[Chem. Pharm. Bull. 16(5) 897—908 (1968)] UDC 547.943.07

Study on the Synthesis of *rac*-3-Methoxy-6-oxo-N-methylmorphinan

Ryozo Maeda and Eiichi Ohsugi

Shionogi Research Laboratory, Shionogi & Co., Ltd.[1]

(Received July 21, 1967)

rac-3-Methoxy-6-oxo-N-methylmorphinan was synthesized from 1-(*p*-methoxybenzyl)-2-methyl-6-oxo-$\Delta^{9,10}$-octahydroisoquinoline and also from 1-(*p*-methoxybenzyl)-2-methyl-6-oxo-$\Delta^{5,10}$-octahydroisoquinoline by the action of 85% phosphoric acid according to Grewe's cyclization, respectively. 1-(*p*-Methoxybenzyl)-2-methyl-6,6-ethylenedioxy-$\Delta^{9,10}$-octahydroisoquinoline, which was used as a starting material, was prepared from 2-(*p*-methoxybenzyl)-2-methyl-6,6-ethylenedioxy-$\Delta^{9,10}$-octahydroisoquinolinium chloride by means of Stevens' rearrangement.

Cyclization methods for the morphinan synthesis hitherto appeared in literatures can be classified as follows: (1) cyclization of 1-benzyl-$\Delta^{9,10}$-octahydroisoquinolines (Grewe's cyclization),[2-5] and (2) ring closure of hydrophenanthrene derivatives having a suitable side chain, which is converted to ethanamine group (Gates'[6] and Ginsburg's[7] cyclizations).

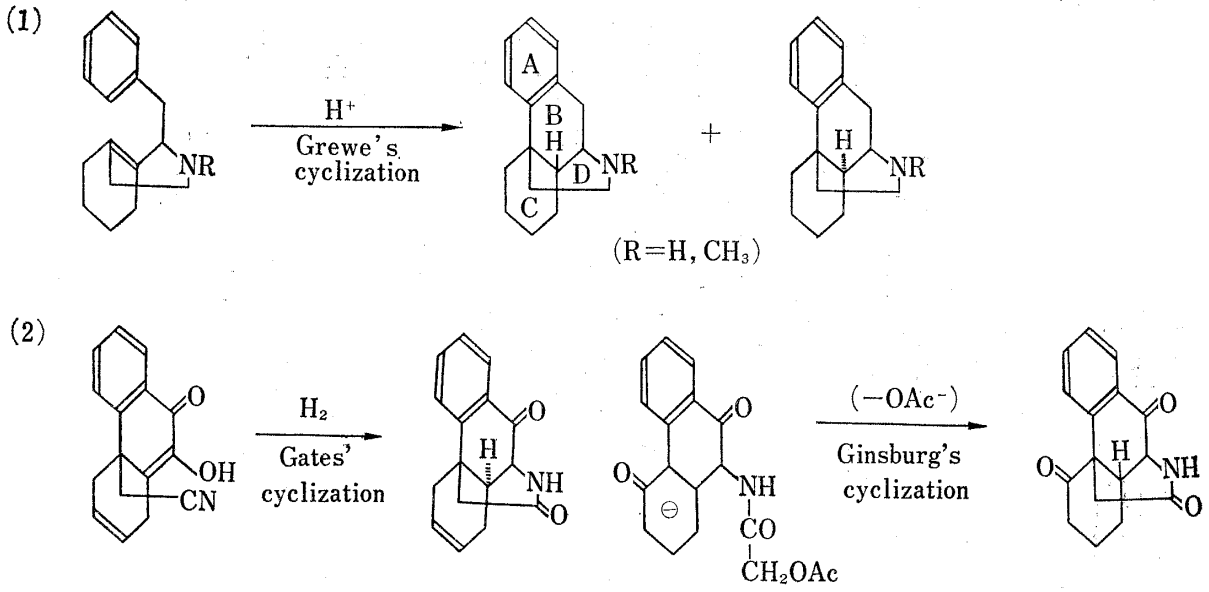


Chart 1

In the course of our research on the syntheses of 3,4-lutidine derivatives, it was found that 3-aminomethyl-4-methylpyridine was easily converted into 3-hydroxymethyl-4-methylpyridine (I) in excellent yield. This compound (I) has two reactive functional groups,

1) Location: *Sagisu, Fukushima-ku, Osaka.*
2) *a*) R. Grewe, *Angew. Chem.*, **59**, 194 (1947); R. Grewe and A. Mondon, *Ber.*, **81**, 279 (1948); R. Grewe and W. Friedrichsen, *ibid.*, **100**, 1550 (1967); *b*) O. Schnider and A. Grüssner, *Helv. Chim. Acta*, **32**, 821 (1949).
3) O. Schnider and H. Hellerbach, *Helv. Chim. Acta*, **33**, 1437 (1950).
4) H. Hennecka, *Ann.*, **583**, 110 (1953).
5) E. Ochiai and M. Ikehara, *Chem. Pahrm. Bull.* (Tokyo), **2**, 109 (1954).
6) M. Gates, R. B. Woodward, W. F. Newhall, and R. Kiinzli, *J. Am. Chem. Soc.*, **72**, 1141 (1950); M. Gates and G. Tschudi, *ibid.*, **72**, 4839 (1950); **74**, 1109 (1952); **78**, 1380 (1956); M. Gates and W.G. Webb, *ibid.*, **80**, 1186 (1958).
7) D. Elad and D. Ginsburg, *J. Chem. Soc.*, 3052 (1954); S. Bien and D. Ginsburg, *ibid.*, 2065 (1963).

γ–methyl group and β–carbinol. Therefore, conversions of γ–methyl to γ–acetic and of β–carbinol to β–propionic acids would give a suitable intermediate for the preparation of 6–oxo–5,6,7,8–tetrahydroisoquinoline derivative, which was assumed to be serviceable for the purpose of the Grewe's morphinan synthesis. Under these assumption, exploratory work in the synthesis of *rac*–3–methoxy–6–oxo–N–methylmorphinan was studied.

