59—60° undepressed with an authentic sample. Yield, 71%. *Anal.* Calcd. for C_8H_9ON: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.60; H, 6.72; N, 10.47.

Reaction with 5-Phenethylaminomethylenebarbituric Acid: Even after 20 hr of reaction period, 47% of the starting aminomethylene compound was recovered as a material remaining undissolved in the reaction mixture. The residue obtained by concentration of the filtrate was processed by the same procedures as in the reaction with 5-anilinomethylenebarbituric acid. Yield of triethylammonium 5-methylbarbiturate, 26%. Concentration of the etheral extract followed by distillation under reduced pressure gave phenethylformamide, bp 127—128° (0.2 mmHg). Yield, 29%. *Anal.* Calcd. for $C_9H_{11}ON$: C, 72.45; H, 7.43; N, 9.39. Found: C, 71.94; H, 7.53; N, 9.24.

Reaction with 5-Cyclohexylaminomethylenebarbituric Acid: The residue obtained by the general procedure (reaction period: 10 hr) was processed by the same procedures as in the reaction with 5-anilinomethylenebarbituric acid. Yield of triethylammonium 5-methylbarbiturate, 62%. Concentration of the etheral extract followed by distillation under reduced pressure gave N-cyclohexylformamide, bp 135—140° (15 mmHg). mp 26—27°. Yield, 72%. *Anal.* Calcd. for $C_7H_{13}ON$: C, 66.10; H, 10.30; N, 11.01. Found: C, 66.31; H, 10.36; N, 11.17.

Reaction with 1-Methyl-5-anilinomethylenebarbituric Acid: The residue obtained by the general procedure (reaction period: 3 hr) was processed by the same procedures as in the reaction with 5-anilinomethylenebarbituric acid. 1,5-Dimethylbarbituric acid was obtained as free acid in 67% yield. Recrystallization from ethanol gave crystals of mp 169—170°, undepressed with an authentic sample prepared previously. *Anal.* Calcd. for $C_6H_8O_3N_2$: C, 46.16; H, 5.16; N, 17.94. Found: C, 46.10; H, 5.27; N, 17.82. Yield of formanilide, 70%, which was identified by mixed melting point test with an authentic sample.

Reaction with 1,3-Dimethyl-5-anilinomethylenebarbituric Acid: The residue obtained as indicated in the general procedure (reaction period: 2 hr) was extracted with ether. After removal of ether from the extract, the residue was distilled under reduced pressure to give formanilide, mp 46—47°, undepressed by admixture with an authentic sample. Yield, 67%. The foregoing unextracted residue was crystallized by addition of chloroform–ether. Filtration gave 1,3,5-trimethyldialuric acid. Yield, 61%. Recrystallization from benzene gave needles, mp 107°. *Anal.* Calcd. for $C_7H_{10}O_4N_2$: C, 45.16; H, 5.41; N, 15.05. Found: C, 45.21; H, 5.43; N, 15.24.

Acknowledgement The authors are indebted to the Members of the Central Analysis Room of this college for elementary analyses.

[Chem. Pharm. Bull. 17(4) 814—818 (1969)]

UDC 547.833.9.07 : 547.94.07

Dienone Synthesis by Phenolic Oxidation of Dihydroxy-1-phenethyl-1,2,3,4-tetrahydroisoquinoline and Sodium Borohydride Reduction[1)]

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(Received February 27, 1968)

It has been reported that phenolic oxidation of 1-phenethylisoquinolines (II, III) gave dienones (Va, Vb, VI), whose dienone–phenol and dienol-benzene rearrangements afforded homoaporphines.[3–6)]

1) This forms Part CCCIX of "Studies on the Syntheses of Heterocyclic Compounds," by T. Kametani.
2) Location: *No. 85, Kita-4-bancho, Sendai.*
3) T. Kametani, K. Fukumoto, H. Yagi, and F. Satoh, *Chem. Comm.*, **1967**, 878.
4) A.R. Battersby, R.B. Bradbury, R.B. Herbert, M.H.G. Munro, and R. Ramage, *Chem. Comm.*, **1967**, 450.
5) A.R. Battersby, E. McDonald, M.H.G. Munro, and R. Ramage, *Chem. Commun.*, **1967**, 934.
6) T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *Chem. Commun.*, **1967**, 1103; *idem*, *J. Chem. Soc. (C)*, **1968**, 271; *idem*, *J. Org. Chem.*, 33, 690 (1968).

