[Chem. Pharm. Bull. 13(4) 420~426 (1965)]

UDC 547.94 : 615.711.7

54. Zen-ichi Horii, Toshio Watanabe, Takushi Kurihara, and Yasumitsu Tamura : Studies on Ergot Alkaloids and Related Compounds. XII.*1 Syntheses of Ethyl 4-Methyl-2,3,4,4*a*,5,6-hexahydrobenzo[*f*]quinoline-2-carboxylate and its Dihydro Derivative.

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The ergot alkaloids[1] have attracted interest for many years by their potent pharmacological activity. Since the elucidation of their structures,[1] a number of relatively simple analogues[2] of lysergic acid (I), the common component of the alkaloids, have been prepared in order to test oxytocic, sympatholytic, hypotensive and anti-serotonine activity. 3-(N-Methyl phenethylamino)propionate[3] (II), 2-methyl-3-(1,2,3,4-tetrahydro-2-naphthylamino)propionate[4] (III) and 5-(*p*-methoxyphenyl)-6-methyl-1,2,3,6-tetrahydronicotinate[5] (IV) are among them and have shown noticeable oxytocic activity. Their relation to the structure of lysergic acid (I) suggests that 4-methyl-2,3,4,4*a*,5,6-hexahydrobenzo[*f*]quinoline-2-carboxylate (XII) and its dihydro derivative (XIII) might be of considerable pharmacological interest. This possibility has prompted us to investigate the syntheses of these simplified analogues of lysergic acid (I). These are regarded as constituting of rings A, C, and D of the structure I but lacking ring B.

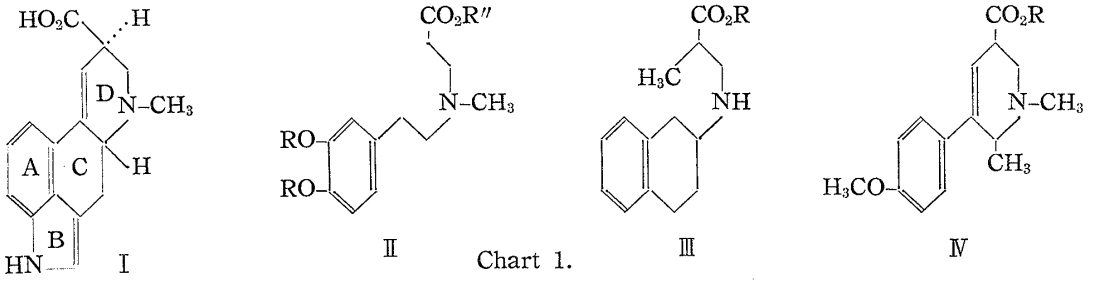

Chart 1.

A promising method for elaborating this tricyclic system would be provided by the total synthesis of I, achieved in 1956 by Kornfeld, *et al.*[6] However, this route requires to employ special solvent such as liquid hydrogen cyanide and liquid sulfur dioxide. We have now found that the Mannich reaction of ethyl *β*-oxo-3,4-dihydro-1-naphthenepropionate (VI) effects cyclization to give ethyl 1-oxo-4-methyl-*trans* (4*a* : 10*b*)-

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1) For recent reviews of this subject, see R. Voigt : Pharmazie, **17**, 318 (1962); D. F. Downing : Quart. Revs., **16**, 133 (1962); J. E. Saxton : "The Alkaloids," Vol. 7, R. H. F. Manske, Ed., Academic Press. N. Y. and London, p. 9 (1960); J. H. Birkinshaw, C. E. Stickings : "Progress in the Chemistry of Organic Natural Products," Vol. 20, L. Zechmeister, Ed., Springer-Verlag, Vienna, p. 17 (1962). See also H. G. Leemann, S. Fabbri : Helv. Chim. Acta, **42**, 2696 (1959); P. A. Stadler, A. Hofmann : Helv. Chim. Acta, **45**, 2055 (1962).

2) For leading reference on this subject, see J. Cymerman-Craig, D. M. Temple, B. Moore : Aust. J. Chem., **14**, 84 (1961); G. N. Walker, B. N. Weaver : J. Org. Chem., **26**, 4441 (1961); A. M. Akkerman : Rec. trav. chim., **73**, 629 (1954); A. Kraushaar : Arzneim.-Forsch., **4**, 273 (1954); literatures 3), 4), 5), and 26); And related papers reported by these authors.