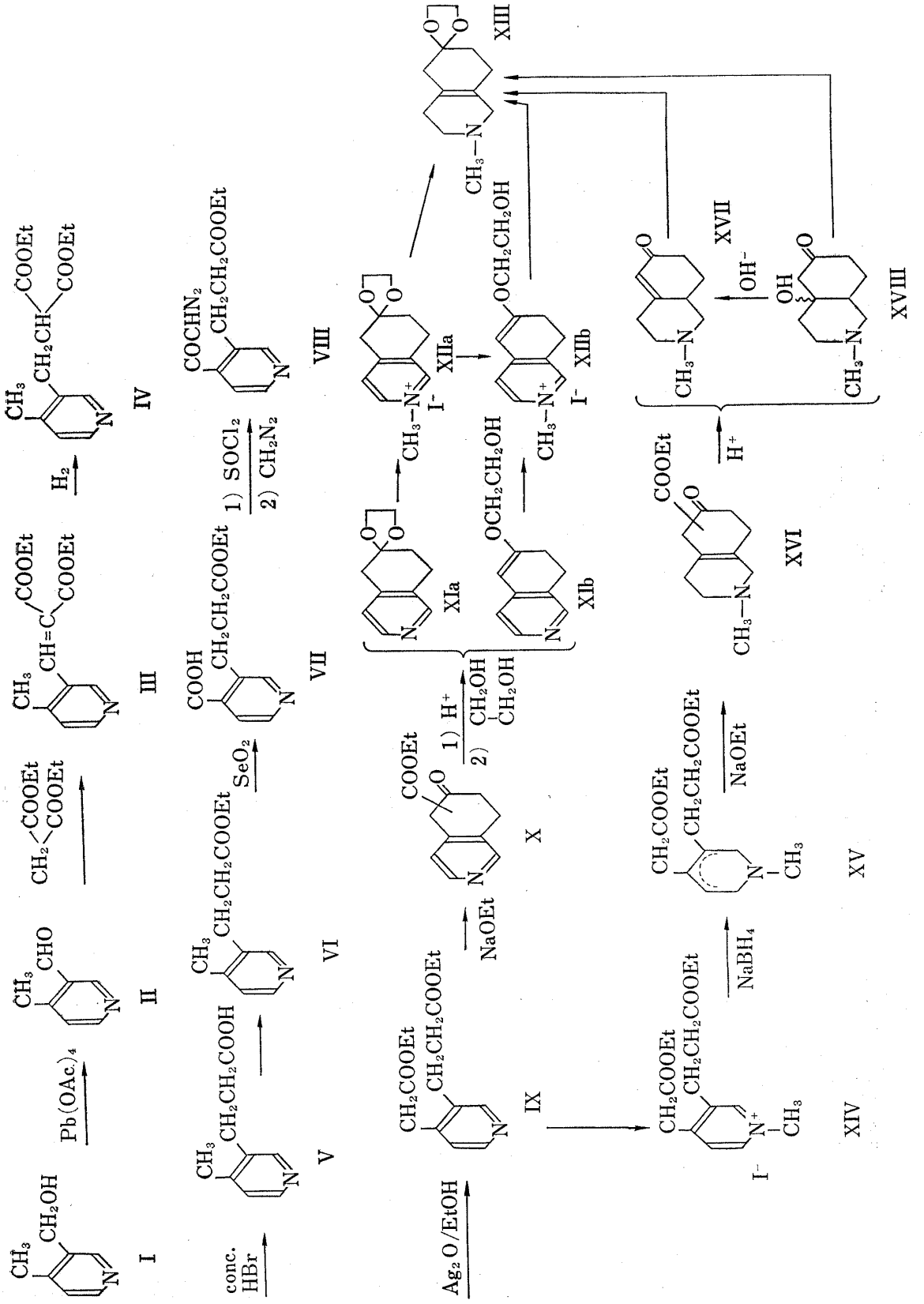


Chart 2

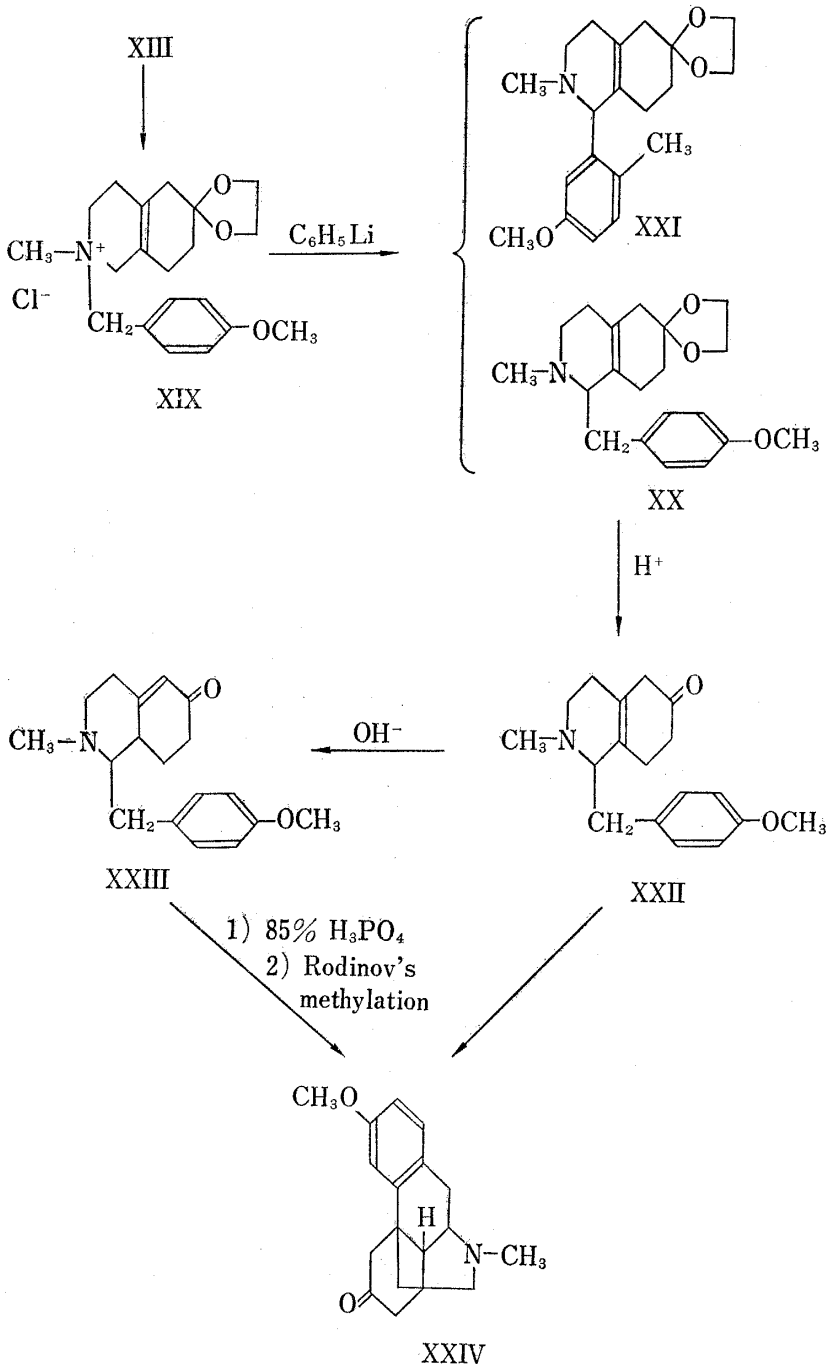


Chart 3

This paper describes the results of this exploratory work using the Grewe's cyclization reaction. The reaction course are summarized in the accompanying scheme.

Ethyl (4–methyl–3–pyridal)malonate (III) has already been synthesized from the carbinol (I) *via* 4–methyl–3–pyridinecarboxaldehyde (II) by Bobbitt and Scola.[8] Catalytic hydrogenation of III gave a saturated compound (IV), which was converted to 4–methylpyridine–3–propionic acid (V) by the action of conc. hydrobromic acid. Esterification of V gave ethyl 4–methylpyridine–3–propionate (VI) in 89% yield based on the malonate (III). The selective oxidation of the γ–methyl group[9] was effected by the action of selenium dioxide to give

8) J.M. Bobbitt and D.A. Scola, *J. Org. Chem.*, **25**, 560 (1960).
9) D. Jerchel and J. Heider, *Ann.*, **613**, 153 (1958).

3-β-carboethoxyethylisonicotinic acid (VII) in 75% yield. The compound (VII) was converted to ethyl 4-carboethoxymethylpyridine-3-propionate (IX) by the Arndt-Eistert reaction in 60% yield.

Dieckmann cyclization of IX with sodium ethoxide proceeded smoothly to yield the β-keto-ester (X) in 83% yield. The ketonic cleavage of X was carried out by the action of 8% hydrochloric acid. Although the desired 6-oxo-5,6,7,8-tetrahydroisoquinoline was not easily isolated, the treatment of the crude product with ethyleneglycol under the general procedure for the preparation of the ketal derivatives gave two components, a faint yellow oily material, bp 148—151° (3 mmHg), and colorless needles, mp 127—128°, in 20 %yields, respectively. The elemental analyses showed that these components had the same formula $C_{11}H_{13}O_2N$. The crystalline component showed an absorption band at 288 mμ (ε=15100) due to the double bond conjugated with pyridine ring in ultraviolet spectrum. The nuclear magnetic resonance (NMR) spectrum displayed one proton signal (singlet) at 4.51 τ due to the olefinic proton and one hydroxyl proton signal at 5.2 τ, which disappeared on addition of deuterium oxide. In consideration of these data, the structure of the crystalline component should be represented as 6-β-hydroxyethoxy-7,8-dihydroisoquinoline (XIb). On the other hand, the oily material did not show the presence of any functional groups such as enol-ether and hydroxyl group in the infrared spectrum. Therefore, the oily component must be 6,6-ethylenedioxy-5,6,7,8-tetrahydroisoquinoline (XIa). On recrystallization from ethanol, the methiodide of XIa partly changed into the methiodide of XIb. The same treatment of the latter methiodide (XIIb), however, did not change its enolic nature. In the case of sodium borohydride reduction, the former methiodide (XIIa) afforded 2-methyl-6,6-ethylenedioxy-$\Delta^{9,10}$-octahydroisoquinoline (XIII) in nearly quantitative yield. On the other hand, the latter (XIIb) gave, in about 40% yield, the enolic compound and an approximately equal amount of a ketal compound, which was identical with XIII prepared from XIIa. Although the structure of the enolic compound was not clearly confirmed, the treatment of this compound with 2 N hydrochloric acid followed by the ketallization with ethyleneglycol afforded the ketal compound (XIII).

