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Aza-steroids. I. Synthesis of 9-Aza-steroid Ring System[1]

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6,7-Cyclobutano-1,2-cyclopropanoquinolizidine (I) (9-azasteroid ring system) and perhydrodibenzo[*c,f*]quinolizine (II) (9-aza-D-homosteroid) were synthesized by the routes shown in Chart 1 and 3.

Synthesis of aza-steroids has been reported in large numbers in recent years. Of these steroids, those having a bridgehead nitrogen atom are 8-[3], 13-,[4] and 14-aza-steroids.[5] We have now synthesized the most simple type 9-aza-steroid (I), and 9-aza-D-homosteroid (II) as its model compound, which are described herein.[6]

9-Aza-D-homosteroid (Perhydrodibenzo[*c,f*]quinolizine) (II)

Heating of a mixture of 2-(1-cyclohexenyl)ethylamine[7] (III) and ethyl 3-(2-oxocyclohexyl)propionate[8] (IV) effected cyclization to the enamine lactam (V) in 86.1% yield. V was

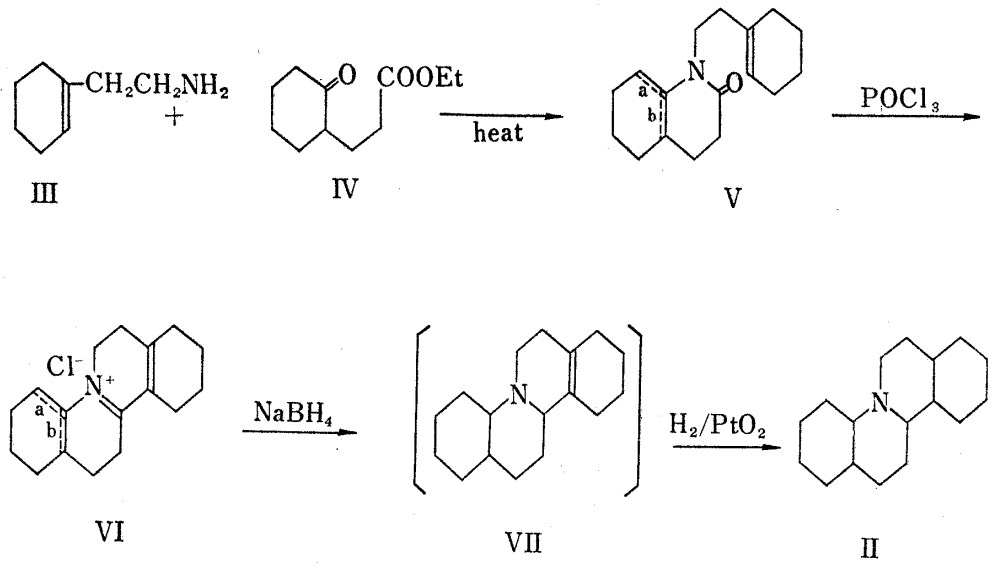


Chart 1

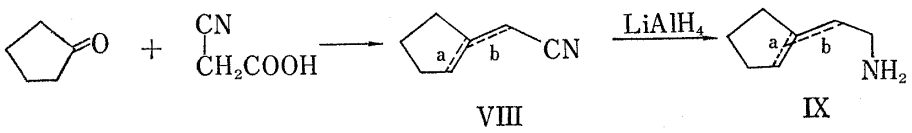
1) This paper forms Part XXI of "Synthesis of Quinolizine Derivatives." Part XX: S. Ohki, M. Akiba, H. Shimada (née Masumoto), and K. Kunihiro, *Chem. Pharm. Bull.* (Tokyo), **16**, 1889 (1968).
2) Location: *Women's Division, Ueno Sakuragi 1–10–19, Daito-ku, Tokyo, 110 Japan.*
3) R.E. Brown, D.N. Lustgarten, R.J. Stanaback, and R.I. Meltzer, *J. Org. Chem.*, **31**, 1489 (1966); A.I. Meyers and J.C. Sircar, *Tetrahedron*, **23**, 785 (1967).
4) W.R. Schleigh, A. Calata, and F.D. Popp, *J. Heterocyclic Chem.*, **2**, 379 (1965); A.J. Birch and G.S.R. Subba Rao, *J. Chem. Soc.*, **1965**, 3007.
5) E.R.H. Jones, British Patent 1.017.700 (1966) (*Chem. Abstr.*, **64**, 14243 (1966)); U.K. Pandit, K. de Jonge, G.J. Koomen, and H.O. Hinsmann, *Tetrahedron Letters*, 3529 (1967).
6) Recently, during the course of the present experiment, A.I. Meyers and W.N. Beverung reported the synthesis of 18-nor-9-aza-androst-13(14)-en-6-one (*Chem. Commun.*, 877 (1968)). *Cf.* A.I. Meyers, J. Schneller, and N.K. Ralhan, *J. Org. Chem.*, **28**, 2944 (1963); G. Jones and J. Wood, *Tetrahedron*, **21**, 2524, 2961 (1965); W.R Schleigh and F.D. Popp, *J. Chem. Soc.*, (C), **1966**, 760.
7) S. Sugasawa and S. Saito, *Chem. Pharm. Bull.* (Tokyo), **4**, 237 (1956).
8) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