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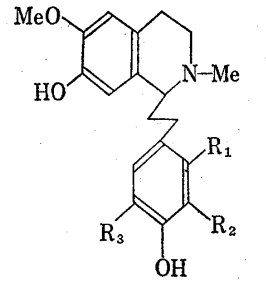
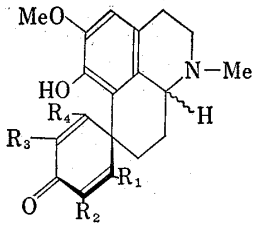
We are currently investigating the potentiality of such reactions in the syntheses of several homoaporphines and we wish to report the result on the oxidation of another 1-phenethylisoquinoline (I), containing a methoxy group at 2′-position on the phenethyl moiety, and on the successive sodium borohydride reduction of the resulting dienone (IVa or IVb) containing a methoxy group at β-position on the cyclohexadienone system.

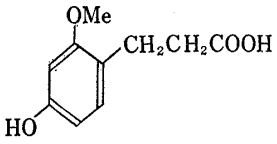
The diphenolic base (I) was synthesised as follows; the fusion of hydroxyphenylpropionic acid (VII)[7] with 4-benzyloxy-3-methoxyphenethylamine at 170—190° for 2 hr afforded the amide (VIII), whose phenolic hydroxyl group was protected as the O-ethoxycarbonyl group with ethyl chlorocarbonate and triethylamine to give the amide (IX). Bischler–Napieralski reaction of this amide (IX) with phosphoryl chloride in toluene gave the 3,4-dihydroisoquinoline (X), which was methylated with methyl iodide to give the methiodide (XI). Reduction of the methiodide with sodium borohydride in methanol, followed by de-ethoxycarbonylation with alkali, gave the monophenolic 1,2,3,4-tetrahydro-2-methylisoquinoline (XII), whose debenzylation with concentrated hydrochloric acid in ethanol afforded the expected diphenolic 1-phenethylisoquinoline hydrochloride.



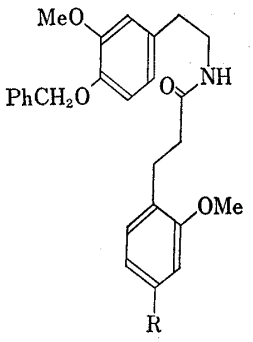
I : R_1=OMe, R_2=R_3=H
II : R_1=R_2=H, R_3=OMe
III : R_1=H, R_2=R_3=OMe



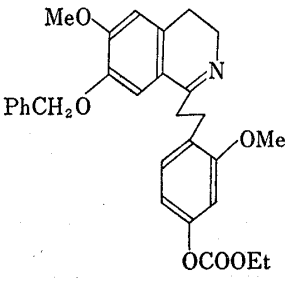
IVa : R_1=OMe, R_2=R_3=R_4=H
IVb : R_1=R_2=R_3=H, R_4=OMe
Va : R_1=R_3=R_4=H, R_2=OMe
Vb : R_1=R_2=R_4=H, R_3=OMe
VI : R_1=R_4=H, R_2=R_3=OMe



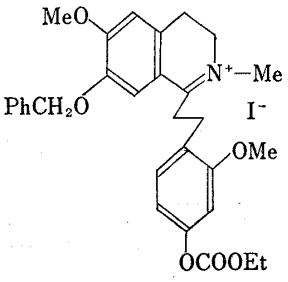
VII



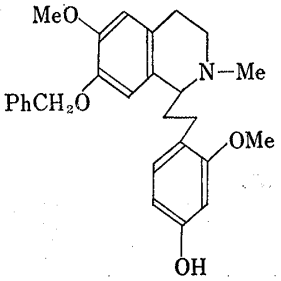
VIII : R=H
IX : R=COOEt



X



XI



XII

Chart 1

7) T. Kametani, K. Fukumoto, T. Hayasaka, and F. Satoh, and K. Kigasawa, *J. Chem. Soc.* (*C*), **1969**, 4.

