Identification of IAN in the Fraction VIb by TLC and VPC——The fraction VIb was submitted to thin-layer chromatography under the above-described conditions. The darkish pink spot (with Ehrlich reagent) corresponding to IAN was detected in each condition. The fraction VIb was submitted to vapor phase chromatography and the presence of IAN in the fraction VIb was confirmed under the above-described conditions.

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UDC 547.833.3.02 : 541.63

23. Masao Okamoto : Stereochemistry of Decahydroisoquinolines and Related Compounds. V.*1 Syntheses of 2-Methyl-decahydro-8-isoquinolinols.

(*Kyoto College of Pharmacy**2)

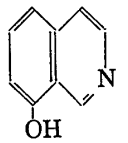
Three isomeric bases of 2-methyl-decahydro-8-isoquinolinol (XIVa, XIVb, XIVc) were prepared by catalytic hydrogenation of 2-methyl-5-chloro-1,2,3,4-tetrahydro-8-isoquinolinol (VIII) and also of 2-methyl-1,2,3,4-tetrahydro-8-isoquinolinol (XIII).

The configuration of the ring juncture of these alcoholic bases and the configuration of their hydroxyl groups were clarified on the basis of chemical evidences and NMR informations and the rates of chromic acid oxidation and so on.

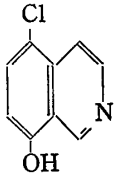
(Received April 28, 1966)

Previously, the authors reported preparation of 2-methyl-decahydroisoquinolinols possessing hydroxyl groups at C_5-, C_6- and C_7-position respectively, and the corresponding ketones and confirmation of steric configuration at ring juncture of these compounds by chemical evidences.[1~3,*1] In the present paper, it deals with the synthetic method of three isomers of 2-methyl-decahydro-8-isoquinolinol, starting from 2-methyl-5-chloro-1,2,3,4-tetrahydro-8-isoquinolinol (VIII), and steric investigations concerning ring junction of these alcohols, including configuration of hydroxyl group.

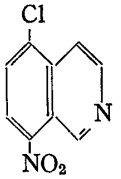
Preparative methods of 2-methyl-decahydro-8-isoquinolinols (XIV), hitherto, taken by us can be classified into two processes. Thus, the one is direct perhydrogenation of corresponding isoquinolinols by one step, followed by N-methylation and the other is partial hydrogenation of 1,2,3,4-tetrahydro derivatives. At first, 8-isoquinolinol (I) was considered to be the useful intermediate on the shortest process leading to the



I



II



III

Chart 1.

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*1 Part IV. S. Kimoto, M. Okamoto : Yakugaku Zasshi, **85**, 371 (1965).

*2 Nakauchi-cho, Yamashina-misasagi, Higashiyama-ku, Kyoto (岡本正夫).

1) S. Kimoto, M. Okamoto : This Bulletin, **9**, 480 (1961).

2) *Idem* : *Ibid.*, **10**, 362 (1962).

3) M. Okamoto, M. Yamada : *Ibid.*, **11**, 554 (1963).

titled compounds, and in spite of tenacious trials to prepare the 8-isoquinolinol (I) satisfactory results were not obtained at all by Robinson method,[4] involving sulfonation of isoquinoline followed by alkali fusion, and also by hydrolysis of the diazonium salt of 8-amino-isoquinoline (IX).

Meanwhile, it was experimentally found that hydrogenation of 4-chlorophenol over Raney nickel in the presence of equimolar amount of potassium hydroxide gave cyclohexanol in good yield. Thus, chlorophenol type compounds, such as 5-chloro-8-isoquinolinol (II) can be considered as useful intermediates. Several kinds of procedures for diazatation of 5-chloro-8-amino-isoquinoline (IV)[5], followed by hydrolysis of the diazonium salt, gave only resinous compounds or dyestoffs. Consequently all efforts to prepare I and II ended in vain. However, it was found to be successful to start with 2-methyl-1,2,3,4-tetrahydro-8-isoquinolinol (XIII) and its 5-chloro derivative (VIII) which are prepared by longer process, but in excellent yields at each step.