In an attempt to prepare 1-(*p*-methoxybenzyl)-2-methyl-6,6-ethylenedioxy-$\Delta^{9,10}$-octahydroisoquinoline (XX) by the reaction of XIIa and *p*-methoxybenzylmagnesium chloride

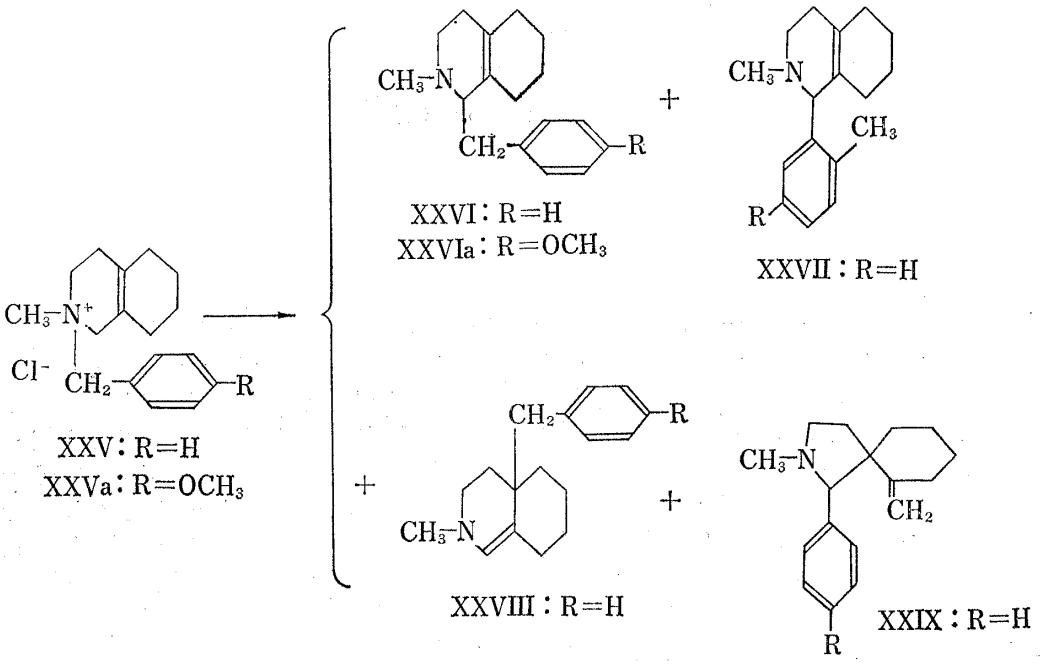


Chart 4

followed by the reduction with Adams' catalyst, it was found that the crude product showed 9—10 spots on the thin-layer chromatogram (TLC).

Recently, the introduction of the benzyl group at C_2 in 1,2,5,6-tetrahydropyridine nucleus was investigated by Fry and May,[10] but no precedent was found in literatures in the case of the $\Delta^{9,10}$-octahydroisoquinoline derivatives.

As a preliminary experiment, Stevens' rearrangement of 2-methyl-2-benzyl-$\Delta^{9,10}$-octahydroisoquinolinium chloride (XXV) was attempted by the action of ethereal phenyl lithium. The crude product, which showed 4 spots on the TLC, was treated with oxalic acid in acetone to separate the salt, from which the oxalate of 1-benzyl-2-methyl-$\Delta^{9,10}$-octahydroisoquinoline (XXVI) was isolated in a yield of 19%. The compound (XXVI) was identical with an authentic sample prepared by the cyclization of cyclohexenylethylamine derivative according to Schnider.[3] Further, the basic product from the acetone solution was separated into three compounds, A (picrate: mp 215—216°), B (picrate: mp 138—140°), and C (picrate: mp 171—172°) in yields of 19%, 5% and 1.5%, respectively. Judging from the analytical data, it was found that these compounds were isomers each other. The NMR spectrum of the compound A clearly showed a signal of a methyl group attached to the aromatic ring at 7.88 τ, and there were also four aromatic protons and one proton (6.38 τ multiplet w/2=6 cps) attached to the carbon atom bearing a phenyl group. The signal due to the allylic two protons located at the vicinal position to the nitrogen atom, however, was not observed. The infrared spectrum in carbon disulfide showed a band at 740 cm^{-1} indicating a presence of the *ortho*-di-substituted phenyl group. Accordingly, the compound A was considered to be 1-(*o*-tolyl)-2-methyl-$\Delta^{9,10}$-octahydroisoquinoline (XXVII). On the other hand, the NMR spectrum of the compound B had benzylic two protons located at the vicinal position to the quaternary carbon atom at 7.14 τ, a singlet vinyl proton at 4.40 τ due to an enamine and five aromatic protons. Therefore, the compound B must be 2-methyl-10-benzyl-$\Delta^{1,9}$-octahydroisoquinoline (XXVIII). The formation of the above mentioned isomers can be explained by an ion pair mechanism according to Jacobson.[11]

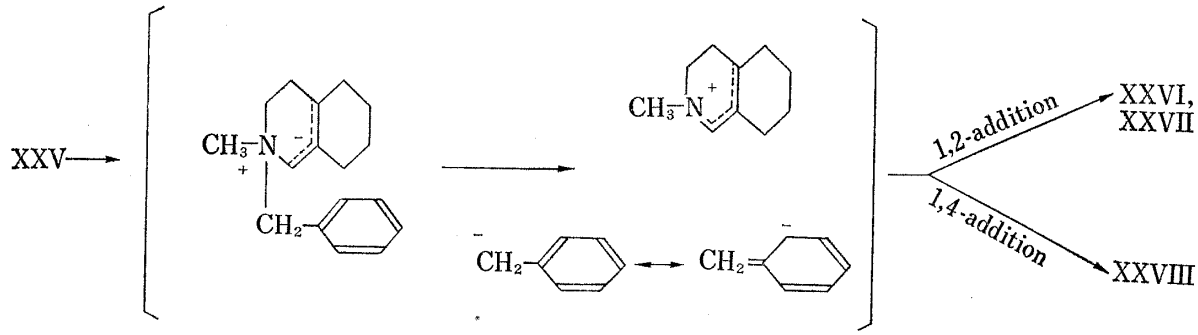
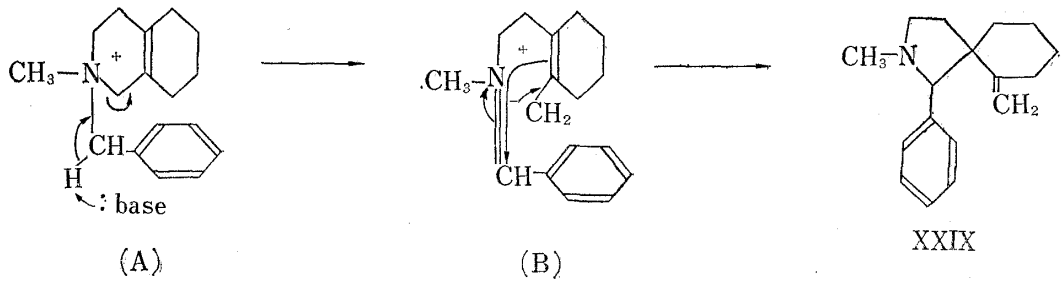


Chart 5

The NMR spectrum of the remaining compound C had a pair of doublets (J=1.5 cps) at 5.18 τ and 5.3 τ, assignable to non-equivalent two protons of exo-methylene group and a singlet signal at 7.82 τ due to the N-methyl group. There were also five aromatic protons and one proton (6.78 τ, singlet) located at the vicinal position to the nitrogen atom and the phenyl group. The signal due to any C-methyl group, however, was not observed. The infrared spectrum in carbon tetrachloride showed an exomethylene band (3080, 1635 and 888 cm^{-1}), monosubstituted phenyl band (3040 and 695 cm^{-1}) and N-methyl band (2760 cm^{-1}). The characteristic bands of the spiro system[12] were observed at 1360 and 1340 cm^{-1}. These data suggest, that the compound C is probably 1-phenyl-2-methyl-6-methylene-2-azaspiro-

10) E.M. Fry and E.L. May, *J. Org. Chem.*, **26**, 2592 (1961).
11) A.E. Jacobson, *J. Org. Chem.*, **31**, 1569 (1966).
12) J.A. Dixon and P.A. Naro, *J. Org. Chem.*, **25**, 2096 (1960).



(A) (B)

Chart 6

[4,5]decane (XXIX). One of the more plausible possibilities of this rearrangement requires: (A), the removal of the benzyl proton, and (B), ring opening to form an allylic carbanion.

The migration of negative charge on ring carbon and the rearrangement of π-electron on the carbon atom of benzyl position would afford the product (XXIX).