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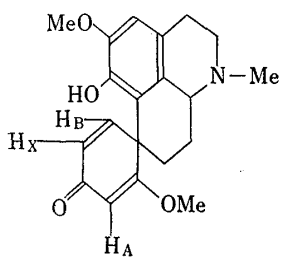
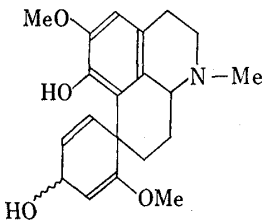
The hydrochloride of the phenolic base (I) was oxidised with six molar equivalents of ferric chloride in water at room temperature for 17 hr. The usual work up involving silica-gel chromatography with chloroform–methanol (98:2) as an eluant gave the oxidised product, $C_{20}H_{23}O_4N$, mp 177—178°, in 26% yield. The structure (XIII) assigned for the oxidised product was supported by its infrared (IR) spectrum (in $CHCl_3$), which showed the typical dienone absorption at 1650 and 1605 cm^{-1} and phenolic hydroxyl group at 3500 cm^{-1}, and ultraviolet (UV) absorption (in MeOH) at λ_{max} 235 and 285 mμ (log ε 4.19, 3.87). The nuclear magnetic resonance (NMR) spectrum (in $CDCl_3$) showed the expected N-methyl (τ 7.60, 3H), olefinic O-methyl (τ 6.44, 3H) and aromatic O-methyl (τ 6.25, 3H) resonances as singlets, respectively. Furthermore, a singlet at τ 3.49 due to one aromatic proton of the isoquinoline ring and a doublet corresponding to one proton at τ 4.52 were observed, the latter of which was assigned to H_A and showed the long range coupling with H_X (J_{AX}=1.3 cps). Another doublet at τ 4.54 with J_{BX}=10 cps, which was associated with one proton, corresponded to H_B and a quartet centered at τ 3.89, equivalent to one proton, was assigned to H_X. Mass spectrometry of the dienone (XIII) supported the molecular formula of $C_{20}H_{23}O_4N$ and showed the strong peaks at the following positions; *m/e*: 341 (M^+), 340 (M^+–H), 324 (M^+–3H–CH_3), 313 (M^+–CO), 312 (M^+–H–CO), 298 (M^+–CH_2=N–CH_3).

Since the presence of two spiro isomers (IVa and IVb) could be possible as in the case of the dienones (Va and Vb),[3,6] the crude product was also investigated spectrometrically by means of the IR and NMR spectra to check whether it would be a mixture of two dienones or not, but no crucial difference was observed in case of the material purified. Therefore, the oxidation of phenolic base (I) gave only one dienone (IV or IVb), but its configuration remains unclear.

Attempted dienone–phenol rearrangement of the dienone (IVa or IVb) under various conditions did not give the homoaporphine, only starting material being recovered. It is notable that the difference of the position of methoxy substituents affects greatly to the easiness of this rearrangement. Therefore, reduction of the dienone (IVa or IVb) was carried

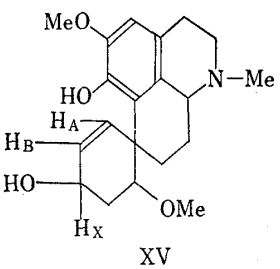


XIII

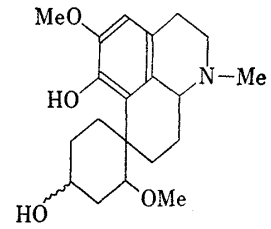


XIV

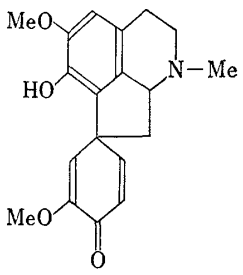
Chart 2



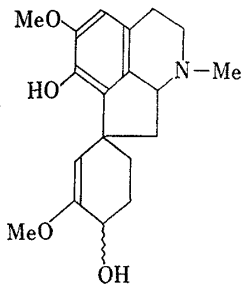
XV



XVI



XVII



XVIII

Chart 3

out, in order to investigate whether the dienol–benzene rearrangement of dienol (XIV) would occur or not.