found from its nuclear magnetic resonance (NMR) spectrum (Fig. 1) to be a 2:11 mixture of the *exo*[9] (Va) and *endo*[9] (Vb) isomers. NMR ($CDCl_3$) τ: 4.60 (1H, nearly singlet; $HC=C\langle$), 4.90 (2/11H, multiplet; $>N-C=CH$), 6.37 (2H, triplet; $>N-CH_2-$), 7.58 (2H, triplet; $-COCH_2-$).

The Bischler–Napieralski reaction of V with phosphoryl chloride gave an unstable quinolizinium salt (VI) (UV λ_{max}^{EtOH}: 260, 340 mμ) (picrate, mp 130—132°). Reduction of VI with sodium borohydride gave a substance considered to be dehydroperhydrobenzoquinolizine (VII) which was difficult to purify and was submitted *per se* to reduction over platinum oxide in acetic acid. The product therefrom was purified by silica gel chromatography and II was obtained as an oil, in 12.3% yield (calculated from V). This oily product (II) gave a single sharp spot in thin-layer chromatography and a single peak in gas–liquid chromatography. IR ν_{max} cm^{-1}: 2770, 2740 (Bohlmann bands, *trans*-quinolizidine), NMR ($CDCl_3$) τ: 6.80 (1H, sextet, N–CHH(eq)–). *m/e* 247 (M^+). Picrate: mp 205—207°.

9-Aza-steroid (6,7-Cyclobutano-1,2-cyclopropanoquinolizidine) (I)

I was synthesized in accordance with that of II. The Cope condensation of cyclopentanone and cyanoacetic acid has been considered to give cyclopenten-1-yl-acetonitrile[9] (VIIIa) but the NMR spectrum of the product obtained here showed it to be a 2:1 mixture of its *endo* (VIIIa) and *exo* (VIIIb) isomers.[10] NMR (CCl_4) τ: 4.28 (nearly singlet, $C\underline{H}=C-CH_2CN$), 4.82 (sextet, $-C=CHCN$), 6.94 (singlet, $CH=CC\underline{H}_2CN$). Proton displacement by the solvent effect (benzene, CCl_4, $CDCl_3$, Me_2SO) was not observed in this mixture.



VIII IX

Chart 2

Reduction of VIII with lithium aluminium hydride afforded the amine (IX) in 23% yield, with by-product formation of a polymer. This product (IX) was found from its NMR spectrum to be a 1:1 mixture of the *endo* (IXa) and *exo* (IXb) isomers. NMR ($CDCl_3$) τ: 6.75 (doublet, J=7.5 cps, $-C=CHC\underline{H}_2NH_2$), 7.20 (triplet, J=7.0 cps, $-CH_2C\underline{H}_2NH_2$).

