The order of the ease with which they are reduced at the dropping mercury electrode are given by the following sequence :

$$o\text{-NQ} > o\text{-AQ} > \text{Ph. Q} > o\text{-DBAQ} > o\text{-BAQ}$$

This order agreed with the resonance theory as in the case of *p*-quinones described in a previous paper.

From the standpoint of the order of $E_{1/2}$'s of the above-mentioned *o*-quinones, it was found that they might play some important rôles in the carcinogenesis of their parent hydrocarbons.

(Received March 29, 1958)

UDC 547.837.07

83. Norio Sugimoto and Hiroshi Kugita : Studies on the Syntheses of Hydrogenated Quinolines and Isoquinolines as Analgesics. XV.[1] Synthesis of 3-Hydroxy-N-methyl-7-aza-des-N-morphinan (9-Hydroxy-3-methyl-5,10b-trimethylene-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]isoquinoline).

(*Osaka Research Laboratory, Tanabe Seiyaku & Co., Ltd.**)

Preliminary studies on the synthesis of the subject compound have already been described in one of earlier papers of this series.[2] This compound is one of the most interesting from the point of location of the nitrogen atom among the morphinan isomers in which the position of nitrogen has been transferred, the synthetic studies of which are being undertaken by Sugimoto and his co-workers. The reason for this is that the position (17) of nitrogen in D-ring would correspond to 7-position in C-ring, considering the position (13) of the quaternary carbon atom in morphinan. In this way, this compound is structurally interesting and studies on its synthesis and pharmacological action are of great interest.

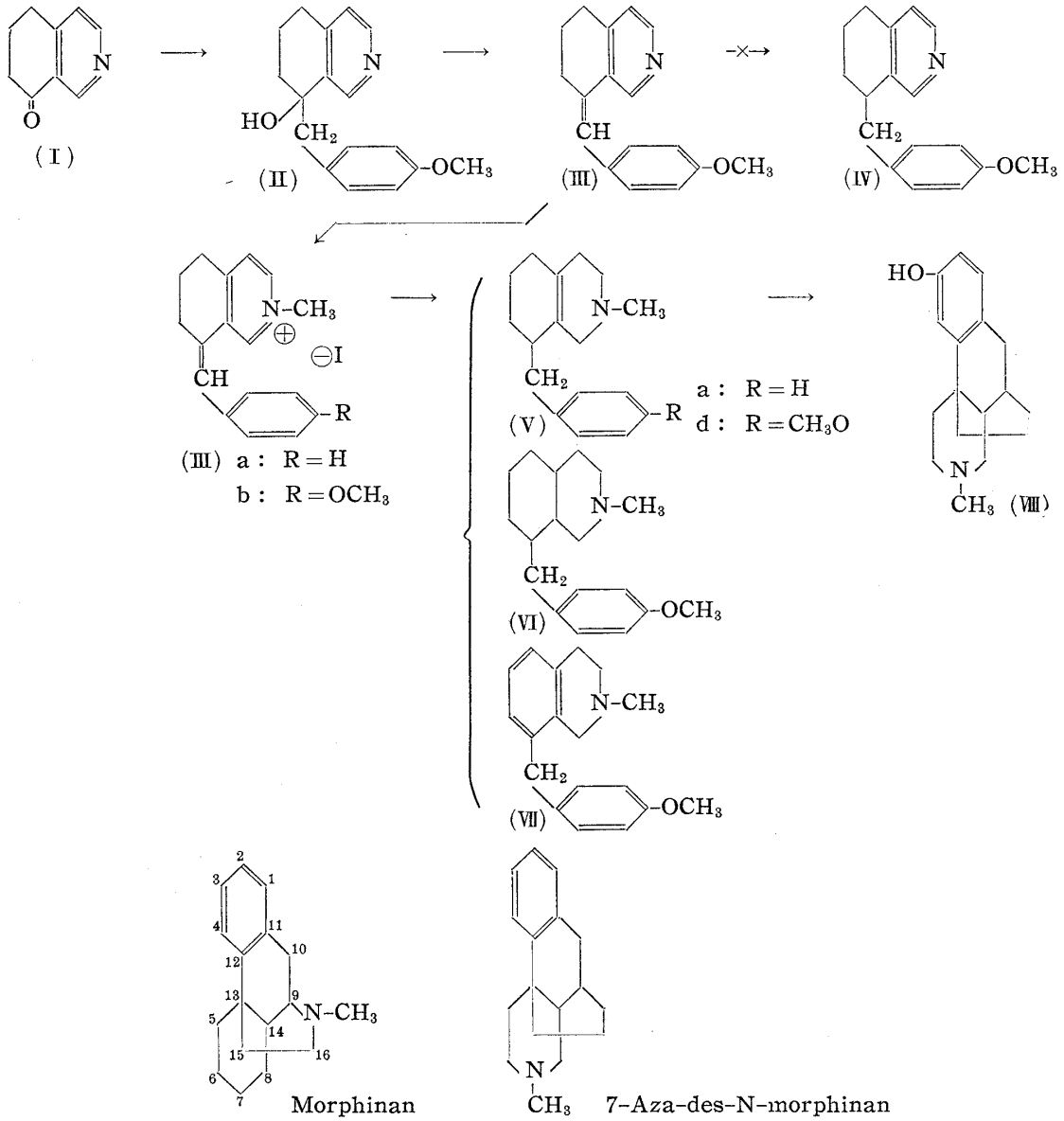
The process of synthesis followed the process described earlier[2] and 8-(*p*-methoxybenzyl)-8-hydroxy-5,6,7,8-tetrahydroisoquinoline (II) was prepared by the Grignard reaction of 8-oxo-5,6,7,8-tetrahydroisoquinoline (I) and *p*-methoxybenzylmagnesium chloride. (II) was heated with dilute hydrochloric acid to effect dehydration and the *p*-methoxybenzylidene compound (III) was obtained. Hydrogenation of all the double bonds in (III) was attempted by catalytic reduction over 5% palladium-carbon to obtain methoxybenzyltetrahydroisoquinoline (IV) but the reduction did not proceed at ordinary pressure and the objective compound was not obtained.