3) R. Baltzly, V. Drookovitz, A. P. Phillips : J. Am. Chem. Soc., **71**, 1162 (1949).

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5) H. Plieninger : Chem. Ber., **86**, 25 (1953).

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1,2,3,4,4*a*,5,6,10*b*-octahydrobenzo[*f*]quinoline-2-carboxylate (Ⅷ), and that sodium borohydride reduction followed by dehydration converts Ⅷ into Ⅻ. In the present paper we describe the syntheses and stereochemistries of Ⅻ and ⅩⅢ. These compounds were found to possess considerably potent oxytocic activity as expected.

The synthesis of Ⅵ was attempted by the following five methods : i) condensation[7] of 1-acetyl-3,4-dihydronaphthalene (Ⅴ) with diethyl carbonate, ii) condensation[8] of Ⅴ with diethyl oxalate, followed by decarbonylation, iii) condensation[9] of 3,4-dihydro-1-naphthoyl chloride with ethyl *tert*-butyl malonate, followed by heating with *p*-toluenesulfonic acid, iv) condensation[10] of 3,4-dihydro-1-naphthoyl chloride with ketene diethylacetal,[11] followed by hydrolysis, and v) condensation[12] of ethyl 3,4-dihydro-1-naphthoate with ethyl acetate. As a result, the first mothod was found to give the highest yield. This reaction was initially carried out by employing sodium hydride and ether as solvent by the method reported previously[7] for ethyl *β*-oxo-1-cyclohexenepropionate, but the yield was very low due to the formation of a considerable amount of resinous byproduct.[13] Employment of diethyl carbonate[14] instead of ether surpressed this undesirable side reaction and improved the yield of Ⅵ.

In the previous paper[7] we reported that the Mannich reaction of ethyl *β*-oxo-1-cyclohexenepropionate with each one molar equivalent of methylamine and formalin produced ethyl 1-methyl-4-oxo-*trans*-decahydro-3-quinolinecarboxylate. The same Mannich reaction condition, however, converted Ⅵ into a base of molecular formula, $C_{20}H_{26}O_3N_2$, characterized as a perchlorate. The infrared spectrum of this perchlorate showed absorption at 1739 cm^{-1} due to an ester-carbonyl and at 1724 cm^{-1} due to a ketone-carbonyl, but no absorption due to an enolizable ketonic group.[15] In addition, a ferric chloride test of the free base was negative. Therefore, structure (Ⅶ) was assigned to this product (cf. Fig. 1). When this Mannich reaction was carried out by employing more than three molar equivalents of methylamine and formalin, Ⅷ was obtained as a sole product, although in a low yield. The structure of Ⅷ was confirmed from its conversion to the known 4-methyl-*trans*-3,4,4*a*,5,6,10*b*-hexahydrobenzo[*f*]quinoline-1(2*H*)-one[16] (Ⅸ) by hydrolysis and simultaneous decarboxylation. Since the ethoxycarbonyl group attached to C_2 is easily epimerizable, Ⅷ is assumed to exist in the most stable configuration as indicated.

Sodium borohydride reduction of Ⅷ followed by chromatographical purification through an alumina column employing benzene as eluent, gave two stereoisomers of ethyl 1-hydroxy-4-methyl-*trans*-1,2,3,4,4*a*,5,6,10*b*-octahydrobenzo[*f*]quinoline-2-carboxylate, (Xa), m.p. 151° and (Xb), m.p. 165°. These gave the corresponding acetates, (ⅪⅠa) and (ⅪⅠb), respectively. Dehydration of Xa and Xb were best effected by heating[17] with phosphorous oxychloride and phosphoric acid in pyridine to give Ⅻ, characterized as an oxalate. Yields were 58% from Xa and 40% from Xb. Fusion with soda-lime at 240°[18] or warming with methanesulfonyl chloride in pyridine[19] also effected the dehydration

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11) Org. Syntheses, Coll. Vol. Ⅲ, 506 (1955).
12) E. E. Royals : J. Am. Chem. Soc., **70**, 489 (1948).
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18) J. F. Spilsbury, S. Wilkinson : *Ibid.*, **1961**, 2085.
19) R. Jeanloz, D. Prins, J. V. Euw : Helv. Chim. Acta, **30**, 374 (1947).