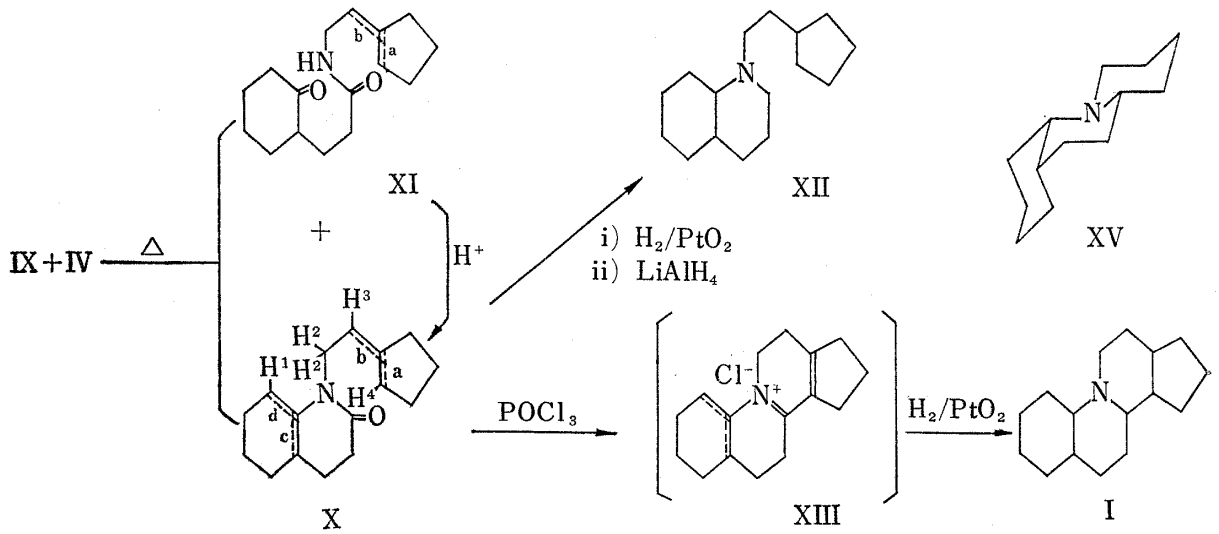


Chart 3

9) The designations a—d indicate the position of the double bond.

10) Recently, presence of isomers was also clarified by N. Itoh, K. Yonezawa, K. Abe, and M. Onda, *Chem. Pharm. Bull.* (Tokyo), **17**, 206 (1969).

The enamine lactam (X), bp 175—180° (2 mmHg), was obtained in 70% yield by heating a mixture of IX and IV, but about 10% amount of an amide (XI) was formed as a by-product. X was considered from its NMR spectrum to be a mixture of isomers (Xac, Xad, Xbc, and Xbd)[9] differing in the position of the double bond. NMR ($CDCl_3$) (Fig. 2) τ: 4.65 (nearly singlet, H^4), 4.90 (multiplet, H^1+H^3), 5.85 (doublet, $J=5$ cps, $2H^2$ (Xb)), 6.32 (triplet, $J=7.5$ cps, $2H^2$ (Xa)). Decoupling of the multiplet peak at τ 4.90 changes the doublet at τ 5.85 to a singlet. From the ratio of $2H^2$, the ratio of Xa to Xb would be 6:5.

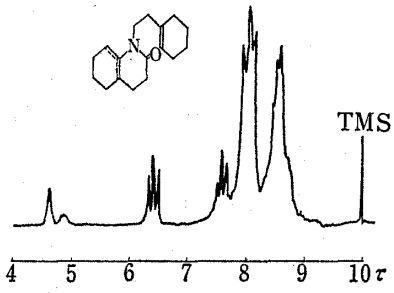


Fig. 1.

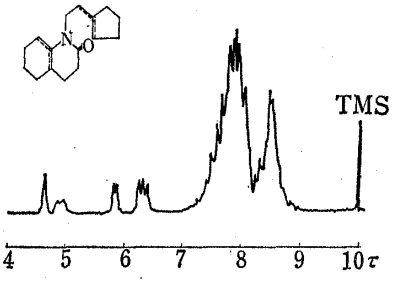


Fig. 2.

XI was obtained as a viscous oil and was purified by silica gel chromatography. The NMR spectrum of the product showed it to be a 3:1 mixture of XIa and XIb. NMR ($CDCl_3$) τ: 6.0 (broad, NHCO), 4.60 (nearly singlet, $-CH_2\overset{|}{C}=\overset{|}{C}\underline{H}$), 4.73 (multiplet, $-CH_2\underline{C}H=C\langle$), 6.20 (triplet, $-CONHC\underline{H}_2CH=C\langle$), 6.65 (quartet, $-CONHC\underline{H}_2CH_2\overset{|}{C}=$). The fact that D_2O substitution resulted in disappearance of τ 6.0, and changes of 6.20 and 6.65 signals to a doublet, and a triplet, respectively, indicated coupling of NH and CH_2. A part of XI crystallized to a product of mp 85—87° when allowed to stand for a long time. However, this crystallized product was also found to be a mixture of XIa and XIb. A part of XI was converted into X when left for a long time in a protic solvent or in the presence of H^+.