As a preliminary experiment, 8-benzylidene-5,6,7,8-tetrahydroisoquinoline methiodide[1] (IIIa) was submitted to catalytic reduction in methanol with Raney nickel, in the presence of potassium hydroxide at ordinary pressure. The base obtained on absorption of three moles of hydrogen was proved to be entirely identical with the base (Va) formed by the same catalytic reduction of 8-benzyl-5,6,7,8-tetrahydroisoquinoline methiodide after absorption of two moles of hydrogen. In accordance with this process, the methiodide (IIIb) of the *p*-methoxybenzylidene compound (III) was submitted to catalytic

* Honjo-Kawasaki-cho, Ohyodo-ku, Osaka (杉本典夫, 釘田博至).

1) Part XIV : This Bulletin, **5**, 378(1957).

2) Part XII : *Ibid.*, **5**, 67(1957).



reduction under identical conditions and absorption of approximately three moles of hydrogen at ordinary pressure was observed. The base thereby obtained was recrystallized as an oxalate and separated into three kinds of salt.

Oxalate-A, m.p. 202~203°. Its base, m.p. 69~70.5°, is labile in the air, possessing no unsaturated bonds. From its various derivatives and infrared spectral analysis (strong absorption at 12.0 μ), it was identified as 8-(*p*-methoxybenzyl)-2-methyl-decahydroisoquinoline (VI).

Oxalate-B, m.p. 164~166°. Its base, m.p. 64~64.5°, is stable in the air and does not possess any unsaturated bond. Its infrared spectrum exhibits a broad absorption in the region of 12.7 to 13.7 μ and strong absorptions at 12.0 and 12.4 μ, which are characteristic of *para*-substituted benzene ring and another 1,2,3-trisubstituted benzene ring. From analytical values of its various derivatives, the compound was identified as 8-(*p*-methoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (VII). It is assumed that

3) R. Grewe, *et al.* : Ber., **81**, 279(1948).
4) Sugimoto, *et al.* : This Bulletin, **4**, 353(1956).
5) *Idem.* : *Ibid.*, **5**, 62(1957).
6) *Idem.* : *Ibid.*, **5**, 67(1957).

a transition and rearrangement of double bonds took place during the reduction and a stable 1,2,3,4-tetrahydroisoquinoline ring had been formed, by which the reduction failed to proceed any further.

Oxalate-C (amorphous), m.p. 60~90°. Its base is a liquid of b.p_3 164~165° and colors markedly in the air. It decolorized potassium permanganate and absorbed ca. one mole of hydrogen on catalytic reduction. Analytical values of its derivatives agreed with those for 8-(*p*-methoxybenzyl)-2-methyl-octahydroisoquinoline (V).

The octahydroisoquinoline (V) oxalate so obtained was heated with 48% hydrobromic acid and 3-hydroxy-N-methyl-7-aza-des-N-morphinan (Ⅷ) was obtained but in a poor yield, the majority turning into a pale yellow, resinous substance with a phenolic hydroxyl. Evidence for rearrangement-cyclization was provided by infrared absorption bands at 11.35, 11.95, and 12.25 μ.