In the hope of proving this successful experiment, the similar reaction of *p*-methoxybenzyl analog (XXVa) was further examined and the expected compound (XXVIa) was isolated in 35% yield.

As a result of these model experiments, it became necessary to prepare 2-(*p*-methoxybenzyl)-2-methyl-6,6-ethylenedioxy-$\Delta^{9,10}$-octahydroisquinolinium chloride (XIX). For this purpose, the synthesis of XIII from IX was reexamined. Conversion to the methiodide (XIV) followed by sodium borohydride reduction gave tetrahydrobase (XV) in 84% yield. Dieckmann cyclization of XV gave, in 95% yield, an oily product (XVI), which showed 2 spots on the TLC. The ketonic cleavage of XVI was achieved by the action of 6% hydrochloric acid to give two carbonyl compounds; a faint yellow oil, bp 114—115° (4 mmHg), and colorless needles, mp 171—172°, in 60% and 30% yields, respectively. The oily compound showed absorption bands at 1665 cm^{-1} and 1630 cm^{-1} due to α,β-unsaturated carbonyl in the infrared spectrum. The NMR spectrum showed a singlet vinyl proton signal at 4.17 τ. Therefore, the oily compound should be formulated as 2-methyl-6-oxo-$\Delta^{5,10}$-octahydroisoquinoline (XVII). On the other hand, the infrared spectrum of the crystalline material in carbon tetrachloride showed bands at 3610 cm^{-1} and 3421 cm^{-1} indicating a presence of partly bonded hydroxyl group and at 1721 cm^{-1} due to the carbonyl group. Moreover, this compound was easily transformed, by the action of 10% potassium hydroxide, into XVII in almost quantitative yield. Judging from these results, the structure of this product should be represented as 2-methyl-6-oxo-10-hydroxydecahydroisoquinoline (XVIII). Ketalization of both XVII and XVIII in the presence of toluene-*p*-sulphonic acid gave, in excellent yields, the same ketal compound, which was identical with 2-methyl-6,6-ethylenedioxy-$\Delta^{9,10}$-octahydroisoquinoline (XIII) prepared from XIIa.

The ketal (XIII) was converted to the quaternary salt (XIX) with *p*-methoxybenzyl chloride and was subjected to Stevens' rearrangement. Careful chromatography followed by the picrate formation gave 1-(*p*-methoxybenzyl)-2-methyl-6,6-ethylenedioxy-$\Delta^{9,10}$-octahydroisoquinoline (XX) in about 30% yield. In the NMR spectrum no vinyl proton signal was observed, and signals at 6.05 τ, 6.22 τ and 7.65 τ were respectively assigned to ketal, methoxyl and N-methyl groups, and there were four aromatic protons. In the course of the isolation procedure on column chromatography, 1-(2-methyl-5-methoxyphenyl)-2-methyl-6,6-ethylenedioxy-$\Delta^{9,10}$-octahydroisoquinoline (XXI) was obtained in about 10% yield as its picrolonate. The NMR spectrum of the base (XXI) revealed the presence of a methyl group attached to the aromatic ring (7.83 τ, singlet), a ketal group (6.09 τ, singlet), a methoxyl group (6.25 τ, singlet) and a N-methyl group (7.69 τ, singlet), and there were also three aromatic protons. The signals due to two protons located at the benzylic position and any olefinic protons, however, were not observed. The infrared spectrum in carbon disulfide showed the presence of a 1,2,4-trisubstituted phenyl group (1140 and 805 cm^{-1}) and the

N–methyl group (2760 cm^{-1}). The hydrolysis of XX with 1 N hydrochloric acid at room temperature gave 1–(*p*–methoxybenzyl)–2–methyl–6–oxo–$\Delta^{9,10}$–octahydroisoquinoline (XXII) in nearly quantitative yield. Transformation of XXII into the α,β–unsaturated carbonyl derivative was carried out by the action of 2 N potassium hydroxide in 90% ethanol solution. The product, 1–(*p*–methoxybenzyl)–2–methyl–6–oxo–$\Delta^{5,10}$–octahydroisoquinoline (XXIII), was isolated as its picrate in 55% yield.

The ultimate work for the preparation of 3–methoxy–6–oxomorphinan derivatives consisted in the cyclization and the methylation of the above mentioned two carbonyl compounds (XXII and XXIII). The ring closure of each compound was carried out by the action of 85% phosphoric acid at 140°, and the product was methylated with the Rodinov's reagent. Preparative thin–layer chromatographic separation over silicagel followed by crystallization from cyclohexane gave *rac*–3–methoxy–6–oxo–N–methylmorphinan (XXIV) in 10% yield. This compound (XXIV) was identical with an authentic sample given through the courtesy of Dr. Sawa. In these experiments *rac*–3–methoxy–6–oxo–N–methylisomorphinan, however, could not be separated even by means of careful preparative thin–layer chromatography.

Experimental

All melting points and boiling points were uncorrected. The ultraviolet absorption spectra were measured with a Hitachi Recording ultraviolet spectrophotometer EPS–3, and the infrared spectra with a Nippon Bunko infrared spectrophotometer DS–201. The NMR spectra were run in deuterochloroform solution with a Varian A–60 spectrometer, serving tetramethyl silane as internal reference.

Ethyl 4-Methylpyridine-3-propionate (VI)——According to the method of Bobitt and Scola,[8] ethyl (4–methyl–3–pyridal)malonate (III) was prepared by oxidation of 3–hydroxymethyl–4–methylpyridine (I) with lead tetraacetate followed by condensation with ethyl malonate. A solution of 154.6 g of III in 1540 ml of 90% ethanol was hydrogenated over 3.1 g of Adams' catalyst. The reaction mixture was acidified with dil. hydrobromic acid, filtered through charcoal, and then evaporated to dryness under reduced pressure. The residual hydrobromide was refluxed with 1 liter of conc. hydrobromic acid for 24 hr. The residue from the removal of the excess reagent under reduced pressure was dissolved into a small amount of water, and the solution adjusted to pH 5 with solid potassium acetate. The acidic solution was evaporated to dryness under reduced pressure and the residue was extracted with anhyd. ethanol. Evaporation of the solvent gave 110.6 g of the crude carboxylic acid (V), which was used for the next step without further purification. For analysis, a small sample was purified from ethanol to give colorless needles, mp 155—156°. *Anal.* Calcd. for $C_{19}H_{11}O_2N$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.29; H, 6.71; N, 8.29. To a solution of the crude V (110 g) in 1.45 liter of anhyd. ethanol, 106 g of conc. sulfuric acid was added and the mixture was refluxed for 5 hr. The residue obtained after removal of the ethanol was poured onto ice–water, the solution was made alkaline with potassium carbonate and extracted with ether. The crude base from the ether solution was distilled to yield 102. 5 g of VI, bp 131—134° (2 mmHg), as a colorless oil. The picrate, crystallized from ethanol, mp 110.5—111.5°. *Anal.* Calcd. for $C_{11}H_{15}O_2N \cdot C_6H_3O_7N_3$: C, 48.34; H, 4.30; N, 13.27. Found: C, 48.22; H, 4.44; N, 13.11.

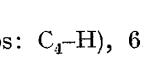
3-β-Carboethoxyethylisonicotinic Acid (VII)——To a solution of 50 g of VI in 425 ml of pyridine, 53.4 g of selenium dioxide was added and the mixture refluxed under vigorous stirring at 145° (bath temp.) for 1.5 hr. The precipitated metallic selenium was removed and most of the solvent was distilled off under reduced pressure, then water was added and distilled to strip off the pyridine. The solid product was crystallized from ethanol to give 44.6 g of VII, mp 175—176°, as colorless needles. *Anal.* Calcd. for $C_{11}H_{13}O_4N$: C, 59.18; H, 5.89; N, 6.28. Found: C, 59.49; H, 6.04; N, 6.09.

The methyl ester of VII, prepared by methylation with diazomethane, bp 134—136° (2 mmHg). UV λ_{max}^{EtOH} mμ (ε): 279 (3280). The picrolonate, crystallized from ethanol, mp 140° (decomp.). *Anal.* Calcd. for $C_{12}H_{15}O_4N \cdot C_{10}H_8O_5N_4$: C, 52.69; H, 4.62; N, 13.97. Found: C, 52.80; H, 4.77; N, 13.92. The hydrochloride, crystallized from ethanol–ether, mp 134—135°. *Anal.* Calcd. for $C_{12}H_{15}O_4N \cdot HCl$: C, 52.65; H, 5.89; N, 5.12; Cl, 12.96. Found: C, 52.34; H, 5.99; N, 5.14; Cl, 12.89.