On heating with acetic anhydride, an amine (IV) was converted to the acetate (V), m.p. 208~210°, which was led to the methiodide by treating with methyl iodide in ethanolic solution. Reduction of the methiodide, m.p. 245°, with sodium borohydride in methanolic solution gave 2-methyl-5-chloro-8-acetamino-1,2,3,4-tetrahydroisoquinoline (VI), hydrolysis of which afforded the corresponding 8-amino derivative (VII), m.p. 80~82°. Hydrolysis of the diazonium salt of the amine (VII) gave 2-methyl-5-chloro-1,2,3,4-tetrahydro-8-isoquinolinol (VIII), m.p. 171.5~172.5°, which was hydrogenated over Raney nickel in the presence of half amount of potassium hydroxide with elimination of

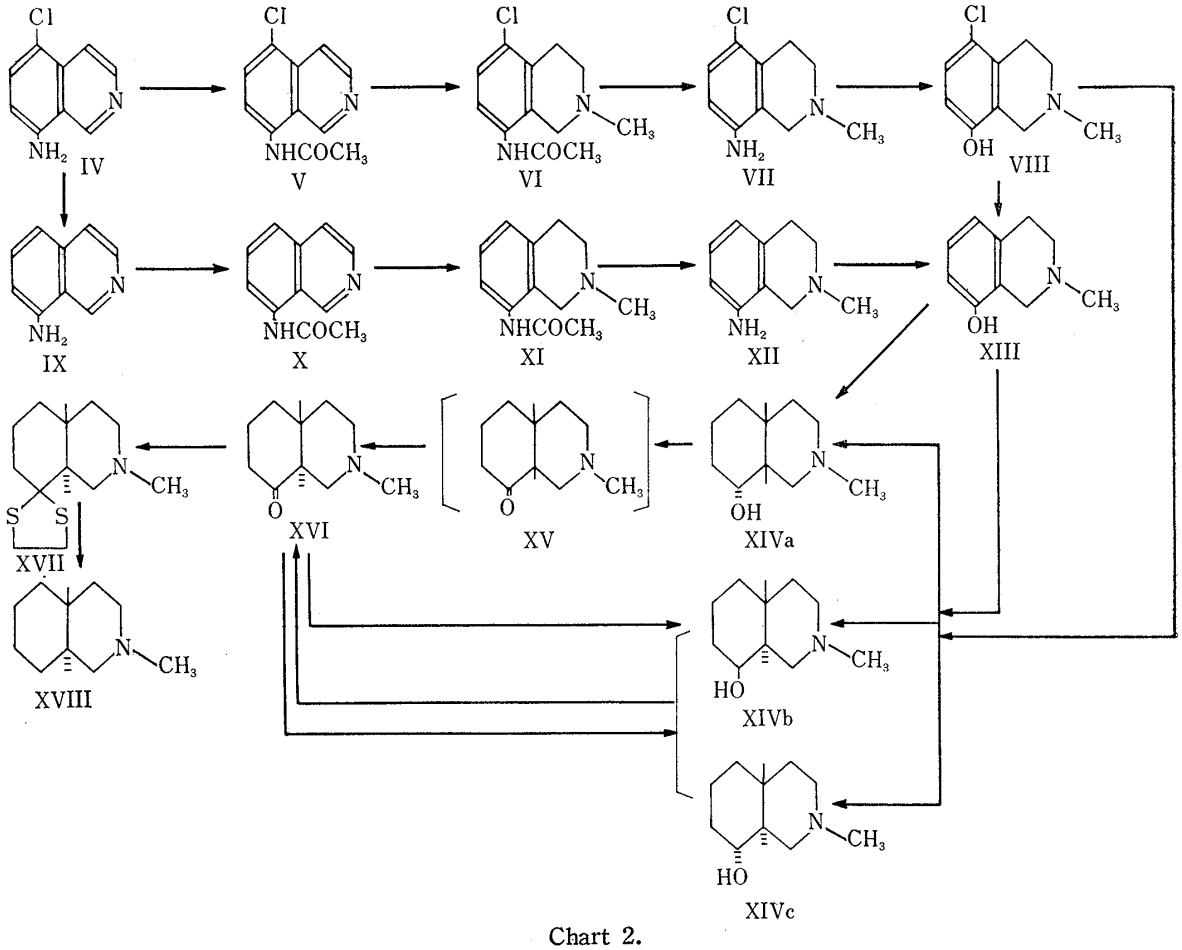


Chart 2.