The ease or difficulty of the Grewe cyclization of 4-,[4] 5-,[5] and 8-benzyl[6] compounds, and of 1-,[7] 4-,[8] 5-,[9] and 8-(*p*-methoxybenzyl) compounds with phosphoric and hydrobromic acids and their yield, as well as the cyclization reaction of 1-benzyl-2-methyl-octahydroisoquinoline by Grewe,[3] are compared in Table I.

Table I.

Octahydroisoquinoline	Reagent	Reaction		Yield (%)	Product
		Time (hrs.)	Temp. (°C)		
1-Benzyl-	85% H_3PO_4	70	150	50	N-Methylmorphinan
4-Benzyl-	85% H_3PO_4	70	170	36.5	N-Methyl-16-aza-des-N-morphinan
5-Benzyl-	48% HBr	20	135	38.5	N-Methyl-6-aza-des-N-morphinan
8-Benzyl-	85% H_3PO_4	70	170	1~2	N-Methyl-7-aza-des-N-morphinan
1-(*p*-MeO-benzyl)-	48% HBr	6	135	30	N-Methyl-3-hydroxymorphinan
4-(*p*-MeO-benzyl)-	48% HBr	20	135	27	N-Methyl-3-hydroxy-16-aza-des-N-morphinan
5-(*p*-MeO-benzyl)-	48% HBr	15	135	56	N-Methyl-3-hydroxy-6-aza-des-N-morphinan
8-(*p*-MeO-benzyl)-	48% HBr	20	135	6.3	N-Methyl-3-hydroxy-7-aza-des-N-morphinan

From the foregoing results, it is known that the rearrangement reaction is most easily effected in the 5-benzyl compound, followed in that order by 1-, 4-, and 8-benzyl compounds. In spite of the fact that the 8-benzyl compound was obtained under the same conditions as for the 5-benzyl compound, its rearrangement reaction was the most difficult.

When the double bond in 4-, 5-, and 8-benzyl-octahydroisoquinolines undergoes rearrangement to the aromatic ring, it would easily be surmised that the steric configuration of the junction between C-13 and C-14 is more likely to take the *trans* form (B/C=*cis*, C/D=*trans*), because the proton then approaches the B-ring to be formed from the far side, and such a result has actually been observed in the synthesis of morphinan. There is no doubt that 16-, 6-, and 7-aza-des-N-morphinans prepared under similar conditions would take the same steric configuration (C/D=*trans*) as that of morphinan.

Analgesic activity of the subject compound was determined by Dr. H. Fujimura of the Pharmacological Department, University of Kyoto, by the Haffner method using mice. Subcutaneous injection of 0.3 mg./10 g. results in analgesic state, indicating a tail reaction, but its effect is around 10%. With injection of 0.5 mg./10 g., the activity is ca. 25% but causes clonic spasm due to irritation. Concurrent use of 0.05 mg./10 g. of morphine with 0.2 mg./10 g. indicated approximately 60% activity. Toxicity of the compound is over 1 mg./10 g. while that of morphine is 0.15 mg./10 g., its ED_{50} being 50%.

7) O. Schnider, *et al.*: Helv. Chim. Acta, **32**, 821(1949).
8) Sugimoto, *et al.*: This Bulletin, **4**, 357(1956).
9) *Idem.*: *Ibid.*, **5**, 316(1957).

Antitussive action of this compound, determined by Dr. Y. Kasé of the Pharmaceutical Department, University of Kumamoto, by Kasé's method using a dog showed that it had no such action at 5 mg./kg.

The authors express their gratitude to Prof. S. Sugasawa of the Universtiy of Tokyo and to Dr. Fujisawa, Director of this Laboratory, for their kind encouragement during the course of this work. They are also indebted to Mr. K. Kodera for infrared analysis, and to Mrs. F. Hisamichi and Mr. T. Yoda for elemental analyses.