Arndt-Eistert Reaction of 3-β-Carboethoxyethylisonicotinic Acid (VII)——A solution of 30 g of VII in 300 ml of thionyl chloride was heated at 50—53° for 1 hr, and the excess reagent removed by distillation under reduced pressure. The crystalline hydrochloride (38.3 g) was triturated with a solution of 15.8 g of pyridine in 200 ml of ether, and the precipitated pyridine–hydrochloride was filtered. The filtrate was added dropwise into a solution of diazomethane (prepared from 63.9 g of nitrosomethylurea) in 900 ml of ether with stirring and ice–cooling. After being kept standing for 24 hr at room temperature, the solvent was removed to yield 32.8 g of the crude diazoacetyl compound (VIII), which was used for the next step without

further purification. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2110, 1625, 1350 (diazoacetyl). A small sample was converted to picrate, which was crystallized from ethanol, mp 127.5—128.5° (decomp.). *Anal.* Calcd. for $C_{12}H_{13}O_3N \cdot C_6H_3O_7N_3$: C, 45.38; H, 3.39; N, 17.64. Found: C, 45.59; H, 3.64; N, 17.15. To a stirred solution of 32 g of the crude VIII in 350 ml of anhyd. ethanol, silver oxide (prepared from 5.4 g of silver nitrate) was added in a small portion over a 2 hr period at 50—55°, and the mixture was refluxed for 2 hr. The reaction mixture was filtered with application of charcoal and the solvent removed. The crude product was distilled to give 22.8 g of ethyl 4-carboethoxymethylpyridine-3-propionate (IX), bp 155—158° (1 mmHg), as a colorless oil. UV λ_{max}^{EtOH} mμ (ε): 262 (2130), 267 (1800). The picrolonate, crystallized from ethanol, mp 144—145.5°. *Anal.* Calcd. for $C_{14}H_{19}O_4N \cdot C_{10}H_8O_5N_4$: C, 54.44; H, 5.14; N, 13.23. Found: C, 54.19; H, 5.19; N, 13.04. The hydrochloride, crystallized from anhyd. ethanol–ether, mp 127—128°. *Anal.* Calcd. for $C_{14}H_{19}O_4N \cdot HCl$: C, 55.72; H, 6.68; N, 4.67; Cl, 11.75. Found: C, 55.86; H, 6.70; N, 4.49; Cl, 11.84.

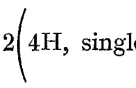
Dieckmann Condensation of Ethyl 4-Carboethoxymethylpyridine-3-propionate (IX)——To a stirred suspension of 3.9 g of metallic sodium in a solution of 7.8 g of anhyd. ethanol and 350 ml of toluene was added a solution of 30 g of IX in 200 ml of toluene over a 2 hr period at 90—100°, and the mixture was refluxed under nitrogen for 16 hr. After cooling, dil. hydrochloric acid was added to dissolve the precipitates, and the solution was adjusted to pH 8 with potassium carbonate. The separated crystalline material was filtered and dried to give 22.7 g (91.5%) of the crude product, mp 187° (decomp.). Recrystallization from ethanol gave 20.6 g of the enolized β-keto-ester(X) as colorless needles, mp 192° (decomp.). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1660 (chelated C=O), 1620 (double bond). *Anal.* Calcd. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.66; H, 6.15; N, 6.34. The picrate, crystallized from ethanol, mp 179° (decomp.). *Anal.* Calcd. for $C_{12}H_{13}O_3N \cdot C_6H_3O_7N_3$: C, 48.22; H, 3.60; N, 12.50. Found: C, 48.38; H, 3.86; N, 12.33. The hydrochloride, crystallized from ethanol–ether, mp 160° (decomp.). *Anal.* Calcd. for $C_{12}H_{13}O_3N \cdot HCl$: C, 56.75; H, 5.52; N, 5.48; Cl, 13.87. Found: C, 56.61; H, 5.78; N, 5.40; Cl, 14.26.

6,6-Ethylenedioxy-5,6,7,8-tetrahydroisoquinoline (XIa), and 6-β-Hydroxyethoxy-7,8-dihydroisoquinoline (XIb)——A solution of 10 g of X in 8% hydrochloric acid was refluxed for 3.5 hr. After cooling, the reaction mixture was made alkaline with ammonium hydroxide and extracted with dichloromethane. The organic layer was diluted with 100 ml of benzene and the dichloromethane was removed by fractional distillation. The benzene solution was added to the suspension of 23.8 g of ethyleneglycol in 400 ml of benzene and the mixture was heated azeotropically under reflux in the presence of 25.5 g of toluene-*p*-sulphonic acid for 14 hr. The brownish residue obtained by decantation of the benzene layer was treated with conc. ammonium hydroxide and taken into chloroform. The residue from distillation of the solvent was treated with benzene to separate 2.04 g of the crystalline product, from which 1.75 g of the pure XIb was obtained by recrystallization from benzene, mp 127—128°, 20%. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 1630 (enol–ether). *Anal.* Calcd. for $C_{11}H_{13}O_2N$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.84; H, 7.01; N, 7.35. The picrate, crystallized from ethanol, mp 155.5—156°. *Anal.* Calcd. for $C_{11}H_{13}O_2N \cdot C_6H_3O_7N_3$: C, 48.57; H, 3.84; N, 13.33. Found: C, 48.59; H, 4.01; N, 13.12. The benzene solution obtained by the treatment of the crude product was chromatographed over alumina and developed with benzene to give 1.78 g (20.4%) of an oily ketal (XIa), which had bp 148—151° (3 mmHg). UV λ_{max}^{EtOH} mμ (ε): 261.5 (2310), 268.5 (1935). NMR τ: 1.68 (singlet: C_1–H), 1.74 (doublet J=5 cps: C_3–H), 3.08 (1H doublet J=5 cps: C_4–H), 6.03 (4H, singlet: ). The picrate, crystallized from ethanol, mp 136°. *Anal.* Calcd. for $C_{11}H_{13}O_2N \cdot C_6H_3O_7N_3$: C, 48.57; H, 3.84; N, 13.33. Found: C, 48.65; H, 3.96; N, 13.39.

2-Methyl-6,6-ethylenedioxy-5,6,7,8-tetrahydroisoquinolinium Iodide (XIIa), and 2-Methyl-6-β-hydroxyethoxy-7,8-dihydroisoquinolinium Iodide (XIIb)——a) A solution of 2.0 g of XIa in 20 ml of ethyl acetate was kept standing with 1.78 g of methyl iodide at room temperature overnight. The crude methiodide (3.28 g; 95%), mp 123—125°, was used for the next step without further purification. For analysis, recrystallization of 463 mg of the crude methiodide from anhyd. ethanol gave 240 mg of the pure XIIa, mp 123—124°. *Anal.* Calcd. for $C_{12}H_{16}O_2NI$: C, 43.26; H, 4.84; N, 4.20; I, 38.09. Found: C, 43.35; H, 4.91; N, 4.35; I, 38.00. The infrared spectrum of the pure sample in nujol was identical with that of the crude product. The residue from the ethanol solution was crystallized from isopropanol to give 91 mg of XIIb, mp 138—139°, and mixed melting point with a sample prepared from XIb (described below), 138—139° and with XIIa, 91—112°.

b) A solution of 6 g of XIb in 400 ml of ethyl acetate was kept standing with 5.9 g of methyl iodide at room temperature overnight. The crude methiodide, 10.05 g (96%), mp 139—140°, was crystallized from isopropanol giving 9.57 g of the pure XIIb, mp 139—140°. IR ν_{max}^{Nujol} cm^{-1}: 3360 (OH). *Anal.* Calcd. for $C_{12}H_{16}O_2NI$: C, 43.26; H, 4.84; N, 4.20; I, 38.09. Found: C, 43.36; H, 4.94; N, 4.32; I, 37.85. Recrystallization of 103 mg of XIIb from anhyd. ethanol gave 96 mg of the original XIIb, mp 139—140°, and XIIa was not isolated.