Reduction of dienone (IVa or IVb) with an excess of sodium borohydride under heating afforded two compounds (XV and XVI). One of them was assigned to the structure (XV) by the following physical data; in the NMR spectrum (in $CDCl_3$) one aliphatic O-methyl signal was shown at τ 6.68 as a singlet and a multiplet associated with one proton at τ 5.93 was assigned to H_X. A doublet at τ 4.55 with J_{AB}=10.5 cps, associated with one proton, was reasonably assigned to H_A and a quartet (1H) centered at τ 4.23 was assigned to H_B. All the remaining signals had also been interpreted quite reasonably as shown in the experi-

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mental section. The IR spectrum showed no absorption band due to the ketone and microanalysis supported the formula of structure (XV). Battersby had also obtained the dihydroorientalinol (XVIII) by reduction of orientalinone (XVII) with sodium borohydride.[8] The other compound was assigned to the structure (XVI) by microanalysis and the NMR spectrum showed aliphatic O-methyl signal at τ 6.78 and no olefinic proton.

Experimental[9]

N-(4-Benzyloxy-3-methoxyphenethyl)-3-(4-hydroxy-2-methoxyphenyl)propionamide (VIII)——A mixture of 20 g of 4-benzyloxy-3-methoxyphenethylamine and 15 g of 4-hydroxy-2-methoxyphenylpropionic acid (VII) was heated in an oil-bath at 170—190° for 2 hr. The resultant mixture was extracted with $CHCl_3$, washed with 10% HCl, saturated $NaHCO_3$ solution and water, and dried over Na_2SO_4. Evaporation of the solvent gave a pale brown solid, which was recrystallised from $CHCl_3$–ether to give 28 g of a pale brown solid, mp 103° (decomp.). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3505 (OH), 3400 (NH), 1660 (amide C=O). *Anal.* Calcd. for $C_{26}H_{29}O_5N$: C, 71.70; H, 6.71; N, 3.22. Found: C, 71.76; H, 6.28; N, 3.41.

N-(4-Benzyloxy-3-methoxyphenethyl)-3-(4-ethoxycarbonyloxy-2-methoxyphenyl)propionamide (IX)——To a mixture of 13 g of VIII, 100 ml of triethylamine and 300 ml of $CHCl_3$ was added portionwise 4 g of ethyl chlorocarbonate under cooling, and the resultant mixture was allowed to stand at room temperature for 30 min. The mixture was washed with 300 ml of HCl solution and water, dried over Na_2SO_4 and evaporated to give 14.6 g of a brown viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420 (NH), 1758 (ester C=O), 1660 (amide C=O). This was used in the following reaction without purification.

7-Benzyloxy-1-(4-ethoxycarbonyloxy-2-methoxyphenethyl)-3,4-dihydro-6-methoxyisoquinoline (X)——A mixture of 14.6 g of IX, 10 ml of $POCl_3$ and 200 ml of toluene was heated under reflux at 120—130° for 2.5 hr. Evaporation of the solvent gave a brown caramel, which was basified with saturated sodium bicarbonate solution and extracted with $CHCl_3$. The solvent layer was washed with water, dried over Na_2SO_4 and evaporated to give 13 g of a brown caramel. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760 (ester C=O), 1652 (C=N). This compound was used in the following reaction without purification.