Experimental

8-(*p*-Methoxybenzyl)-8-hydroxy-5,6,7,8-tetrahydroisoquinoline (II)—*p*-Methoxybenzyl chloride (42 g.) dissolved in dehyd. ether (280 cc.) was slowly added during a period of 4 hrs. to a solution of Mg turnings (28 g.) in dehyd. ether (300 cc.) with vigorous stirring and boiling. Then the mixture was refluxed for 1 hr. To the resulting Grignard solution, from which unreacted Mg was removed by decantation, a solution of 8-oxo-5,6,7,8-tetrahydroisoquinoline (15 g.) in dehyd. ether (50 cc.) was added and soon yellow precipitate deposited. After stirring for 1 hr., the reaction mixture was stood over night and decomposed with ice water. Ethereal layer was extracted with 10% HCl and the aqueous layer was basified with K_2CO_3, extracted with AcOEt, and dried. After removal of solvent, the residue (9.5 g.) was recrystallized from AcOEt to white needles of m.p. 136~138°. *Anal.* Calcd. for $C_{17}H_{19}O_2N$: C, 75.81; H, 7.11; N, 5.2. Found: C, 75.45; H, 7.0; N, 5.35.

Hydrochloride: Colorless needles (from acetone+EtOH), m.p. 183~184°. *Anal.* Calcd. for $C_{17}H_{20}O_2NCl$: C, 66.71; H, 6.54; N, 4.57. Fonnd: C, 66.45; H, 6.2; N, 4.55.

8-(*p*-Methoxybenzylidene)-5,6,7,8-tetrahydroisoquinoline (III)—A solution of 8-hydroxyisoquinoline (II) (9.5 g.) in 15% HCl (100 cc.) was refluxed for 2 hrs. Most of HCl was removed under reduced pressure, the residue was basified with K_2CO_3, extracted with ether, and dried. After evaporating the solvent, the residue was recrystallized from petr. ether to yield 8.5 g. of colorless pillars, m.p. 75~77°. *Anal.* Calcd. for $C_{17}H_{17}ON$: C, 81.24; H, 6.82; N, 5.57. Found: C, 80.95; H, 6.75; N, 5.75.

Catalytic Reduction of 8-Benzylidene-5,6,7,8-tetrahydroisoquinoline Methiodide[2] (IIIa) with Raney Ni—Methiodide (IIIa) (0.68 g.), dissolved in a mixture of MeOH (30 cc.) and *N* NaOH (5 cc.), was catalytically hydrogenated with Raney Ni (1 g.) at atmospheric pressure. The absorption of hydrogen (41 cc.) finished in 50 mins. (3 moles H_2=43 cc./12°). After filtration of the catalyst the filtrate was acidified with 10% HCl and the solvent was distilled off *in vacuo*. The residue was basified with K_2CO_3 and the separated free base was extracted with ether, which was dried and evaporated. The product (0.3 g.) was obtained by distillation as a colorless liquid of $b.p_2$ 145~147°.

Picrolonate of m.p. 159~162° was obtained by repeated recrystallization from EtOH, which showed no depression of mixed melting point with 8-benzyl-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline picrolonate.[2]

Catalytic Reduction of 8-(*p*-Methoxybenzylidene)-5,6,7,8-tetrahydroisoquinoline Methiodide (IIIb)—A solution of 8-(*p*-methoxybenzylidene)-tetrahydroisoquinoline (III) (9.5 g.) in MeOH (30 cc.) was refluxed with CH_3I (10 cc.) for 5 hrs. Removal of the solvent and recrystallization from EtOH gave 11.2 g. of methiodide (IIIb), m.p. 205~207°. *Anal.* Calcd. for $C_{18}H_{21}ONI$: C, 54.80; H, 5.33; N, 3.55. Found: C, 55.1; H, 5.1; N, 3.85.

The methiodide dissolved in a mixture of MeOH (330 cc.) and *N* NaOH (80 cc.) was hydrogenated over Raney Ni (12 g.) as above. The solution became colorless when about 2 moles of H_2 had been taken up. Hydrogenation was further progressed until total absorption of 1830 cc. H_2 (3 moles H_2= 1960 cc./12°). After removal of the catalyst, the solution was acidified with 10% HCl and worked up as above. The basic product was extracted with ether, dried, and evaporated. The product (6.4 g.) was obtained as a pale yellow liquid of $b.p_3$ 175~180°. The distillate formed oxalate in ether, which was recrystallized from a mixture of acetone (30 cc.) and EtOH (30 cc.), affording the first crop (1.2 g.) of oxalate-A, and the mother liquor was concentrated to one-half its original volume. After standing, the second crop of crystals, oxalate-B (2.5 g.), were collected. The mother liquor was again concentrated to dryness, and oxalate-C (4.0 g.) was obtained as amorphous substance.

Oxalate-A was identified as 8-(*p*-methoxybenzyl)-2-methyl-decahydroisoquinoline oxalate (VI), white needles (acetone+EtOH), m.p. 202~203°, (1.0 g.). *Anal.* Calcd. for $C_{20}H_{29}O_5N$: C, 66.09; H, 8.04; N, 3.85. Found: C, 66.25; N, 7.7; N, 3.9.