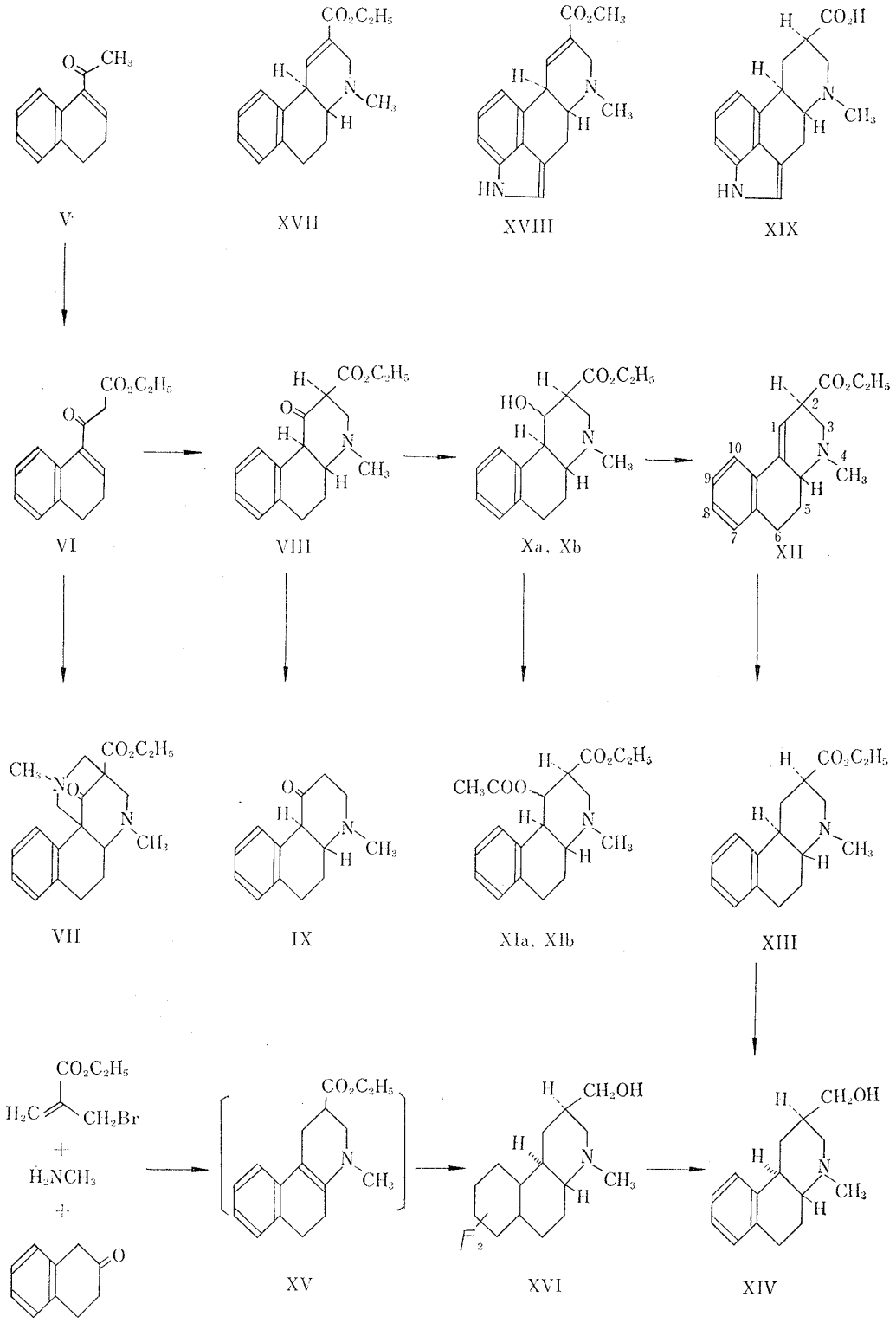

Chart 2.

of Xa, but did not that of Xb.*3 Difference in these behaviors of Xa and Xb towards dehydrations[20] as well as their relative retention times in vapor-phase and column

*3 Dehydrations of Xa and Xb by heating with toluenesulfonic acid in pyridine were unsuccessful.

20) S. Bernstein, R. H. Lenhard, J. H. Williams: J. Org. Chem., **19**, 41 (1954); I. Moritani, H. Taniguchi: Chemistry, **18**, 447 (1963).

chromatographies[21] (Xa was eluted faster than Xb) may indicate that the hydroxyl group (or the acetoxyl group) is axial in Xa (or XIa), while equatorial in Xb (or XIb). Attempts to deacetoxylate of XIa and XIb to XII were made by fusing over magnesium oxide[22] or heating with toluenesulfonic acid in acetic acid,[23] but were unsuccessful.

