for 2 hr. under a N_2 atmosphere. The solvent was removed under reduced pressure, water added, and the product was extracted with Et_2O . The extract was washed with 2% $NaHCO_3$ solution, dried, and the solvent removed to give 2.63 g. of an oily residue, which was chromatographed on neutral alumina (Woelm; grade III). The benzene fraction gave 743 mg. of 6-oxapregna-2,4-diene-7,20-dione (VIIc), which on recrystallization from hexane-benzene gave needles, m.p. 157~159°. *Anal.* Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 75.98; H, 8.56. IR λ_{max}^{KBr} cm^{-1} : 1750 (lactone CO), 1710 (20-CO), 1650, 1590 ($\Delta^{2,4}$). UV: λ_{max}^{EtOH} 273 $m\mu$ (ϵ 8,400).

3 β -Acetoxy-5-hydroxy-6-aza-5 ξ -pregnan-7-one (Xc)—A solution of 500 mg. of the formate IIIc in 150 cc. of dry benzene was bubbled with dry NH_3 for 2.5 hr., and left standing overnight at room temperature. The solvent was removed to give an amorphous substance, which on repeated recrystallization from hexane-benzene afforded 3 β -acetoxy-5-hydroxy-6-aza-5 ξ -pregnan-7-one (Xc) as fine needles, m.p. 127~127.5° (decomp.). *Anal.* Calcd. for $C_{22}H_{33}O_5N$: C, 67.49; H, 8.50; N, 3.58. Found: C, 67.26; H, 8.32; N, 3.61. IR λ_{max}^{KBr} cm^{-1} : 3450 (OH), 3230, 3100 (NH), 1725 (AcO), 1708 (20-CO), 1655 (CONH).

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Summary

Ozonolysis of 3 β -acetoxycholest-5-en-7-one (Ia), 3 β -acetoxyandrost-5-en-7,17-dione (Ib), and 3 β -acetoxypregn-5-en-7,20-dione (Ic) afforded 3 β -acetoxy-5-formoxy-6-oxa-5 ξ -cholestan-7-one (IIIa), 3 β -acetoxy-5-formoxy-6-oxa-5 ξ -androstan-7,17-dione (IIIb), and 3 β -acetoxy-5-formoxy-6-oxa-5 ξ -pregnan-7,20-dione (IIIc), respectively. The corresponding δ -keto acids (IIa, b, c) were also isolated from the reaction mixture. Some 6-oxa- and 6-aza-steroids were derived from the δ -keto acid II as well as from its pseudo acid formate III and acetate IV.

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40. Tanezo Taguchi, Keiro Yoshizue,*¹ and Shiro Anzai*²: Configurational Effect in N-Alkylation of Diastereomeric 2-Aminocyclohexanol.*³

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Some years ago Taguchi and Nakayama¹⁾ reported N-ethylation of DL-*trans*- and DL-*cis*-2-aminocyclohexanols (I) with ethyl tosylate or ethyl bromide and potassium carbonate, in which *trans*-I underwent N-diethylation, whereas *cis*-I gave an N-monoethyl derivative, which resisted further ethylation. This phenomenon was considered due to a hydrogen bond,^{2~4)} $\begin{array}{c} | \\ -N \cdots H-O- \end{array}$, which exists in the N-ethyl derivative of *cis*-I,

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4) The hydrogen bond was erroneously drawn between O and H attached to N in the diagram of the N-ethyl derivative of *cis*-I in the preceding paper.¹⁾

but not in the corresponding *trans* form. The effect of the hydrogen bond upon alkylation was also confirmed in other alkylation reactions of I which are dealt with in the present paper. Alkylating agents, products and reaction conditions are shown in Table I.

TABLE I. Alkylations of DL-2-Aminocyclohexanols (I)

Alkylating agents ^{a)}	Product from		Reaction conditions
	<i>cis</i> -I	<i>trans</i> -I	
A) methyl tosylate	R-NHCH ₃ ^{b)}	R'-N(CH ₃) ₂	boiled in toluene for 3 hr.
B) ethyl bromide	R-NHC ₂ H ₅	R'-N(C ₂ H ₅) ₂	in EtOH with K ₂ CO ₃ on a water bath for 5 hr.
C) n-propyl bromide	R-NHC ₃ H ₇	R'-N(C ₃ H ₇) ₂	"
D) iso-propyl bromide	R-NHCH(CH ₃) ₂	R'-NHCH(CH ₃) ₂	"
E) n-butyl bromide	R-NHC ₄ H ₉	R'-NHC ₄ H ₉	boiled in <i>n</i> -butanol or toluene with K ₂ CO ₃ for 3 hr.

a) 2.2-2.5 moles per mole of I were used.

b) R: DL-*cis*-2-hydroxycyclohexyl. R': DL-*trans*-2-hydroxycyclohexyl.

When methyl tosylate (A), ethyl bromide (B) and n-propyl bromide (C) were allowed to react under conditions described, as indicated in Table I, *trans*-I yielded mainly N-dialkyl derivatives, while *cis*-I gave only N-monoalkyl derivatives. Also in this case difference in configuration between the *trans* and *cis* isomers seems to control the degree of alkylation, and this finding supports the aforesaid presumption. On the other hand, when iso-propyl bromide (D) and n-butyl bromide (E) were used as alkylating agents, both *cis*- and *trans*-I suffered N-monoalkylation. In this case, the bulky alkylating agents (D) and (E) seem to produce and/or suffer a steric hindrance which causes a resistance to further alkylation even in the *trans* configuration.