Base: White needles (from petr. ether), m.p. 69~70.5°. *Anal.* Calcd. for $C_{18}H_{27}ON$: C, 79.09; H, 9.95; N, 5.12. Found: C, 79.45; H, 9.5; N, 5.3.

Picrolonate: Yellow pillars (EtOH+dioxane), m.p. 245°. *Anal.* Calcd. for $C_{28}H_{35}O_6N_5$: C, 62.55; H, 6.56; N, 13.03. Found: C, 62.95; H, 6.35; N, 13.15.

Oxalate-B was identified as 8-(*p*-methoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline oxalate (VII), white needles (acetone+EtOH), m.p. 164~166° (2.3 g). *Anal.* Calcd. for $C_{20}H_{23}O_5N$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.0; H, 6.45; N, 3.9.

Base : White needles (petr. ether), m.p. 64~64.5°. *Anal.* Calcd. for $C_{18}H_{21}ON$: C, 80.86; H, 7.92; N, 5.24. Found : C, 80.7; H, 7.65; N, 5.15.

Oxalate-C was 8-(*p*-methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline oxalate (V). It formed white and very hygroscopic semicrystalline mass (3.5 g.) from acetone.

Base : Colorless liquid of $b.p_3$ 164~165°, which decolorized 2% $KMnO_4$ solution in acetone.

Picrolonate : Yellow granules (EtOH+dioxane), m.p. 219~222°. *Anal.* Calcd. for $C_{28}H_{33}O_6N_5$: C, 62.79; H, 6.21; N, 13.08. Found : C, 62.65; H, 6.3; N, 13.35.

3-Hydroxy-N-methyl-7-aza-des-N-morphinan (VIII)—A solution of octahydroisoquinoline oxalate (V) (6.7 g.) in 48% HBr (70 cc.), containing ca. 20 mg. of hydroquinone as an inhibitor of polymerisation, was refluxed for 20 hrs. After removal of HBr *in vacuo*, the residue was dissolved in water, filtered with charcoal, basified with NH_4OH, and the separated voluminous white precipitate was extracted with ether. After being dried, solvent was concentrated to a volume of about 10 cc., cooled in an ice-box over night, and the crystalline solid (230 mg.) was collected. After evaporating the liquor, the residue was dissolved in benzene and chromatographed over Al_2O_3. Elution with acetone gave an additional 120 mg. of crude product. The combined product was recrystallized from AcOEt to colorless granules (300 mg.), m.p. 202~203°. It gave a yellow green color with $FeCl_3$. *Anal.* Calcd. for $C_{17}H_{23}ON$: C, 79.32; H, 9.01; N, 5.44. Found : C, 79.25; H, 9.2; N, 5.7.

Summary

3-Hydroxy-N-methyl-7-aza-des-N-morphinan was synthesized. Analgesic action of this compound, contrary to expectations, was not strong.

(Received March 20, 1953)

UDC 547.826.1-234 : 547.483

84. Morizo Ishidate and Terumi Nakajima : Structure of the Condensation Product of Isonicotinylhydrazine and Sodium Glucuronate.

(*Faculty of Pharmaceutical Sciences, University of Tokyo**)

Passedonet, *et al.*[1] first reported the reaction product of isonicotinylhydrazine (INAH) and glucuronolactone and gave it the structure of isonicotinylhydrazone of glucuronolactone (I) analogous to that of various aldoses.[2]

When this product is treated with an equivalent amount of sodium hydroxide, a sodium salt (IIa) of the compound separates out. The latter compound is also obtained by heating an aqueous ethanolic solution of one mole each of sodium glucuronate and

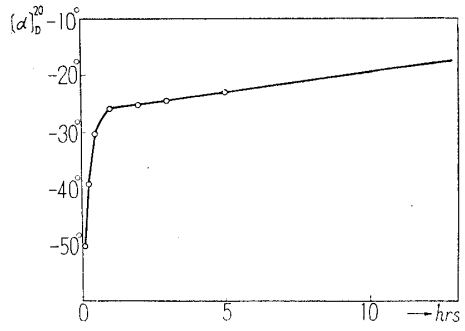


Fig. 1. Mutarotation of Sodium Isonicotinylhydrazino-(glucopyranosid)uronate (c=1.0, in water)

* Hongo, Tokyo (石館守三, 中島暉躬).

1) H. Passedonet, P. Fusey, M. Roussos : Rev. Tuberc. (Paris), **17**, 784(1953).
2) H. Zinner, W. Bock : Chem. Ber., **89**, 1124(1956).