2-Methyl-6,6-ethylenedioxy-$\Delta^{9,10}$-octahydroisoquinoline (XIII) from the Methiodides (XIIa and XIIb)——a) A suspension of 4 g of the crude XIIa in 30 ml of anhyd. ethanol was treated with a solution of one gram sodium borohydride in 40 ml of anhyd. ethanol at room temperature. The residue from removal of the solvent was treated with chloroform. The product from the chloroform solution was chromatographed on alumina and eluted with ether followed by distillation, giving a colorless oil 2.45 g (95%) of XIII, bp

105° (2 mmHg). NMR τ: 6.12(4H, singlet: C_6 ), 7.28 (2H, multiplet w/2=5 cps: C_1 ), 7.73 (3H singlet: N–CH_3). The picrate, crystallized from ethanol, mp 161—162°. *Anal.* Calcd. for $C_{12}H_{19}O_2N \cdot C_6H_3O_7N_3$: C, 49.31; H, 5.06; N, 12.78. Found: C, 49.47: H, 5.28; N, 12.76.

b) The sodium borohydride reduction of 4 g of XIIb was carried out as above to yield 2.8 g of the crude product, which was chromatographed on 30 g of alumina and eluted in turn with *n*–hexane, benzene, ether, chloroform and then 10% methanol–chloroform. The products (1.0 g) obtained with 450 ml of *n*–hexane and with 150 ml of benzene were combined and converted to the picrate, which was crystallized from ethanol to yield 1.93 g (36.6%), XIII–picrate, mp 161—162°. This picrate showed no depression of melting point on admixture with the picrate prepared as in a). The products obtained with further 200 ml of benzene and 200 ml of ether were combined to give 0.39 g of a mixture of two components. The products obtained with 200 ml of chloroform and 200 ml of 10% methanol–chloroform were combined to give 0.96 g of an unstable enolic base, which was used for the next reaction withourt further purification. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3640 (OH), 1620 (enol–ether). NMR τ: 5.25 (singlet: vinyl proton), 6.21 (singlet: C_6–OCH_2CH_2–O–), 6.37 (singlet: OH) (disappeared on addition of D_2O), 7.13 (multiplet w/2=5 cps: C_1), 7.66 (singlet: N–CH_3). This material is presumably 2–methyl–6–β–hydroxyethoxy–1,2,3,4,7,8–hexahydroisoquinoline.

A solution of 0.55 g of the enolic compound in 5 ml of 2 N–hydrochloric acid was refluxed for 3.5 hr. The reaction mixture was made alkaline with ammonium hydroxide and extracted with benzene. The benzene solution was subjected to ketallization using ethyleneglycol. The crude product (0.35 g) was chromatographed on alumina and eluted with ether to give 0.23 g of the ketal compound, which was identified by infrared spectral comparison with XIII prepared as in a).

Sodium Borohydride Reduction of 1-Methyl-3-β-carboethoxyethyl-4-carboethoxymethylpyridinium Iodide (XIV)——A solution of 10 g of IX in 30 ml of ethyl acetate was kept standing with 6.5 g of methyl iodide at room temperature overnight. The crude methiodide (14.5 g: 94.5%) was crystallized from ethyl acetate–isopropanol to give 1.42 g (92.5%), XIV, mp 84—85°. *Anal.* Calcd. for $C_{15}H_{22}O_4NI$: C, 44.24; H, 5.45; N, 3.44; I, 31.16. Found: C, 44.53; H, 5.56; N, 3.60; I, 30.92.

A solution of 30 g of XIV in 260 ml of anhyd. ethanol was treated with a solution of 7.5 g of sodium borohydride in 300 ml of anhyd. ethanol at room temperature. The reaction mixture was worked up as described in the reduction of XIIa to yield 20.2 g of the crude base, from which 19 g (91%) of the tetrahydro compound (XV) was obtained by distillation, bp 151—154° (3 mmHg).

Dieckmann Condensation of the Tetrahydro Compound (XV)——To a stirred suspension of 2.3 g of metallic sodium in a solution of 4.6 g of anhyd. ethanol and 250 ml of toluene was added a solution of 18.2 g of XV in 150 ml of toluene over 2 hr period at 70°. The mixture was worked up as described for the preparation of X to give 14.4 g of an oily crude β–keto–ester (XVI) (95.6%), which was used for the next step without further purification.

Hydrolysis of the β-keto-ester (XVI)——A solution of 12.8 g of the crude XVI in 75 ml of 6% hydrochloric acid was refluxed for 5 hr. The cooled solution was made alkaline with potassium carbonate and extracted with chloroform. The product from the chloroforn solution was treated with benzene to separate 2.96 g (30%) of the crude hydroxy–ketone (XVIII), mp 164—166°. Recrystallization from benzene raised its melting point to 171—172°. UV λ_{max}^{EtOH} mμ (ε): 280 (21.6). *Anal.* Calcd. for $C_{10}H_{17}O_2N$: C, 65.54; H, 9.35; O, 17.46; N, 7.64; mol. wt., 183. Found: C, 65.52; H, 9.35; O, 17.33; N, 7.67; mol. wt., 191. The picrate crystallized from ethanol, mp 220° (decomp.). *Anal.* Calcd. for $C_{10}H_{17}O_2N \cdot C_6H_3O_7N_3$: C, 46.60; H, 4.89; N, 13.59. Found: C, 46.44; H, 4.94; N, 13.49. The oily material obtained on the separation of the crude XVIII was chromatographed on alumina and elution with ether gave 6.04 g (67.8%) of the crude α,β–unsaturated carbonyl compound (XVII), from which 5.16 g (58%) of the pure XVII was obtained by distillation, bp 114—115° (4mmHg). UV λ_{max}^{EtOH} mμ (ε): 234 (15800). The picrate, crystallized from acetone, mp 201—202°. *Anal.* Calcd. for $C_{10}H_{15}ON \cdot C_6H_3O_7N_3$: C, 48.73; H, 4.60; N, 14.21. Found: C, 48.82; H, 4.85; N, 14.14.

Dehydration of the Hydroxy-ketone (XVIII)——A solution of 50 mg of XVIII in one milliliter of 10% potassium hydroxide was heated on a steam bath for one minute. The separated oily product was extracted with ether. Evaporation of the ether gave 45 mg of the crude XVII. The infrared spectrum in carbon tetrachloride was identical with that of XVII described in the above experiment. The picrate, crystallized from acetone, mp and mixed mp with the sample prepared in the above experiment, 202°.

2-Methyl-6,6-ethylenedioxy-$\Delta^{9,10}$-octahydroisoquinoline (XIII) from XVII and XVIII——a) A mixture of 19.7 g of XVII and 59.4 g of ethyleneglycol in 700 ml of benzene was azeotropically refluxed with 49.5 g of toluene–*p*–sulphonic acid. The reaction mixture was worked up as described for the preparation of XIa. The crude product was chromatographed on alumina, and the product eluted with ether was distilled to yield 21.6 g (86.5%) of the pure XIII, bp 127—129° (4 mm Hg). The infrared spectrum in carbon tetrachloride was identical with that of the sample prepared from XIIa. The methiodide, crystallized from isopropanol, mp 163—164°. *Anal.* Calcd. for $C_{13}H_{22}O_2NI$: C, 44.45; H, 6.32; N, 3.99; I, 36.13. Found: C, 44.60; H, 6.35; N, 3.88; I, 36.18.

b) The ketallization of XVIII was carried out under similar conditions as in the case of XVII. A mixture of 21 g of XVIII and 56.6 g of ethyleneglycol in 700 ml of benzene was azeotropically refluxed with 46.2 g of toluene-*p*-sulphonic acid for 10 hr. The crude product (26.3 g) was purified by distillation to yield 19.2 g (80%) of XIII, bp 134—139° (6 mm Hg). The infrared spectrum in carbon tetrachloride was identical with that of the foregoing sample.

Attempted Synthesis of 1-(*p*-Methoxybenzyl)-2-methyl-6,6-ethylenedioxy-$\Delta^{9,10}$-octahydroisoquinoline (XX) by the Grewe's Method[2]——A stirred suspension of 5.0 g of XIIa in 100 ml of dry ether was treated with 50 ml of ethereal *p*-methoxybenzylmagnesium chloride, prepared from 1.65 g of magnesium-ribbon, 1.65 g of magnesium-powder and 5.0 g of *p*-methoxybenzyl chloride in ether, under nitrogen for 3 hr. The mixture was poured onto 30 ml of ice-water containing 9 g of ammonium chloride. The crude product from the organic layer was dissolved into 50 ml of ethanol and the solution was hydrogenated over 0.1 g of Adams' catalyst at 27°. After 75 min, the absorption was complete and 92 ml (0.65 mole equivalent) of hydrogen was consumed. The reduction product (2.1 g) was chromatographed over 40 g of alumina and eluted in turn with *n*-hexane, benzene, ether and chloroform. Evaporation of the solvent from each eluate afforded complicated mixture and the desired compound colud not be obtained.