The location of double bond in structure (XII) was proved from the following spectral evidences. The infrared spectrum of XII showed an unconjugated ester-carbonyl band at 1725 cm^{-1}, which was not shifted in the dihydro derivative (XIII) prepared by hydrogenation of XII over platinum oxide. The ultraviolet spectrum of XII showed a band characteristic to a styrene grouping*4 (Fig. 1) and it was not affected in position and intensity by adding acid. The dehydration of Xa or Xb should involve an alternative possibility leading to a double-bond isomer (XVII), but the product isolated from the reaction mixture was only XII. Thus, the formation of this product could be interpreted to be brought about mainly by two reaction courses: one is elimination reaction leading directly to XII, which requires a removal of the hydrogen at C_{10b}, and the other is an elimination to XVII by removal of the hydrogen at C_2, followed by rearrangement to XII. The rearrangement in the latter course can be rationalized from the basis of the easy isomerization[24] of methyl 7-methyl-$\Delta^{10,10a}$-ergoline-9-carboxylate (XVIII) to lysergic acid methyl ester (I, $COOCH_3$ instead of COOH). Such consideration on the reaction would suggest that relative configuration at C_2 and C_{4a} in XII is the same as that in Xa or Xb, that is, a more stable one similar to lysergic acid (I).

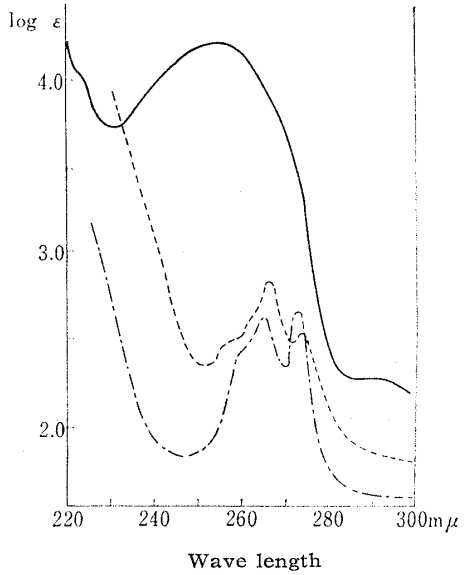

Fig. 1. Ultraviolet Absorption Spectra of VII (– – – –), XII (————), and XIII (— – —) in Ethanol Solution

It has been known that the hydrogenation of I gives only the most stable dihydro derivative (XIX), while isolysergic acid (I, carboxyl group is α-oriented) gives two other isomeric dihydro derivatives.[25] An analogous stereochemical consideration would lead to the configuration of XIII and the alcohol (XIV) prepared by lithium aluminum hydride reduction of XIII.

The structure of XIV was confirmed by the following alternative synthesis. Condensation of β-tetralone, ethyl 2-(bromomethyl)-acrylate and methylamine according to the method of Grob and Renk,[26] followed by the Birch reduction[27] of a resulted crude intermediate (XV) with lithium, *tert*-butanol, and liquid ammonia, gave XVI, whose structure came from its elemental and spectral analyses. Aromatization[28] of XVI by means of palladium-charcoal in xylene gave XIV, identified with the sample prepared from

*4 An ultraviolet absorption band due to a C_6H_5-C=C-NR_2 are expected to appear at ca. 300 mμ [N. A. Nelson, J. E. Ladbury, R. S. P. Hsi: J. Am. Chem. Soc., **80**, 6633 (1958); I. J. Speziale, L. R. Smith: J. Org. Chem., **28**, 1805 (1963)].

21) D. H. R. Barton: J. Chem. Soc., **1953**, 1027; H. S. Aaron, G. E. Wicks, Jr., C. P. Rader: J. Org. Chem., **29**, 2248 (1964).
22) R. McCrindle, K. H. Onerton, R. A. Raphael: J. Chem. Soc., **1960**, 1560.
23) C. W. Marschal, R. E. Ray, I. Laos, B. Riegel: J. Am. Chem. Soc., **79**, 6308 (1957).
24) H. Kobel, E. Schreiner, J. Rutschmann: Helv. Chim. Acta, **47**, 1052 (1964).
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26) C. A. Grob, E. Renk: *Ibid.*, **44**, 1531 (1961).
27) D. H. R. Barton, C. H. Robinson: J. Chem. Soc., **1954**, 3045.
28) S. Sugasawa, R. Tachikawa: Tetrahedron, **4**, 205 (1958).