The effect of hydrogen bond upon N-alkylation was also examined in the ethylation reaction of DL-*trans*- and DL-*cis*-2-methylcyclohexylamines⁵⁻¹²⁾ (II), both of which produce no detectable hydrogen bonding.

Prior to this examination, the inversion of *trans*-II to *cis*-II via 2-methylcyclohexanone oxime^{6,11,12)} (III) was attempted. *Trans*-II was oxidized with the Caro's acid in the presence of magnesium oxide¹³⁾ or with potassium permanganate in the presence of formaldehyde.¹⁴⁾ The former oxidizing agent gave III in a poor yield which had already

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DL-*trans*-2-*n*-Butylaminocyclohexanol, b.p.₄₆ 150~153°. Hydrochloride : m.p. 230~231°. *Anal.* Calcd. for C₁₀H₂₁ON·HCl : C, 57.81; H, 10.68; N, 6.74. Found : C, 57.22; H, 10.26; N, 6.87.

DL-*cis*-2-Methylaminocyclohexanol, yield 50%. Picrate : m.p. 142°. *Anal.* Calcd. for C₇H₁₅ON·C₆H₃O₇N₃ : N, 15.64. Found : N, 15.98.

DL-*cis*-2-Ethylaminocyclohexanol.¹⁾

DL-*cis*-2-*n*-Propylaminocyclohexanol, b.p.₃₀ 110~112°, m.p. 74~76°, yield 82%. Hydrochloride; m.p. 215~216°. Picrate : m.p. 164~165°. *Anal.* Calcd. for C₉H₁₉ON·C₆H₃O₇N₃ : C, 46.63; H, 5.69; N, 14.54. Found : C, 46.52; H, 5.29; N, 14.39.

DL-*cis*-2-*n*-Butylaminocyclohexanol, b.p.₂₀ 117~119°, m.p. 50~55°, yield 80%. Picrate : m.p. 135~136°. *Anal.* Calcd. for C₁₀H₂₁ON·C₆H₃O₇N₃ : N, 14.00. Found : N, 13.87.

DL-1-Methyl-2-nitrosocyclohexane—To an aqueous solution (10 cc.) of *trans*-II (1.3 g.) were added 26% HCHO (2.8 cc.) and an aqueous solution (30 cc.) of KMnO₄ (1.9 g.) under stirring at 40°. After stirring for an hour, the reaction mixture was chilled, extracted with Et₂O and evaporated to dryness to leave a solid mass which was recrystallized from MeOH to form needles, m.p. 96~98°, yield 504 mg. A mixed m.p. with DL-2-methylcyclohexanone oxime¹²⁾ showed a depression. *Anal.* Calcd. for C₇H₁₃ON : C, 66.26; H, 10.02. Found : C, 66.10; H, 10.30.

DL-2-Methylcyclohexanone Oxime—a) An aqueous solution of Caro's acid was prepared from 18 g. of K₂S₂O₈, 20 g. of H₂SO₄ and 99 g. of ice by the usual method and neutralized with K₂CO₃ (active H₂SO₅ 4.1 g.). To a mixture of the Caro's acid and 2.7 g. of MgO was added 1.6 g. of *trans*-II at 18~20°. After agitation for 15 hr., the reaction mixture was made weakly acid with H₂SO₄, extracted with Et₂O, washed with a sat. aq. NaHCO₃, dried over anhyd. Na₂SO₄ and evaporated to dryness; yield 0.44 g. Distillation of the residue under diminished pressure (6 mm.) gave two fractions; a distillate below 90°, 0.04 g. and a distillate between 90° and 105°, 0.27 g. The first fraction gave the 2,4-dinitrophenylhydrazone of DL-2-methylcyclohexanone. The second fraction (50 mg.) was benzoylated by the Schotten-Baumann method; yield, 40 mg., m.p. 70~71° after recrystallization from petroleum ether. A mixed m.p. with an authentic sample of the benzoate of DL-2-methylcyclohexanone oxime^{6,11,12)} showed no depression. b) To a 95% EtOH solution of NaOH (35 mg.) was added 1-methyl-2-nitrosocyclohexane and the mixture boiled for an hour. After evaporation of the EtOH, the residue was benzoylated by the Schotten-Baumann method, yield, 130 mg. Recrystallization from petroleum ether gave the benzoate of DL-2-methylcyclohexanone oxime, m.p. 70~71° alone or on admixture with an authentic sample.

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Summary

The N-alkylation of DL-*trans*- and DL-*cis*-2-aminocyclohexanols was effected with alkylating agents in the presence of potassium carbonate. When lower alkylating agents were used, the *trans* form gave N-dialkyl derivatives, while the *cis* form gave only N-monoalkyl derivatives. The use of higher alkylating agents led both forms to N-monoalkyl derivatives. The resistance of the *cis* form to dialkylation in the presence of the lower alkylating agents was presumably due to a hydrogen bond between the hydroxyl and the amino groups in the *cis* relationship. This assumption may be supported by an analogous phenomenon which was already found in the Schotten-Baumann benzoylation of diastereomeric 2,2'-dihydroxydicyclohexylamine.^{2,15)}

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