The Stevens Rearrangement of 2-Benzyl-2-methyl-$\Delta^{9,10}$-octahydroisoquinolinium Chloride (XXV)——To a solution of 3.5 g of 2-methyl-$\Delta^{9,10}$-octahydroisoquinoline,[13] prepared by the sodium borohydride reduction of 2-methyl-5,6,7,8-tetrahydroisoquinolinium iodide,[15] in 35 ml of acetone, 3.5 g of benzyl chloride was added with swirling. After being kept standing overnight, the separated quaternary salt was filtered and dried to give 6.1 g (94.8%) of XXV, mp 208—210°.

a) Phenyl lithium reagent was prepared from 4.3 g of bromobenzene and 0.38 g of metallic lithium in 100 ml of dry ether. 2-Benzyl-2-methyl-$\Delta^{9,10}$-octahydroisoquinolinium chloride (3.0 g) was added rapidly to the ethereal phenyllithium with vigorous stirring. The stirring under nitrogen was continued for 1.5 hr at 30° after the exothermic reaction had ceased. Ice-water was added to the reaction mixture to decompose the excess reagent, and the basic compound was extracted with dil. hydrochloric acid. The acidic solution was made alkaline with potassium carbonate. The crude product (2.53 g) obtained by the extraction with ether was treated with oxalic acid in acetone.

The separated crystalline material was filtered and dried to give 0.68 g (18.7%) of 1-benzyl-2-methyl-$\Delta^{9,10}$-octahydroisoquinoline (XXVI)-oxalate, mp 165—166°. Recrystallization from ethanol-acetone (2:1) raised its melting point to 167—168°. *Anal.* Calcd. for $C_{17}H_{23}N \cdot C_2H_2O_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.42; H, 7.61; N, 4.29. This compound showed no depression of melting point on admixture with an authentic sample prepared by the cyclization of cyclohexenylethylamine derivative according to Schnider.[3] The picrate from the liberated base melted at 132—134°. *Anal.* Calcd. for $C_{17}H_{23}N \cdot C_6H_3O_7N_3$: C, 58.71; H, 5.57; N, 11.91. Found: C, 58.54; H, 5.58; N, 12.12.

The liberated base (1.54 g) obtained from the acetone solution on the oxalate formation was converted to the picrate in ether. The crude picrates (1.71 g: mp 172—185°) were dissolved into 150 ml of ethanol and concentrated to about 60 ml yielding 1.13 g of the crude XXVII-picrate, mp 209—212°. Recrystallization from ethanol gave 984 mg (19.3%) of the pure picrate, mp 215—216°. *Anal.* Calcd. for $C_{17}H_{23}N \cdot C_6H_3O_7N_3$: C, 58.71; H, 5.57; N, 11.91. Found: C, 58.59; H, 5.51; N, 12.12. The mother liquor of the crude XXVII-picrate was concentrated to about 10 ml giving 280 mg (5.5%) of the XXVIII-picrate, mp 138—140°. Recrystallization from ethanol did not raise its melting point. *Anal.* Calcd. for $C_{17}H_{23}N \cdot C_6H_3O_7N_3$: C, 58.71; H, 5.57; N, 11.91. Found: C, 58.60; H, 5.51; N, 12.12.

The ether solution on the picrate formation was concentrated to about a half the original volume and kept standing for a few days, during which time the crude XXIX-picrate (76 mg: 1.5%), mp 168—170°, separated. Recrystallization from benzene raised its melting point to 171—172°. *Anal.* Calcd. for $C_{17}H_{23}N \cdot C_6H_3O_7N_3$: C, 58.71; H, 5.57; N, 11.91. Found: C, 58.37; H, 5.68; N, 11.90.

b) To a stirred solution of phenyllithium prepared from 4.37 g of bromobenzene and 0.38 g of metallic lithium in 100 ml of dry tetrahydrofuran at 35°, 3.03 g of XXV was added rapidly under nitrogen, and the mixture was refluxed on a steam bath for 1 hr. Ice-water was added to the reaction mixture to decompose the excess reagent, and the tetrahydrofuran was removed by distillation under reduced pressure. The residue was worked up as above. The crude base (2.32 g) was chromatographed on 55 g of alumina and eluted with *n*-hexane and then ether.

The product (0.82 g) obtained with 120 ml of *n*-hexane was converted to picrates (1.42 g: mp 125—135°), which were treated with acetone to give 46 mg (0.8%) of the crude XXVII-picrate, mp 213—214°. Recrystallization from ethanol raised its melting point to 215—216°. The picrates obtained from the acetone solution

13) This sample had signals at 7.32 τ (2H, multiplet w/2=5 cps; $>N-CH_2-C\langle$), 7.7 τ(3H, singlet; $N-CH_3$) and did not show the presence of any vinyl proton signal in the NMR spectrum. The picrate, mp 180° (Grewe[14] gives mp 187° for the pure sample and mp 183° for the mixture of double bond isomers). *Anal.* Calcd. for $C_{10}H_{17}N \cdot C_6H_3O_7N_3$: C, 50.52; H, 5.30; N, 14.73. Found: C, 50.55; H, 5.47; N, 14.72.

14) R. Grewe, R. Hamann, G. Jacobsen, E. Nolte, and K. Riecke, *Ann.*, **581**, 85 (1953).

15) E. Ochiai and Y. Kawazoe, *Chem. Pharm. Bull.* (Tokyo), **5**, 606 (1957).

were crystallized from 20 ml of ethanol to give 975 mg (19%) of the XXVIII–picrate, mp 139—141°. Concentration of the mother liquor to about 2 ml gave 117 mg (2.3%) of the crude XXIX–picrate, mp 168—170°. Recrystallization from benzene raised its melting point to 171—172°.

The products (940 mg in total) obtained with a further 400 ml of *n*–hexane and with 300 ml of ether were combined and converted to the oxalate, which was crystallized from acetone–ethanol (1:2) to yield 300 mg (8.3%) of the XXVI–oxalate, mp 167°. The residue obtained from the acetone solution on the oxalate formation was treated with dil. ammonium hydroxide and extracted with ether. The base from the ether solution was converted to the picrate giving 410 mg (8%) of the crude product, from which 2–methyl–$\Delta^{9,10}$–octahydroisoquinoline–picrate, mp 180—181°, was obtained after crystallization from ethanol followed by recrystallization from isopropanol. This picrate showed no depression of melting point on admixture with the sample prepared from the starting material.

1-(*p*-Methoxybenzyl)-2-methyl-$\Delta^{9,10}$-octahydroisoquinoline (XXVIa)——A solution of 2.3 g of 2–methyl–$\Delta^{9,10}$–octahydroisoquinoline in 30 ml of acetone and 2.6 g of *p*–methoxybenzyl chloride was kept standing at room temperature overnight. The crude product obtained by evaporation of the solvent was triturated with dry ether to give 4.7 g of hygroscopic quaternary salt (XXVa) after having been dried for 2 days over phosphorous pentoxide under reduced pressure. The crude XXVa was used for the rearrangement without further purification.

To a stirred solution of phenyllithium prepared from 4.8 g of bromobenzene and 0.42 g of metallic lithium in 125 ml of dry ether, 3.7 g of XXVa was added rapidly under nitrogen. The mixture was worked up as described for the rearrangement of XXV to yield 3.04 g of an oily crude base. Conversion to the oxalate gave 1.54 g(35.5%) of the crude XXVIa–oxalate, mp 162—164°. Recrystallization from acetone–isopropanol (1:1) raised its melting point to 163—164°. *Anal.* Calcd. for $C_{18}H_{25}ON \cdot C_2H_2O_4$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.43; H, 7.71; N, 4.00. The infrared spectrum of the liberated base in carbon tetrachloride was identical with that of an authentic sample prepared according to Schnider.[2)]

The Stevens Rearrangement of 2-(*p*-methoxybenzyl)-2-methyl-6,6-ethylenedioxy-$\Delta^{9,10}$-octahydroisoquinolinium Chloride (XIX)——A solution of 21.57 g of XIII in 100 ml of acetone and 18.8 g of *p*–methoxybenzyl chloride was worked up as above to give 40.6 g of hygroscopic quaternary salt (XIX). This crude salt (XIX) was used for the rearrangement without further purification.