7-Benzyloxy-1-(4-ethoxycarbonyloxy-2-methoxyphenethyl)-3,4-dihydro-6-methoxy-2-methylisoquinolinium Iodide (XI)——A mixture of 13 g of X, 10 ml of MeI and 100 ml of MeOH was heated under reflux for 1 hr and evaporation of the solvent gave a brown caramel, which was washed with ether to give 12.7 g of a brown caramel. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760 (ester C=O), 1630 (C=N). This was also used in the following reaction without purification.

7-Benzyloxy-1,2,3,4-tetrahydro-1-(4-hydroxy-2-methoxyphenethyl)-6-methoxy-2-methylisoquinoline (XII) Hydrochloride——To a stirred mixture of 12.7 g of XI, 20 ml of MeOH and 10 ml of $CHCl_3$ was added portionwise 3 g of $NaBH_4$ under cooling within 30 min, and evaporation of the solvent from the above reaction mixture gave a yellow oil. A mixture of 16 g of the above oil, 10% NaOH solution and 50 ml of EtOH was heated under reflux for 1 hr. Evaporation of the organic solvent under reduced pressure gave an alkaline solution, to which was added an excess of NH_4Cl, and the resultant ammoniacal solution was extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated to give 9.5 g of a brown caramel, which was converted into its HCl salt to give 5.8 g of a yellow solid. This was recrystallised from MeOH to give pale yellow prisms, mp 231—233°. *Aanl.* Calcd. for $C_{27}H_{32}O_4NCl \cdot H_2O$: C, 66.40; H, 6.97; N, 2.87. Found: C, 66.24; H, 6.76; N, 3.39.

1,2,3,4-Tetrahydro-7-hydroxy-1-(4-hydroxy-2-methoxyphenethyl)-6-methoxy-2-methylisoquinoline (I) Hydrochloride——A mixture of 5 g of XII, 100 ml of conc. HCl and 100 ml of EtOH was heated under reflux on a water-bath for 1.5 hr and evaporated to give a brown caramel, which was extracted with water. The resultant aqueous solution was washed with benzene and hexane and evaporated to give 4.3 g of a brown caramel. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH). This was used in the following reaction without pruification.

Phenolic Oxidation of I——To a mixture of 23.6 g of $FeCl_3 \cdot 6H_2O$ and 300 ml of water was added a solution of 4.3 g of I in 300 ml of water within 1 min and the resultant mixture was allowed to stand at room temperature for 17 hr. The above mixture was basified with 10% NH_4OH and extracted with $CHCl_3$. The extract was washed with saturated NaCl solution, dried over Na_2SO_4 and evaporated to give 3.2 g of a brown glass. This was purified by chromatography on 60 g of silica gel using $CHCl_3$–MeOH (98:2) as an eluant. Evaporation of the apropriate fractions gave colourless crystals, which were recrystallised from EtOH–petroleum ether to give 950 mg of colourless needles, mp 177—178°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH), 1605 (C=O), 1605 (C=O). NMR (in $CDCl_3$)[10] τ: 7.60 (3H, singlet, N-CH_3), 6.44 (3H, singlet, olefinic O-CH_3), 6.25 (3H, singlet, aromatic O-CH_3), 4.52 (1H, doublet, J=1.3 cps, H_A), 3.89 (1H, a pair of doublets, J=10.0,

8) A.R. Battersby and T.H. Brown, *Chem. Commun.*, **1966**, 170.
9) All melting points were not corrected.
10) NMR spectra were measured in $CDCl_3$ using tetramethylsilane as an internal standard.

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1.3 cps, H_X), 4.54 (1H, doublet, $J=10.0$ cps, H_B), 3.49 (1H, singlet, C_5–H). UV λ_{max}^{MeOH} mμ (log ε): 235 (4.19), 285 (3.87). Mass spectrum *m/e*: 341 (M^+), 340 (M^+–H), 324 (M^+–3H–CH_3), 313 (M^+–CO), 312 (M^+–H–CO), 298 (M^+–CH_2=N–CH_3). *Anal.* Calcd. for $C_{20}H_{23}O_4N \cdot H_2O$: C, 66.9; H, 7.16; N, 3.51. Found: C, 67.27; H, 7.40; N, 3.76.