Catalytic reduction of XI over platinum oxide, followed by reduction with lithium aluminium hydride gives cyclopentylethylperhydroquinoline (XII), which forms a perchlorate of mp 173—176°, as a sole product.

The Bischler-Napieralski reaction[11] of X with phosphoryl chloride gave XIII (UV λ_{max}^{EtOH}: 265, 350 mμ) which was submitted to catalytic reduction over platinum oxide without further purification, and the oily product was purified by silica gel chromatography. I was obtained in 7.2% yield (calculated from X) as an oil which showed a single sharp spot in thin-layer chromatography and a single peak in gas-liquid chromatography. The structure of I was confirmed by IR, NMR, and mass spectra, and by elemental analysis. IR ν_{max} cm^{-1}: 2786, 2747 (*trans*-quinolizidine), NMR ($CDCl_3$) τ: 6.95 (multiplet, $\rangle N-\overset{|}{C}H\underline{H}$(eq)). *m/e* 233 ($M^+$). Picrate: mp 200—202°. From these data, it is considered that only Xa had undergone cyclization reaction. Meyers, Schneller, and Ralhan,[6] and Wechter and others[12] had failed in the reduction of the double bond between the C and D rings but the fact that I is a perhydro compound was proved from its mass spectrum which did not show the peak originating from the retro-Diels-Alder reaction and showed *m/e* 233 as in the case of II.

In the NMR spectrum of I and II, the proton signals around nitrogen are similar to that of one (XV)[1] (picrate, mp 203—205°) of the stereoisomers of perhydrobenzo[*c*]quinolizine. Consequently, the A-B-C rings in I and II probably have the same steric structure as those in XV, and the C-D ring has a *cis*-juncture by the *cis* addition of hydrogen.

Further examinations on the steric structure of I and II, and the synthesis of 9-aza-steroids having a functional group are now under way.

11) The Bischler-Napieralski reaction of this kind of compounds is reported to be difficult[7].
12) W.J. Wechter, *Chem. Ind.* (London), **1959**, 294; M. Nussim and F. Sondheimen, *ibid.*, **1960**, 400.

Experimental

Enamine Lactam (V)——A mixture of 1.26 g of 2-(1-cyclohexenyl)ethylamine (III) and 2 g of ethyl 3-(2-oxocyclohexyl)propionate (IV) was heated under reflux in N_2 stream for 15 hr. The mixture was cooled and distilled *in vacuo* to collect 2.2 g (86%) of a distillate of bp 190—200° (2 mmHg). IR $\nu_{max}^{liq. film}$ cm^{-1}: 1661 (>NCO), 1631 (>N–C=C). *Anal.* Calcd. for $C_{17}H_{25}ON$: N, 5.40. Found: N, 5.15.

Quinolizinium Salt (VI)——A mixture of 2 g of the enamine lactam (V), 5 ml of $POCl_3$, and 10 ml of toluene was refluxed for 4 hr. After removal of the solvent *in vacuo*, 10 ml of water was added to the residue. The mixture was warmed, the aqueous layer was separated, washed with benzene, treated with charcoal, taken up in $CHCl_3$, and the extract was dried over anhyd. Na_2SO_4. The brown residue obtained on evaporation of $CHCl_3$ gave 1.46 g (68.2%) of the chloride (VI). A part of aqueous solution of the chloride was saturated with KI, the iodide separated as an oil was taken up in $CHCl_3$, and the extract was dried. The residue obtained on evaporation of $CHCl_3$ did not crystallize. The UV spectrum of the chloride showed absorptions at 260 and 340 mμ (in EtOH). Picrate: Yellow scales (from EtOH–H_2O), mp 130—132°. *Anal.* Calcd. for $C_{23}H_{26}O_7N_4$: N, 11.91. Found: N, 11.89.

