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 mμ (ε 8,400).

3β-Acetoxy-5-hydroxy-6-aza-5ξ-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 3β-acetoxy-5-hydroxy-6-aza-5ξ-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).

The authors wish to express their appreciation to Prof. K. Tsuda of the Institute of Applied Microbiology, University of Tokyo, and to Mr. M. Matsui Director of this Laboratory, for their kind encouragements. They are also indebted to Dr. T. Onoe, Messrs. K. Ono, H. Nagashima, H. Higuchi, N. Higosaki, and T. Fujimura, and to Misses N. Sawamoto, and M. Gonda, all of this Laboratory, for elemental analysis and spectral measurements.

Summary

Ozonolysis of 3β-acetoxycholest-5-en-7-one (Ia), 3β-acetoxyandrost-5-en-7,17-dione (Ib), and 3β-acetoxypregn-5-en-7,20-dione (Ic) afforded 3β-acetoxy-5-formoxy-6-oxa-5ξ-cholestan-7-one (IIIa), 3β-acetoxy-5-formoxy-6-oxa-5ξ-androstan-7,17-dione (IIIb), and 3β-acetoxy-5-formoxy-6-oxa-5ξ-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.

(Received March 28, 1962)

UDC 547.593.07

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 Nakayama[1] reported N-ethylation of DL-*trans*-and DL-*cis*-2-aminocyclohexanols (I) with ethyl tosylate or ethyl bromide and potassium carbo nate, 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] $-\overset{|}{\underset{|}{N}}\cdots H-O-$, which exists in the N-ethyl derivative of *cis*-I,

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*4 Katakasu, Fukuoka (田口胤三, 吉末敬郎, 案西司郎).

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3) E.D. Bergmann, E. Gil-Av, S. Pinchas: J. Am. Chem. Soc., **75**, 68 (1953).
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.

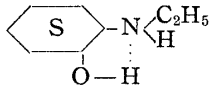


Table I. Alkylations of DL-2-Aminocyclohexanols (I)

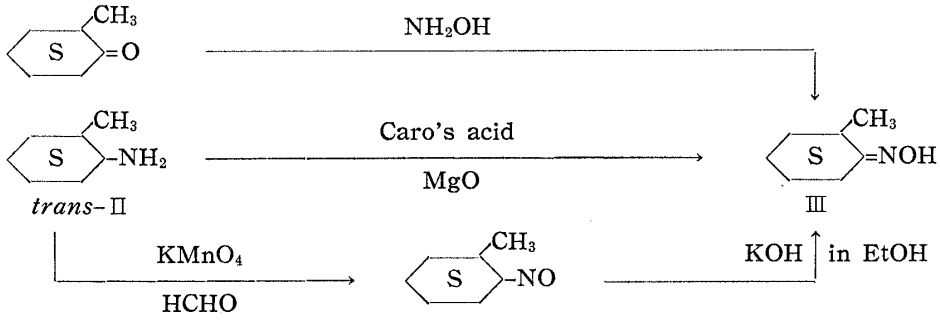
Alkylating agents[a]	Product from *cis*-I	Product from *trans*-I	Reaction conditions
A) methyl tosylate	R-NHCH$_3$[b]	R′-N(CH$_3$)$_2$	boiled in toluene for 3 hr.
B) ethyl bromide	R-NHC$_2$H$_5$	R′-N(C$_2$H$_5$)$_2$	in EtOH with K_2CO_3 on a water bath for 5 hr.
C) n-propyl bromide	R-NHC$_3$H$_7$	R′-N(C$_3$H$_7$)$_2$	〃
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 *n*-butanol or toluene with K_2CO_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-methylcyclohexylamines[5~12] (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 oxide[13] 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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been prepared by condensation of 2-methylcyclohexanone and hydroxylamine.[6,11,12] On the other hand, the latter gave 1-methyl-2-nitrosocyclohexane in a yield of 49%, which was then isomerized to III on treatment with alcoholic potassium hydroxide. III was led to *cis*-II by catalytic hydrogenation in an acidic medium according to the known methods.[6,11,12]

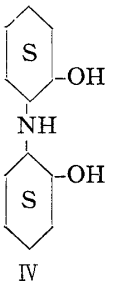
Ethylation of *trans*- and *cis*-II was conducted under the conditions shown in Table II. Both forms of II underwent N-mono- as well as N-diethylations, though in a different ratio. This phenomenon may be due to the absence of a hydrogen bond in *cis*-II as well as in *trans*-II.