Reduction of Dienone (IVa or IVb) with $NaBH_4$——To a mixture of 300 mg of the dienone (IVa or IVb), 50 ml of MeOH and a small amount of water was added portionwise 1.0 g of $NaBH_4$ within 1 min at room temperature, and the above mixture was heated under reflux for 1 hr. Evaporation of the solvent gave an orange oil, to which was added 10 ml of water and extracted with $CHCl_3$. The extract was washed with saturated NaCl solution, dried over Na_2SO_4 and evaporated to give 300 mg of a colourless caramel, which was chromatographed on 9 g of silicagel to give two compounds using $CHCl_3$–MeOH (99:1) and (98:2) as an eluant. The first compound was crystallised from $CHCl_3$–*n*-hexane to give 60 mg of XV as colourless needles, mp 186—187°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH), 1640 (C=C). NMR (in $CDCl_3$) τ: 7.57 (3H, singlet, N–C<u>H</u>$_3$), 6.68 (3H, singlet, aliphatic O–C<u>H</u>$_3$), 6.18 (3H, singlet, aromatic O–C<u>H</u>$_3$), 5.93 (1H, multiplet, H_X), 4.55 (1H, doublet, $J=10.5$ cps, H_A), 4.23 (1H, a pair of doublets, $J=10.5$, 5.0 cps, H_B), 3.5 (1H, singlet, C_5–H). *Anal.* Calcd. for $C_{20}H_{27}O_4N$: C, 69.54; H, 7.88. Found: C, 70.01; H, 7.37.

The second compound (XVI) was obtained as a green oil (54 mg). NMR (in $CDCl_3$) τ: 7.58 (3H, singlet, N–C<u>H</u>$_3$), 6.78 (3H, singlet, aliphatic O–C<u>H</u>$_3$), 6.16 (3H, singlet, aromatic O–C<u>H</u>$_3$), 5.87 (2H, broad, 2O<u>H</u>), 3.52 (1H, singlet, C_5–H). This compound (XVI) was converted into its hydrochloride, which was recrystallised from MeOH–ether to give 30 mg of pale yellowish prisms, mp 208—210°. *Anal.* Calcd. for $C_{20}H_{29}O_4N \cdot HCl$: C, 62.58; H, 7.82; N, 3.65. Found: C, 62.53; H, 7.94; N, 3.69.

Acknowledgement We thank Miss R. Hasebe and Miss T. Yamaki for microanalysis and Miss Y. Tadano for NMR spectral measurement.

[Chem. Pharm. Bull. 17(4) 818—821 (1969)]

UDC 615.463.07 : 543.422.8

Quantitative Analysis of Pharmaceutical Preparations by X-Ray Diffractometry. IX.[1] Direct Quantitative X-Ray Diffraction Analysis of Salicylic Acid Plaster

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(Received April 19, 1968)

For the precise determination of active components in plasters, the chemical assay has long been used. The method of chemical assay used for salicylic acid plaster, for instance, is prescribed in the "United States Pharmacopoeia". An extraction with chloroform was made to liberate salicylic acid from plaster masses. After several steps of procedures, the determination was made finally by the bromine titration. It takes about a day for each measurement.

In the preceding paper,[1] the direct X-ray diffraction technique was reported to be very useful for the assay of the active components in oral suspensions. In this paper, this technique was attempted to utilize for the assay of salicylic acid plaster with acceptable accuracy and minimum investment of operation time.

The assay of salicylic acid contents in plaster by the direct X-ray diffraction method was developed as an alternative method for the chemical assay.

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1) Part VIII: K. Kuroda, G. Hashizume, and K. Fukuda, *J. Pharm. Sci.*, **57**, 250 (1968).
2) Location: *a*) *Kusunoki-cho, Ikuta-ku, Kobe*; *b*) *Kamitezaki-cho, Suma-ku, Kobe.*

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