XIII by comparison of their infrared spectra and retention times in vapor-phase chromatography. Since it is well known[29] that the Birch reduction, in general, produces a thermodynamically more stable isomer, the formation of XIV with the most stable configuration is reasonably acceptable, providing in turn the confirmation to the stereochemical assignments of XII, XIII, and XIV as well as their constitutions.

Compounds (XII, XIII, and VII) showed one-sixteenth, one-fifteenth, and one-twenty-seventh of the oxytocic activity of ergometrine, respectively.*5 Detail of the results, together with those of their other pharmacological tests will be reported elsewhere.

Experimental*6

Ethyl β-Oxo-3,4-dihydro-1-naphthalenepropionate (VI)——To a stirred suspension of 54% NaH in oil (1.5 g.) in $(C_2H_5O)_2CO$ (10 g., freshly distilled over NaH) was added dropwise a solution of 1-acetyl-3,4-dihydronaphthalene[30] (V, 4.5 g.) and $(C_2H_5O)_2CO$ (6 ml.) at 100° in N_2 atmosphere during 2 hr., and stirring was continued for another 30 min. After cooling with ice, AcOH (2.5 ml.) and then H_2O (10 ml.) were added. The reaction mixture was extracted with ether. The ether extract was shaken with 5% NaOH, the aqueous layer was washed with ether and acidified with 10% HCl under ice-cooling. The separated oily material was extracted with ether, the ether extract was dried over $MgSO_4$ and evaporated. The residual oil was distilled under reduced pressure to give 1.8 g. of VI as a pale yellow oil, b.$p_{0.1}$ 180°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1724, 1695, 1647～1629, 1597. Ferric chloride test gave an orange red coloration. *Anal.* Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.90; H, 6.40.

Mannich Reaction of VI——a) Formation of Ethyl 1-Oxo-4-methyl-*trans* (4*a*:10*b*)-1,2,3,4,4*a*,5,6,10*b*-octahydrobenzo[*f*]quinoline-2-carboxylate (VIII): To a vigorously stirred solution of 37% HCHO (1.35 ml.) and EtOH (5 ml.) were added dropwise 30% aqueous CH_3NH_2 solution (2.6 ml.) and then a solution of VI (12 g.) in EtOH (20 ml.) under ice-cooling. After the addition was completed, enough amount of EtOH to make the reaction mixture homogeneous was added and the resulted solution was kept in a refrigerator overnight. Most parts of EtOH and CH_3NH_2 were removed from the reaction mixture in a water bath under reduced pressure. The residue was diluted with ether (20 ml.) and extracted with four 5 ml. portions of 20% aqueous tartaric acid solution. The aqueous extracts were combined, washed well with ether, basified with $KHCO_3$ and the separated oil was extracted with ether. The ether extract was washed with H_2O, dried over anhyd. $MgSO_4$ and evaporated, giving 2.7 g. of VIII as a pale red viscous oil. Ferric chloride test gave a cherry red coloration. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1648, 1640, 1620, 1613. The perchlorate was recrystallized from EtOH, pale orange needles, m.p. 141～143°. IR ν_{max}^{Nujol} cm^{-1}: 1656, 1613. *Anal.* Calcd. for $C_{17}H_{21}O_3N \cdot HClO_4$: C, 52.64; H, 5.71; N, 3.61. Found: C, 52.54; H, 5.63; N, 3.67.

b) Formation of Ethyl 13-Oxo-2,6-dimethyl-2,3,4,5,6,6*a*,7,8-octahydro-4,12*b*-methano-1*H*-naphtho[2,1-*b*][1,5]diazocine-4-carboxylate (VII): To a vigorously stirred solution of 37% HCHO (0.81 ml.) and EtOH (2 ml.) were added dropwise 30% aqueous CH_3NH_2 solution (1.04 ml.) and then a solution of VI (2.4 g.) in EtOH (20 ml.) under ice-cooling. The reaction mixture was worked up by the same procedure as described above for the formation of VIII. The sole product was 1.3 g. of an oily VII, whose ferric chloride test was negative. The perchlorate of VII was recrystallized from 80% EtOH, colorless needles, m.p. 206° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 1739 (COOEt), 1724 (C=O). *Anal.* Calcd. for $C_{20}H_{26}O_3N \cdot HClO_4$: C, 54.23; H, 6.15; N, 6.33. Found: C, 54.11; H, 6.13; N, 6.33.