Table II. N-Ethylation of DL-2-Methylcyclohexylamines (II) with Ethyl Bromide[a] and Potassium Carbonate

Products from *trans*-II		Products from *cis*-II		Reaction conditions
monoethyl	diethyl	monoethyl	diethyl	
40	60	68	32	in EtOH, on a water bath for 6 hr.
15	85	57	43	〃 for 10 hr.

a) Six moles per mole of II were used.

In the preceding papers[2,15] concerning N-benzoylation of the six compensated isomers of 2,2′-dihydroxydicyclohexylamine (IV) by the Schotten-Baumann method, it was reported that the *trans-trans* isomers readily underwent N-benzoylation, while neither the *trans-cis* nor the *cis-cis* isomers suffered N-benzoylation. However, N-benzoylation of the *trans-cis* isomers proceeded when the *cis*-hydroxyl group was masked with an acyl group. Hence it may be concluded that the hydrogen bond between the *cis*-hydroxyl and the amino groups would result in the decrease of the electron density of N, which might be a leading factor for the inhibition of N-benzoylation. It may be pertinent to add that the hydrogen bond fixed electrons of N down to an unfavorable site for the electrophylic attack. On the basis of the present data, however, it is not certain whether other steric factors would operate or not. An analogous mechanistic explanation might be offered to the N-alkylations of DL-*cis*-2-aminocyclohexanol (*cis*-I) and its *trans*-I isomer.



IV

Experimental

N-Alkylation of DL-*trans* (or *cis*)-2-Aminocyclohexanol (I). General Method——The reaction was carried out under the conditions described in Table I, and the reaction mixture, after filtrating was evaporated to dryness. The residue was treated with conc. aq. NaOH, extracted with ether, and the ether extract was dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was distilled to give either an N-monoalkyl derivative or an N-dialkyl derivative as described below (see Table I).

DL-*trans*-2-Dimethylaminocyclohexanol, b.p_{10} 71～75°, yield 57%. Picrate : m.p. 147～148°. *Anal.* Calcd. for $C_8H_{17}ON \cdot C_6H_3O_7N_3$: N, 15.05. Found : N, 15.23.

DL-*trans*-2-Diethylaminocyclohexanol, b.p_{30} 135～137°, yield 56%. Hydrochloride : m.p. and a mixed m.p. with an authentic sample[1] 173°.

DL-*trans*-2-Di-*n*-propylaminocyclohexanol. Picrate : m.p. 122°. *Anal.* Calcd. for $C_{12}H_{25}ON \cdot C_6H_3O_7N_3$: N, 13.08. Found : N, 12.82.

DL-*trans*-2-Isopropylaminocyclohexanol, b.p_{32} 118°, yield 71%. Hydrochloride : m.p. 204～205°. *Anal.* Calcd. for $C_9H_{19}ON \cdot HCl$: C, 55.67; H, 10.40; N, 7.23. Found : C, 55.74; H, 9.90; N, 7.04. Picrate : m.p. 149～150°.

15) T. Taguchi, Y. Kawazoe : J. Org. Chem., **26**, 2699 (1961).

DL-*trans*-2-*n*-Butylaminocyclohexanol, b.p_{46} 150~153°. Hydrochloride : m.p. 230~231°. *Anal.* Calcd. for $C_{10}H_{21}ON \cdot HCl$: 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 $C_7H_{15}ON \cdot C_6H_3O_7N_3$: 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 $C_9H_{19}ON \cdot C_6H_3O_7N_3$: 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 $C_{10}H_{21}ON \cdot C_6H_3O_7N_3$: 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 $KMnO_4$ (1.9 g.) under stirring at 40°. After stirring for an hour, the reaction mixture was chilled, extracted with Et_2O and evaporated to dryness to leave a solid mass which was recrystallized from MeOH to form needless, m.p. 96~98°, yield 504 mg. A mixed m.p. with DL-2-methylcyclohexanone oxime[12] showed a depression. *Anal.* Calcd. for $C_7H_{13}ON$: 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 $K_2S_2O_8$, 20 g. of H_2SO_4 and 99 g. of ice by the usual method and neutralized with K_2CO_3 (active H_2SO_5 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 H_2SO_4, extracted with Et_2O, washed with a sat. aq. $NaHCO_3$, dried over anhyd. Na_2SO_4 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-Baumanm 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 boilded for an hour. After evaporation of the EtOH, the residue was benzoylated by the Shotten-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.

The authors are indebted to the members of the Analytical Section of this Institute for microanalyses and IR spectra.

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]

(Received March 29, 1962)