted with three 30 ml portions of benzene, and the combined extract was washed with H_2O and dried over anhydrous K_2CO_3. Evaporation of the solvent gave 380 mg of brown pasty residue, which was chromatographed on 15 g of silica–gel. The first elution with 300 ml of $CHCl_3$ gave 60 mg (14%) of pale brown viscous oil, *cis*–6*α*–chloroperhydrobenzo[*c*]quinolizidine (X). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2800 and 2760. NMR τ: 5.37 (m, C_6–proton) and 6.75 (m, C_1–equatorial proton). Picrate: mp 138.5—141.5°, recrystallized from EtOH. *Anal.* Calcd. for $C_{19}H_{25}O_7N_4Cl \cdot C_2H_5OH$: C, 50.15; H, 6.21; N, 11.14. Found: C, 50.02; H, 5.79; N, 10.97. The second elution with 400 ml of a 10:1 mixture of $CHCl_3$–EtOH and the third elution with 500 ml of EtOH gave 200 mg (50%) of pale brown solid, which was identical with the starting material (VIa) on comparison of their IR spectra. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3584, 3413, 2798, 2752, 1054, 1033 and 1016.

c) With thionyl chloride–pyridine at 50—60°: To a solution of 418 mg of VIa in 10 ml of anhydrous benzene and 20 ml of anhydrous pyridine was added a solution of 1.0 ml of $SOCl_2$ in 5.0 ml of anhydrous benzene with stirring at 15° over a period of 30 min. The solution was stirred at 50—60° for 1 hr, and then made alkaline with 10% NaOH under ice cooling. The organic layer was separated and the aqueous layer was extracted with 100 ml of benzene. The combined extract was washed with H_2O and dried over anhydrous K_2CO_3. Evaporation of the solvent gave 300 mg of brown pasty residue, which was chromatographed on 10 g of silica–gel. The first elution with 250 ml of $CHCl_3$ afforded *ca.* 20 mg of brown paste, but failed to assign its structure. The second elution with 50 ml of $CHCl_3$ gave 150 mg (41%) of pale brown solid, which was identical with IX on comparison of their IR spectra and the mixed melting point determination of their picrates. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2800, 2760 and 835. Picrate: mp 158—161°.

Chlorination of *trans*-6*α*-Hydroxyperhydrobenzo[*c*]quinolizidine (VIIa)——a) With phosphrous pentachloride: A mixture of 1.0 g of pulverized PCl_5 and 680 mg of *trans*–6*α*–hydroxyperhydrobenzo[*c*]quinolizidine (VIIa) was stirred well at R.T. for 10 min and then warmed on a steam–bath for another 10 min. After adding 20 ml of H_2O, the mixture was warmed on a steam–bath for 20 min and then made alkaline with 10% NaOH, and extracted with three 20 ml portions of $CHCl_3$. The combined extract was washed with saturated brine and dried over anhydrous K_2CO_3. Evaporation of the solvent afforded 510 mg of dark brown pasty

residue, which was chromatographed on 20 g of silica-gel. The first elution with 150 ml of $CHCl_3$ and the second elution with 300 ml of a 10:1 mixture of $CHCl_3$–EtOH gave 360 mg (48%) of pale brown oil, *trans*-6*β*-chloroperhydrobenzo[*c*]quinolizidine (XII). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2800 and 2755. NMR τ: 5.81 (m, C_6-proton) and 6.62 (m-d, C_1-equatorial proton). Picrate: mp 189—190°, recrystallized from EtOH. *Anal.* Calcd. for $C_{19}H_{25}O_7N_4Cl$: C, 49.94; H, 5.51; N, 12.26. Found: C, 50.09; H, 5.61; N, 12.46.

b) With thionyl chloride in benzene at 65—70°: To a solution of 400 mg of VIIa in 20 ml of anhydrous benzene was added a solution of 1.0 ml of $SOCl_2$ in 5 ml of anhydrous benzene dropwise at R.T. with stirring. After stirring was continued at 65—70° for 3 hr, was added 10% NaOH to make the solution alkaline with ice cooling. The organic layer was separated and the aqueous layer was extracted with four 40 ml portions of benzene. The combined extract was washed with saturated brine and dried over anhydrous K_2CO_3. Evaporation of the solvent gave 380 mg of dark brown pasty residue, which was chromatographed on 7.0 g of silica-gel. The first elution with 100 ml of $CHCl_3$ and the second elution with 100 ml of a 10:1 mixture of $CHCl_3$—EtOH gave 270 mg (61%) of pale brown viscous oil, which was identical with XII on comparison of their IR spectra and the mixed melting point determination of their picrates. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2800 and 2755. Picrate: mp 188—190°.