Decarboxylation of VIII——A solution of VIII (100 mg.) in 10% HCl (5 ml.) was heated under reflux for 1.5 hr. After cooling, the solution was washed with ether, basified with Na_2CO_3 and the separated oily material was extracted with ether. The ether extract was washed with H_2O, dried over anhyd. $MgSO_4$ and evaporated, giving 50 mg. of an oily 4-methyl-*trans*-3,4,4*a*,5,6,10*b*-hexahydrobenzo[*f*]quinoline-1(2*H*)-one (IX). The infrared spectra of the free base and picrate (m.p. 160～161° from H_2O) were identical, throughout the range, with those of the corresponding authentic samples prepared previously.[16]

Ethyl 1-Hydroxy-4-methyl-*trans*(4*a*:10*b*)-1,2,3,4,4*a*,5,6,10*b*-octahydrobenzo[*f*]quinoline-2-carboxylate (Xa) and (Xb)——To an ice-cooled and stirred solution of VIII (8.6 g.) in EtOH (40 ml.) was added $NaBH_4$ (0.8 g.) in small portions and the mixture was allowed to stand overnight. The excess reagent was destroyed by dropwise addition of AcOH. EtOH was removed from the reaction mixture under reduced pressure, the residue was poured into $NaHCO_3$ solution and extracted with $CHCl_3$. The $CHCl_3$ extract was

*5 The tests have been carried out in the School of Pharmacy, Osaka University by Professor S. Aonuma and his co-workers, to whom we are indebted for the results quoted.

*6 Melting points and boiling points are uncorrected. Vapor-phase chromatography was carried out with Shimazu gas chromatography GC-IB equipped with a hydrogen flame ionization detector, employing SE-30 column (column temperature 185°).

29) A. J. Birch, H. Smith: Quart. Revs., **12**, 17 (1958).

30) M. F. Ansell, G. T. Brooks: J. Chem. Soc., **1961**, 201.

washed with H_2O, dried over anhyd. $MgSO_4$ and evaporated. Trituration of the residual red-brown viscous oil (8 g.) with a small amount of EtOH gave a crystalline material. Filtration and then washing with EtOH gave 2.2 g. of colorless crystals, m.p. 132~140°. The filtrate and washing were combined, evaporated, and the residue was chromatographed through Al_2O_3 column using benzene as eluent to give further 0.5 g. of crystals, m.p. 132~140°. The crystals were combined and recrystallized from benzene and then EtOH to give 1.3 g. of Xb as colorless needles, m.p. 165°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3559 (OH), 1721 (COOEt). *Anal.* Calcd. for $C_{17}H_{23}O_3N$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.35; H, 7.84; N, 4.75. The mother liquor of recrystallization was passed through Al_2O_3 column using benzene as eluent, giving crystals of m.p. 149° as the first fraction. Recrystallization from EtOH gave 1.1 g. of Xa as colorless needles, m.p. 151°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3546 (OH), 1718 (COOEt). *Anal.* Calcd. for $C_{17}H_{23}O_3N$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.77; H, 7.86; N, 5.04.

From the second fraction was obtained 50 mg. of Xb, m.p. 161~163°.

Acetylation of Xa——A solution of Xa (298 mg.), pyridine (5 ml.) and Ac_2O (1 ml.) was heated in a water bath for 2 hr. The solution was concentrated under reduced pressure, the residue was poured into a saturated $NaHCO_3$ solution (5 ml.) and extracted with ether. The ether extract was washed with H_2O, dried over anhyd. $MgSO_4$ and evaporated, giving a crude acetate (XIa). The perchlorate of XIa was recrystallized from EtOH, colorless needles, m.p. 208° (decomp.). Yield was quantitative. IR ν_{max}^{Nujol} cm^{-1}: 1739, 1721 (COOR). *Anal.* Calcd. for $C_{19}H_{25}O_4N \cdot HClO_4$: C, 52.83; H, 6.07. Found: C, 52.76; H, 5.99.

Acetylation of Xb——Was carried out by the same procedure as described above for the acetylation of Xa. The perchlorate of XIb was recrystallized from EtOH, colorless needles, m.p. 123° (decomp.). Yield was quantitative. IR ν_{max}^{Nujol} cm^{-1}: 1751, 1739 (COOR). *Anal.* Calcd. for $C_{19}H_{25}O_4N \cdot HClO_4$: C, 52.83; H, 6.07. Found: C, 52.78; H, 6.04.