4) R. A. Robinson : J. Am. Chem. Soc., **69**, 1944 (1947).
5) R. H. F. Manske, M. Kulka : Can. J. Research, **27B**, 161 (1949).

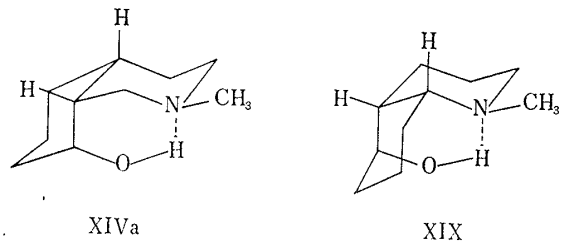
chlorine at C_5 to give 2-methyl-1,2,3,4-tetrahydro-8-isoquinolinol (XIII), m.p. 177~178°. The phenolic base (XIII) was alternatively synthesized from 8-aminoisoquinoline (IX), which was derived from the 5-chloro-8-aminoisoquinoline (IV) by dechlorination with hydrazine hydrate and palladized charcoal in ethanol according to Ahmad procedure[6] (trials of dechlorination of VI with palladized $CaCO_3$ according to Osborn method[7] were unsuccessful), *via* 8-acetaminoisoquinoline (X), 2-methyl-8-acetamino-1,2,3,4-tetrahydroisoquinoline (XI), m.p. 122~123°, and the corresponding 8-amino derivative (XII), b.p_3 120~122°, in the same manner as from IV to VIII. VII, VIII, XII, and XIII are new compounds, and preparation of 2-methyltetrahydroisoquinolinol derivatives from the corresponding amines in similar fashion proceeded without fail in satisfactory yield.

High pressure-high temperature catalytic hydrogenation of the phenolic base (XIII) over Raney nickel catalyst afforded a mixture of three isomeric 2-methyl-decahydro-8-

Table I. Melting Points of Three Isomeric Bases of 2-Methyl-decahydro-8-isoquinolinol (XIV) and their Salts and Approximate Ratio of Products in High Pressure Hydrogenation

	m.p. (°C) of free base	m.p. (°C) of picrate	m.p. (°C) of methiodide	Approx. ratio of products
XIVa	78~80	181~183	229~231	3
XIVb	115	235	183~185	1
XIVc	84	147~150	235	1

isoquinolinols (XIVa, m.p. 78~80°, pKa 9.82; XIVb, m.p. 115°, pKa 9.48; XIVc, m.p. 84°, pKa 9.54) in approximate ratio of 3:1:1 respectively and these isomers were purified by using alumina chromatography with chloroform as solvent. Similar results were also obtained on hydrogenation of chlorophenolic base (VIII) with Raney nickel catalyst in the presence of equimolar amount of potassium hydroxide, and hydrogenation of the phenolic base (XIII) over platinum oxide in acetic acid at a room temperature and atmospheric pressure gave exclusively the alcoholic base (XIVa), which indicated not only intramolecular hydrogen bond at 3200 cm^{-1} in the IR spectrum but higher pKa value than the others. These facts suggested a steric structure that the hydrogen atom of the hydroxyl group should be located near the ring nitrogen, therefore it seems reasonable to assume the base (XIVa) has *cis* ring juncture and an axial hydroxyl group as shown in Chart 3, taking a molecular model into consideration (other structures cannot interpret the presence of the intramolecular hydrogen bonding). Moreover, this evidence is supported with Grob's recent investigation[8] concerning decahydroquinolinols; he gave a steric structure illustrated in Chart 3 for *cis*-1-methyl-5α-decahydroquinolinol (XIX) (IR : λ associated, 3.06μ).



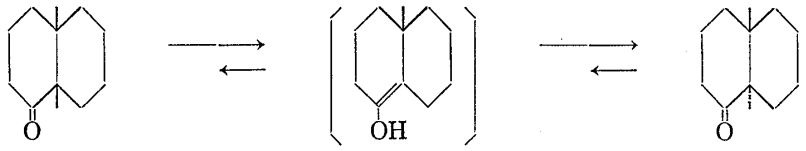
XIVa XIX

Chart 3.