Perhydrodibenzo[*c*,*f*]quinolizine (9-Aza-D-homosteroid) (II)——To a solution of 1.46 g of VI dissolved in 10 ml of EtOH, 5 ml of EtOH solution of 0.4 g of $NaBH_4$ was added dropwise with stirring under ice-cooling. Stirring was continued for 15 hr at room temperature. The solvent was distilled off under a reduced pressure and the residue was extracted with ether. The extract was dried over Na_2SO_4, ether was evaporated, and the residual substance considered to be dehydroperhydrodibenzoquinolizine (VII) which was difficult to purify was submitted *per se* to reduction over 0.2 g of PtO_2 in 15 ml of AcOH at ordinary pressure. After removal of the catalyst by filtration, the solvent was evaporated from the filtrate, the residue was neutralized, salted out with K_2CO_3, and extracted with ether. The extract was dried over Na_2SO_4 and concentrated to a yellow-brown residue. The residue was placed on a column of silica gel. The column was washed well with benzene. Elution of the column with acetone–benzene (1:9) mixture gave 234 mg (17.9%) of II as a colorless oil. Yield from V, 12.3%. II gave a single sharp spot in thin-layer chromatography. IR $\nu_{max}^{liq. film}$ cm^{-1}: 2770, 2740 (*trans*-quinolizidine). *m/e* 247 (M^+). Picrate: Yellow scales (from EtOH), mp 205—207°. *Anal.* Calcd. for $C_{23}H_{32}O_7N_4$: C, 57.97; H, 6.77; N, 11.76. Found: C, 57.59; H, 6.76; N, 11.74.

Enamine Lactam (X)——A mixture of 0.5 g of the amine (IX) and 0.87 g of IV was heated under reflux in N_2 stream for 15 hr. Treatment of the reaction mixture as for V afforded 0.76 g (70%) of a liquid, bp 175—180° (2 mmHg). IR $\nu_{max}^{liq. film}$ cm^{-1}: 1661 (>N–CO), 1642 (>N–C=C<).

Keto-amide (XI)——After removal of X by distillation, the remaining residue was purified by silica gel column chromatography. Elution of the column with acetone–benzene (1:4) mixture gave 87 mg (7.5%) of XI. IR $\nu_{max}^{liq. film}$ cm^{-1}: 1646 (>NHCO), 1712 (>C=O). A part of XI crystallized to a product of mp 85—87° (from hexane–ether). *Anal.* Calcd. for $C_{16}H_{25}O_2N$: C, 72.96; H, 9.57; N, 5.32. Found: C, 73.00; H, 9.61; N, 5.32.

1-(2-Cyclopentylethyl)perhydroquinoline (XII)——A mixture of 190 mg of X, 50 mg of PtO_2, and 5 ml of dehyd. EtOH was submitted to catalytic reduction at ordinary temperature and pressure. The catalyst and solvent were removed. To a suspension of $LiAlH_4$ (60 mg) in dehyd. ether (5 ml) was added dropwise with stirring a solution of the above residue in dehyd. ether (5 ml) under ice-cooling. The mixture was stood over night. The complex salt thereby formed was decomposed with H_2O and the inorganic salt was filtered off. The filtrate was concentrated and the residue was dissolved in ether which was dried over Na_2SO_4 and evaporated. The residue obtained was purified by silica gel column chromatography. Elution of the column with acetone–benzene (4:6) mixture gave 78 mg (45.4%) of XII. Perchlorate: mp 173—176° (from EtOH). *Anal.* Calcd. for $C_{16}H_{30}O_4NCl$: C, 57.21; H, 9.00; N, 4.19. Found: C, 56.82; H, 9.03; N, 3.93.

6,7-Cyclobutano-1,2-cyclopropanoquinolizidine (9-Aza-steroid) (I)——A solution of 0.76 g of X and 2 ml of $POCl_3$ in 10 ml of toluene was refluxed for 4 hr. Treatment of the cooled reaction mixture as for VI afforded XIII. The chloride (XIII) in EtOH absorbs at 265 and 350 mμ. Without purification, a solution of XIII dissolved in 20 ml of anhyd. EtOH, added with 0.3 g of PtO_2, was submitted to catalytic reduction and the reaction mixture was treated as for II. The product was purified by silica gel column chromatography and 52 mg (7.2%) of I was obtained as an oil. This 9-aza-steroid (I) gave a single sharp spot in thin-layer chromatography and a single peak in gas–liquid chromatography. IR $\nu_{max}^{liq. film}$ cm^{-1}: 2776, 2747 Bohlmann band), *m/e* 233 (M^+). Picrate: mp 200—202° (from EtOH). *Anal.* Calcd. for $C_{22}H_{30}O_7N_4$: C, 57.13; H, 6.54; N, 12.12. Found: C, 57.30; H, 6.50; N, 11.90.

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