Thioketalization of V——To a solution of 1.04 g of V and 1 ml of 1,2-ethanedithiol in 5 ml of AcOH was added 0.5 ml of BF_3-etherate at 10° over a period of 10 min. Stirring was continued at 90—95° for 3 hr. After adding 200 ml of saturated $NaHCO_3$, the resulting solution was shaken with four 50 ml portions of $CHCl_3$. The combined extract was washed with H_2O and dried over anhydrous K_2CO_3. Evaporation of the solvent gave 1.32 g of pale orange colored solid, which was crystallized from acetone to give 1.10 g (77%) of colorless prisms of the dithioketal (XIII), mp 91—92°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2798, 2755 and 1427. NMR τ: 6.79 (s, $-S-CH_2-CH_2-S-$) and 6.67 (m, C_1-equatorial proton). *Anal.* Calcd. for $C_{15}H_{25}NS_2$: C, 63.54; H, 8.88; N, 4.94. Found: C, 63.26; H, 8.95; N, 5.00.

Desulfurization of the Dithioketal (XIII)——A suspension of 150 mg of the dithioketal (XIII) and a large excess of freshly prepared Raney nickel (type W-2) in 10 ml of anhydrous EtOH was heated under reflux with stirring for 9 hr under nitrogen atmosphere. The catalyst was filtered off and the filtrate was evaporated to dryness to give 70 mg (70%) of colorless semi-solid, *trans*-perhydrobenzo[*c*]quinolizidine (III). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2800 and 2755. Picrate: mp 180—182°, recrystallized from aq. EtOH. *Anal.* Calcd. for $C_{19}H_{26}O_7N_4$: C, 54.02; H, 6.20; N, 13.26. Found: C, 53.69; H, 6.14; N, 13.24.

Hydrogenolysis of *trans*-6*β*-Chloroperhydrobenzo[*c*]quinolizidine (XII)——a) With 10% palladium on carbon: A mixture of 470 mg of XII, 50 mg of 10% Pd-C and 120 mg of KOH in 10 ml of MeOH was shaken under H_2 stream at R.T. for 10 hr. The catalyst was removed and the filtrate was evaporated to dryness. To the residue was added 20 ml of H_2O and the resulting solution was extracted with 100 ml of $CHCl_3$. The extract was washed with H_2O, and dried over anhydrous K_2CO_3. Evaporation of the solvent gave 400 mg of brown oil, which was identical with XII on comparison of their IR spectra.

b) With 10% sodium amalgam: To a solution of 400 mg of XII in 10 ml of MeOH was added 3.0 g of 10% Na-Hg, and the mixture was vigorously stirred at R.T. for 5 hr. Hg thus formed was filtered off and the filtrate was evaporated to dryness. To the residue was added 40 ml of saturated brine and shaken with four 20 ml portions of $CHCl_3$. The combined extract was washed with saturated brine and dried over anhydrous K_2CO_3. Evaporation of the solvent gave 360 mg of the starting material, judged from the IR spectra.

c) With lithium aluminum hydride: To a solution of 130 mg of XII in 20 ml of anhydrous tetrahydrofuran was added 100 mg of $LiAlH_4$ and the reaction mixture was refluxed for 8 hr. Treated as usual manners, gave 90 mg of the starting material (XII) recovered.

Hydrogenation of Δ^6-Perhydrobenzo[*c*]quinolizidine (IX)——One hundred and forty mg of IX dissolved in 20 ml of EtOH was shaken with 20 mg of PtO_2 at R.T. under H_2 stream. After completion of H_2 absorption, the catalyst was filtered off and EtOH was evaporated *in vacuo* to give 145 mg of brown viscous oil, which was chromatographed on 5.0 g of silica-gel. Elution with 150 ml of a 20:1 mixture of $CHCl_3$—EtOH gave 90 mg (65%) of colorless viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2800 and 2755. From gas chromatographic analysis, this oil is shown to be a mixture of *cis*- and *trans*-perhydrobenzo[*c*]quinolizidines (XIV and III), in the ratio of 1:5 in favor of III, although we failed to analyze XIV due to insufficient amount.

Wolff-Kishner Reduction of V——To a solution of 800 mg of 80% hydrazine hydrate and 800 mg of KOH in 15 ml of trimethylene glycol was added 621 mg of V and the resulting mixture was heated under reflux over a gauze for 3 hr. After cool, was added 20 ml of water to the almost colorless reaction solution, and extracted with five 20 ml portions of $CHCl_3$. The combined $CHCl_3$ extract was washed with water and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave 600 mg of pale brown oil, which was chromatographed on 15 g of silica-gel. The first elution with 250 ml of $CHCl_3$ afforded 130 mg (21%) of pale brown oil, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2800, 2750 and 1710, which was identical with the starting material (V) on comparison of their IR spectra. The second elution with 450 ml of a 40:3 mixture of $CHCl_3$—EtOH afforded 230 mg (40%) of almost colorless semi-solid, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2800 and 2755, which was identical with III obtained by desulfurization of the dithioketal (XIII) on comparison of their IR spectra. Picrate: mp 180—182°, undepressed on admixture with a sample of picrate of III.