In order to clarify ring juncture of the alcohols by chemical means, it was thought advisable that the corresponding ketone derived from each alcohol was reduced to 2-methyl-decahydroisoquinoline by any suitable method which was accompanied without ring inversion. Thus, oxidation of the alcohol (XIVa) with chromic acid in diluted sulfuric acid solution gave the ketone (XVI), m.p. 40~42° (picrate, m.p. 227°), which was also obtained in similar fashion from a mixture of the other alcohols (XIVb,

6) Y. Ahmad, D. H. Hey : J. Chem. Soc., **1961**, 3882.
7) A. R. Osborn, K. Schofield : J. Chem. Soc., **1956**, 4191.
8) C. A. Grob, H. R. Kiefer : Helv. Chim. Acta, **48**, 799 (1965).

XIVc). Then, the ketone (XVI) was converted to the dithioketal (XVII), m.p. 55~57°, which on boiling with Raney nickel in ethanol afforded *trans*-2-methyl-decahydroisoquinoline (XVIII). Therefore, regarding that there is no ring inversion in the course of the reduction (XVI to XVIII), it seems reasonable to consider the ketone (XVI) has *trans* ring juncture. However, it is premature to conclude that the foregoing alcohol (XIVa) has *trans* juncture, because it is wellknown that cyclic ketones possessing carbonyl group attached to the bridgehead such as 1-decalone (XX) undergo rapid isomerization



XXa XXb

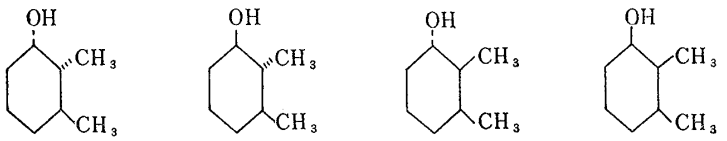
Chart 4.

from *cis* to *trans*, especially in alkaline medium (Chart 4).[9] Furthermore, Grob *et al.*[8] reported that oxidation of *cis*-1-methyl-5α-decahydroquinolinol (XIX) with chromic acid in dilute acetone at 0° gave the corresponding raw *cis* ketone, which was at once converted to the picrate without distillation, or rapidly isomerized to the *trans* ketone. Then in order to obtain the *cis* ketone (XV), oxidation of the alcohol (XIVa) was reexamined according to the Grob's procedure, but it gave only the *trans* ketone (XVI).

Catalytic hydrogenation of the *trans* ketone (XVI) over platinum oxide in ethanolic solution afforded exclusively the alcohol (XIVb) and reduction of the ketone (XVI) with sodium borohydride regenerated a mixture of two alcohols, XIVb and XIVc, in approximately equal amount, and none of the alcohol (XIVa) was produced in each reduction process.

Talking of the nuclear magnetic resonance, the half-widths of the signals of the protons adjacent hydroxyl groups of these alcohols (XIVa, XIVb, XIVc) are 5, 5, and 16 c.p.s. respectively and the rate constants of oxidation of these alcohols with chromic acid are 2.73, 2.81, and 1.14 $(m./L.)^{-3}min^{-1}$ respectively.*3 On the other hand, Kawazoe *et al.*[10] reported that for steroidal alcohols, the half-width of the signal of the axial proton was larger than 16 c.p.s. and the half-width of the signal of the equatorial proton was smaller than 12 c.p.s. and Grob, *et al.*[8] reported that for decahydroquinolinols, the former half-width about 20 c.p.s. and the latter half-width was about 7 c.p.s. The rates of chromic acid oxidation of a series of epimeric pairs of steroidal alcohols have been measured. From the results, it may be seen that in each case the axial alcohol is oxidized more rapidly than the equatorial one.[11] On the basis of these chemical evidences, IR and NMR informations and data of the rates of chromic acid oxidation, it is considered that XIVa is the *cis*-axial alcohol, XIVb is the *trans*-axial one and XIVc is the *trans*-equatorial one.