Dehydration of Xa and Xb to Ethyl 4-Methyl-2,3,4,4*a*,5,6-hexahydrobenzo[*f*]quinoline-2-carboxylate (XII)

A) With CH_3SO_2Cl in Pyridine——A solution of Xa (91 mg.) and CH_3SO_2Cl (0.2 ml.) in anhyd. pyridine (2 ml.) was warmed at 70° for 6 hr. Most of the pyridine was removed under reduced pressure and the residue was dissolved in ether. The ether solution was extracted with 10% HCl. The aqueous extract was washed with ether, saturated with Na_2CO_3 and the separated oily material was extracted with ether. The ether extract was dried over anhyd. $MgSO_4$ and evaporated. Distillation of the residue under reduced pressure gave 55 mg. of XII as a yellow oil, b.$p_{0.2}$ 180~220° (bath temp.). The oxalate of XII was recrystallized from EtOH, colorless needles, m.p. 161~162° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 1724 (COOEt), 1618 (C=C). UV $\lambda_{max}^{EtOH}m\mu$ (ε): 224.5 (14,400). *Anal.* Calcd. for $C_{17}H_{21}O_2N \cdot (COOH)_2$: C, 63.14; H, 6.42; N, 3.88. Found: C, 63.20; H, 6.68; N, 3.90.

A similar reaction of Xb (72 mg.) resulted in the recovery of the starting material (64 mg.).

B) With $POCl_3$ and H_3PO_4——a) From Xa: A solution of Xa (72 mg.), anhyd. pyridine (2 ml.), H_3PO_4 (0.02 ml.) and $POCl_3$ (0.3 ml.) was heated in a water bath for 2.5 hr. Most of the pyridine was removed under reduced pressure and the residue was dissolved in ether. The ether solution was extracted with 10% HCl, the aqueous extract was washed with ether, saturated with Na_2CO_3 and extracted with ether. The ether extract was washed with H_2O, dried over anhyd. $MgSO_4$ and evaporated, giving 40 mg. of an oily XII, identified with the sample prepared in A) by comparison of their IR spectra.

b) From Xb: A solution of Xb (96 mg.), anhyd. pyridine (2 ml.), H_3PO_4 (0.02 ml.) and $POCl_3$ (0.3 ml.) was worked up in the same manner as described in a). In this case, the oily product contained considerable amount of the starting material (Xb). Hence, the oily product was taken up into CCl_4 and the insoluble Xb was removed by filtration. Removal of the solvent from the filtrate gave 36 mg. of an oily XII (the oxalate, m.p. 160~161°), identified with the sample prepared in A) by comparison of their IR spectra and by mixted melting point determination of their oxalates.

C) With Soda-lime——To a solution of Xa (72 mg.) in $CHCl_3$ was added soda-lime (0.5 g.), and $CHCl_3$ was evaporated. Heating the residue at 240° under reduced pressure gave a yellow distillate. The distillate was dissolved in ether and extracted with 10% HCl. The aqueous extract was washed with ether, saturated with Na_2CO_3 and the separated oil was extracted with ether. The ether extract was washed with H_2O, dried over anhyd. $MgSO_4$ and evaporated, giving 130 mg. of an oily XII, identified with the sample prepared in A) by comparison of their IR spectra.

Hydrogenation of XII to Ethyl 4-Methyl-1,2,3,4,4*a*,5,6,10*b*-octahydro-*trans*(4*a*:10*b*)-benzo[*f*]quinoline-2-carboxylate (XIII)——A solution of XII (50 mg.) in AcOH (20 ml.) was hydrogenated over PtO_2 (20 mg.) at room temperature and atmospheric pressure. One mole of H_2 was consumed. The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure. The residue was dissolved in ether, the ether solution was washed with saturated $NaHCO_3$ solution and then H_2O, dried over anhyd. $MgSO_4$ and evaporated, giving 44 mg. of an oily XIII. The perchlorate of XIII was recrystallized from EtOH–ether, m.p. 176~177° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 1724 (COOEt). *Anal.* Calcd. for $C_{17}H_{23}O_2N \cdot HClO_4$: C, 54.61; H, 6.47; N, 3.63. Found: C, 54.78; H, 6.60; N, 3.63.