To a stirred solution of phenyllithium prepared from 10 g of bromobenzene and 0.9 g metallic lithium in 400 ml of dry ether, 10 g of XIX was added rapidly under nitrogen. The stirring was continued for one hour after the exothermic reaction had ceased. Ice–water was added to the reaction mixture to decompose the excess reagents, and the organic layer was washed with dil. ammonium hydroxide. Evaporation of the solvent gave 10 g of the crude product, which was chromatographed over 160 g of alumina and eluted in turn with *n*–hexane, 20% benzene–*n*–hexane, 30% benzene–*n*–hexane, 50% benzene–*n*–hexane, benzene and ether.

The product (0.28 g) obtained with one liter *n*–hexane was crystallized from pet. ether to give the crystalline product, mp 64—67°, which was identified by infrared spectral comparison and by admixture with an authentic sample of biphenyl.

The product (0.4 g) obtained with 600 ml of 20% benzene–*n*–hexane was crystallized from *n*–hexane to give the crystalline material, mp 124—126°, which was identified by infrared spectral comparison and by admixture with an authentic sample of bis(*p*–methoxy)benzyl.

The products (2.14 g) obtained with 1.15 liter of 30% benzene–*n*–hexane and with 800 ml of 50% benzene–*n*–hexane were combined and purified by distillation to give 1.5 g of an oily base, bp 146—165° (0.01 mmHg). The distillate was converted to a picrolonate, mp 204° (decomp.), 1.07 g (7% based on XIII), from which the pure XXI–picrolonate, mp 214.5° (decomp.), was obtained by crystallization from ethanol. *Anal.* Calcd. for $C_{20}H_{27}O_3N \cdot C_{10}H_8O_5N_4$: C, 60.70; H, 5.94; N, 11.80. Found: C, 60.80; H, 6.31; N, 12.04. The picrate was prepared from liberated base and crystallized from ethanol, mp 146—148°. *Anal.* Calcd. for $C_{20}H_{27}O_3N \cdot C_6H_3O_7N_3$: C, 55.91; H, 5.41; N, 10.03. Found: C, 55.83; H, 5.45; N, 9.92.

The product (0.54 g) obtained with further 400 ml of 50% benzene–*n*–hexane was used later.

The products (3.28 g) obtained with 2 liter of benzene and with 400 ml of ether were combined and converted to the picrate giving 4.39 g of the crude picrate, mp 110—120°, from which 3.36 g of 1–(*p*–methoxybenzyl)–2–methyl–6,6–ethylenedioxy–$\Delta^{9,10}$–octahydroisoquinoline (XX)–picrate, mp 123—125°, was obtained by crystallization from ethanol. *Anal.* Calcd. for $C_{20}H_{27}O_3N \cdot C_6H_3O_7N_3$: C, 55.91; H, 5.41; N, 10.03. Found: C, 55.96; H, 5.68; N, 10.03. The liberated base (0.4 g) obtained from the mother liquor on crystallization of the picrate and the product (0.54 g) obtained from the second 50% benzene–*n*–hexane eluate on chromatography were combined and rechromatographed as in above to give 0.68 g of the crude base, from which 0.54 g of the pure XX–picrate, mp 123—125°, was obtained, total yield 3.9 g (27.3% based on XIII).

Preparation of 1-(*p*-Methoxybenzyl)-2-methyl-6-oxo-$\Delta^{9,10}$-octahydroisoquinoline (XXII) and 1-(*p*-Methoxybenzyl)-2-methyl-6-oxo-$\Delta^{5,10}$-octahydroisoquinoline (XXIII)——A solution of 1.8 g of the ketal (XX) in 20 ml of 1 N hydrochloric acid was kept standing at room temperature overnight. The reaction mixture was made alkaline with potassium carbonate and extracted with ether to give 1.5 g (96.2%) of an oily ketonic compound (XXII), which was used immediately for the next reaction. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715 (C=O). The

picrate, crystallized from anhyd. ethanol, mp 146—148°. *Anal.* Calcd. for $C_{18}H_{23}O_2N \cdot C_6H_3O_7N_3$: C, 56.03; H, 5.09; N, 10.89. Found: C, 56.20; H, 5.33; N, 10.91. A solution of 1.5 g of XXII in 50 ml of ethanol and 3 ml of 2 N potassium hydroxide was kept standing at room temperature under nitrogen for one hour. The solution was made acidic with acetic acid, evaporated to dryness under reduced pressure without heating, made alkaline with dil. ammonium hydroxide and extracted with ether. The residue (1.45 g) from the ether solution was chromatographed on alumina and eluted with benzene. The product (1.17 g) was converted to the picrate giving 2.07 g of the crude picrate, from which 1.48 g (55%) of XXIII-picrate, mp 190—191° (decomp.), was obtained after treatment with ethyl acetate followed by crystallization from ethanol. Recrystallization from acetone gave an analytically pure sample, mp 192—193° (decomp.). *Anal.* Calcd. for $C_{18}H_{23}O_2N \cdot C_6H_3O_7N_3$: C, 56.03; H, 5.09; N, 10.89. Found: C, 56.06; H, 5.25; N, 10.97. Liberation of the picrate gave an oily XXIII. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1675 (C=O).

***rac*-3-Methoxy-6-oxo-N-methylmorphinan (XXIV)**——a) A solution of one gram of XXII in 10 g of 85% phosphoric acid was heated under nitrogen at 135—140° for 25 hr. After cooling, 15 ml of water was added and the solution was heated on a steam bath for 2 hr to saponify the phosphonate, which was assumed to be formed on this cyclization. The reaction mixture was made alkaline with conc. ammonium hydroxide and extracted with chloroform. The residue obtained from the chloroform solution was extracted repeatedly with ether. The crude phenolic product (0.75 g) obtained from the combined ether solution was methylated with Rodinov's reagent (prepared from 2.55 g of trimethylphenylammonium tosylate and 0.19 g of sodium methoxide in 8 ml of methanol) at 130—135° for 3 hr. The reaction mixture was steam distilled to remove separated dimethylaniline and extracted with benzene. The basic material was extracted with 10% hydrochloric acid and back extracted with benzene to give 0.52 g of a brownish oil. For the sake of the preparative thin-layer chromatographic separation, Silica Gel G.F. plate and methanol-chloroform (1:4) solvent were used. The part corresponding to an authentic sample of (−)-3-methoxy-6-oxo-N-methylmorphinan[16] was extracted repeatedly with chloroform, and the extracts were combined. Evaporation of the solvent gave 0.1 g (10% based on XXII) of XXIV, mp 155—159°. Crystallization from cyclohexane raised its melting point to 160°. This compound showed no depression of melting point on admixture with an authentic sample of *rac*-3-methoxy-6-oxo-N-methylmorphinan prepared from thebaine and sinomenine derivaitves.[17] The similar treatment of the another part corresponding to an authentic sample of (−)-3-methoxy-6-oxo-N-methylisomorphinan[19] gave 10 mg of an oily basic product. The gas chromatogram of this product showed the presence of complicated mixture.

b) A solution of 1.4 g of the α,β-unsaturated carbonyl compound (XXIII) in 14.5 ml of 85% phosphoric acid was heated under nitrogen at 135—140° for 20 hr. The reaction mixture was worked up as above. Methylation of the crude phenolic product (1.2 g) with Rodinov's reagent gave 0.63 g of an oily base, from which 0.14 g of *rac*-3-methoxy-6-oxo-N-methylmorphinan (XXIV), mp 149—156°, was obtained by preparative thin-layer chromatographic separation in 10% yield based on XXIII. Crystallization from cyclohexane raised its melting point to 160°. The infrared spectrum in nujol was identical with that of an authentic sample of *rac*-3-methoxy-6-oxo-N-methylmorphinan. On the other hand, the product (35 mg) corresponding to (−)-3-methoxy-6-oxo-N-methylisomorphinan showed the presence of complicated mixture on gas chromatography.

Acknowledgement The authors are indebted to Professor Emeritus E. Ochiai of Tokyo University, Dr. K. Takeda, Director of this laboratory, and Dr. Y.K. Sawa for their helpful discussions and suggestions during this work.

16) Y.K. Sawa and S. Maeda, *Tetrahedron*, **20**, 2247 (1964).
17) This authentic sample was prepared by recrystallization of the mixture of (−)-3-methoxy-6-oxo-N-methylmorphinan and (+)-3-methoxy-6-oxo-N-methylmorphinan, which were prepared from thebaine and sinomenine derivatives, respectively.[16,18]
18) Y.K. Sawa, T. Miyamoto, R. Maeda, S. Maeda, and T. Fujioka, *Ann. Rept. Shionogi Res. Lab.*, No. **16**, 1 (1966).
19) Y.K. Sawa, M. Horiuchi, and K. Tanaka, *Tetrahedron*, **21**, 1133 (1965).