It is interesting that the *cis-cis* alcohol (XIVa) was predominantly obtained as well as in



XXIa 18% XXIb 15% XXIc 32% XXId 35%

Chart 5.

*3 These data shall be described in detail in later paper.

9) I. M. Conia, F. Rouessac : Tetrahedron, **16**, 45 (1961). H. E. Zimmerman, A. Maio : J. Am. Chem. Soc., **81**, 3644 (1959).
10) Y. Kawazoe, Y. Sato, T. Okamoto, K. Tsuda : This Bulletin, **11**, 328 (1963).
11) J. Schreiber, A. Eschenmoser : Helv. Chim. Acta, **38**, 1529 (1955).

the case of hydrogenation of 2-methyl-1,2,3,4-tetrahydro-5-isoquinolinol[1],*1) and these observations relatively agree with Cocker's recent investigation[12] that hydrogenation of 2,3-xylenol over Raney nickel in methanol at 150° and 90 atm. gave four isomeric alcohols of 2,3-dimethylcyclohexanol and that the *cis-cis* form (XXId) was obtained in yield greater than the *trans-trans* form (XXIb) (Chart 5), although *trans*-decahydroisoquinoline was mainly produced by similar hydrogenation of isoquinoline.[13]

The author wishes to express his cordial gratitude to Prof. Kimoto for his kind guidance and unfailling encouragement throughout the course of this research, and for his revision of this manuscript. He is also indebted to the members of Analytical Center, University of Kyoto for elemental microanalyses and Dr. Y. Sawa, Dr. K. Tori, Shionogi Research Laboratory, Shionogi & Co., Ltd. for the measurements of NMR spectra and kind advices concerning assignments of these spectra. Thanks are also due to Mr. H. Yoshimits uand Mrs. H. Yoshimitsu, K. Nishijima and S. Kabuto for their excellent technical assistances.

12) W. Cocker, T. B. H. McMurry, E. R. Simmons : J. Chem. Soc., **1965**, 3022.
13) B. Witkop : J. Am. Chem. Soc., **70**, 2617 (1948).

[Chem. Pharm. Bull. 15(2) 172～178 (1967)]

UDC 615.77-092

24. Kiichiro Kakemi, Hitoshi Sezaki, Shozo Muranishi, and Hidefumi Matsui : Absorption and Excretion of Drugs. XXIX.*1 Effect of Surface-active Agents on Rectal Absorption of Sulfisoxazole from Oily Base.

(*Faculty of Pharmaceutical Sciences, Kyoto University**2)

Effect of various types of surface-active agents on the rectal absorption of sulfisoxazole from cocoa butter was investigated by the blood level determination with rabbits. Blood levels were in general increased with increase of surface-active agent, and decreased by addition of the large amount. Surface-active agent accelerated the release of the drug from the base to dissolution medium. On the other hand, surface-active agent reduced the absorption rate of the drug from aqueous solution. These results suggest that the increase of the drug absorption at the low concentrations of surface-active agents is due to release acceleration, but the reduction effect on drug absorption in their higher concentrations is due to predominance of absorption reduction over release acceleration. Cetyltrimethyl ammonium bromide especially stimulated the drug absorption in the very low concentrations.

(Received May 10, 1966)

Surface-active agents are often used as emulsifiers and solubilizers in oily base suppository.[1] Their addition to oily base is presumed to affect the drug absorption to some extent from the rectum. Schroff[2] and Oesch[3] actually confirmed that salicylic acid, sodium salicylate and sodium iodide were rapidly absorbed by emulsifying the

*1 Part XXVIII. Yakugaku Zasshi, **86**, 278 (1966).
*2 Yoshida-shimoadachi-cho, Sakyo-ku, Kyoto (掛見喜一郎, 瀬崎 仁, 村西昌三, 松井秀文).
1) J. Anschel, H. A. Lieberman : Drug & Cosmetic Industry, **96**, 341 (1965).
2) E. Schroff : Pharm. Ztg., **76**, 1239 (1931).
3) P. Oesch : "Über die Herstellung und Prüfung der Suppositorien," Ernst Lang, Zurich (1944).