4-Methyldecahydro-*trans*(4*a*:10*b*)-benzo[*f*]quinoline-2-methanol (XVI)——i) Prepapation of Ethyl 4-Methyl-1,2,3,4,5,6-hexahydrobenzo[*f*]quinoline-2-carboxylate (XV): In a three necked flask fitted with a

Dean Stark water-separator was placed 10% CH_3NH_2 in benzene (30 g.). Ethyl 2-(bromomethyl)acrylate[26] (9 g.) was added dropwise to the solution under stirring and ice-cooling, and stirring was continued for 15 min. Then, β-tetralone (6.8 g.) and anhyd. benzene (60 ml.) were added at once and the mixture was heated under reflux for 3 hr., during which time H_2O formed was removed by means of the water-separator. After cooling, the reaction mixture was extracted with 10% HCl, the aqueous layer was washed with AcOEt, basified with Na_2CO_3 and the separated oily material was extrated with AcOEt. The AcOEt extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. Distillation of the residue under reduced pressure gave 5.8 g. of a crude XV as a red-brown oil, b.p_2 190~210°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1730 (COOEt), 1620 (C=C), 1595 (arom.).

This material was used in subsequent reaction without further purification.

ii) Birch Reduction of XV: To a stirred liq. NH_3 (200 ml.) were added dropwise a solution of XV (0.8 g.) in ether (10 ml.) and then Li (0.8 g.) in small pieces, and the mixture was stirred for 5 hr. A mixture of *tert*-BuOH and ether (1:1) (40 ml.) was added gradually, and stirring was continued for an additional 1 hr. Ammonia was allowed to evaporate and H_2O (100 ml.) was added to the residue. The mixture was acidified with conc. HCl under vigorous stirring and decanted. The insoluble material was further extracted with 10% HCl. The aqueous solutions were combined, washed with ether, basified with Na_2CO_3 and re-extracted with AcOEt. The AcOEt extract was washed with H_2O, dried over anhyd. $MgSO_4$ and evaporated. The residue was distilled under reduced pressure and a distillate of b.p_2 180~220° (bath temp.) was collected, which crystallized partly on trituration with a small amount of ether. Filtration and recrystallization from acetone gave 150 mg. of XVI as cubes, m.p. 128~130°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3571 (OH), no UV absorption maximum. *Anal.* Calcd. for $C_{15}H_{23}ON$: C, 77.20; H, 9.94. Found: C, 77.06; H, 9.85.

4-Methyl-1,2,3,4,4*a*,5,6,10*b*-octahydro-*trans*(4*a*:10*b*)-benzo[*f*]quinoline-2-methanol (XIV)——a) From XIII: A mixture of XIII (20 mg.), $LiAlH_4$ (30 mg.) and anhyd. ether (10 ml.) was refluxed for 4 hr. After cooling, the excess reagent was destroyed by dropwise addition of H_2O and the mixture was extracted with ether. The ether extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. Recrystallization of the residual crystals from acetone gave 0.7 g. of XIV as colorless flakes, m.p. 152~153°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3623 (OH). *Anal.* Calcd. for $C_{15}H_{21}ON$: C, 77.88; H, 9.15; N, 6.05. Found: C, 78.08; H, 9.29; N, 5.83.

b) From XVI: A mixture of XVI (100 mg.) and 10% Pd-C (60 mg.) in xylene (10 ml.) was refluxed for 4 hr. The catalyst was filtered and washed well with AcOEt. The filtrate and washing were combined and evaporated. Recrystallization of the residue from acetone gave 12 mg. of crystals, m.p. 142~145°. This compound was shown to be identical with XIV, prepared from XIII in a), by comparison of their IR spectra and by their behaviors in vapor-phase chromatographies.*6

Summary

The syntheses and stereochemistries of ethyl 4-methyl-2,3,4,4*a*,5,6-hexahydrobenzo[*f*]quinoline-2-carboxylate (XII) and its dihydro derivative (XIII) were described. The Mannich reaction of ethyl β-oxo-3,4-dihydro-1-naphthalenepropionate (VI), which was prepared by condensation of 1-acetyl-3,4-dihydronaphthalene (V) with diethyl carbonate, gave ethyl 1-oxo-4-methyl-*trans*(4*a*:10*b*)-1,2,3,4,4*a*,5,6,10*b*-octahydrobenzo[*f*]quinoline-2-carboxylate (VIII) and compound (VII). Sodium borohydride reduction, followed by dehydration, converted VIII into XII, which was hydrogenated over platinum oxide to XIII. Compounds (XII, XIII, and VII) showed considerably potent oxytocic activity.

(Received October 31, 1964)