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STUDIES ON TOTAL PHOTOLYTIC SYNTHESIS OF ALKALOIDS—III[1,2]

THE PRODUCTS OF PHOTO-PSCHORR REACTION—TOTAL SYNTHESIS OF ISOCORYDINE

T. KAMETANI*, T. SUGAHARA and K. FUKUMOTO

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan

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Abstract—A comparison of photolysis and thermal decomposition of the 1-(2-amino-3-benzyloxy-4-methoxybenzyl)-6-benzyloxy-1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinoline (**8**) is described together with the synthesis of *N*-methyllindecarpine (**28**) by photolysis and the synthetic trials of codeine and sinomenine.

IN PREVIOUS papers,[3–5] we reported the syntheses of the morphinandienones and homomorphinandienones from the corresponding aminoisoquinolines by two methods. One was a thermal decomposition of the diazonium salts derived from the aminoisoquinolines.[3–12] This method was applied to the total syntheses of morphine (**1**) and of sinomenine (**2**) through thebaine (**3**) *via* salutaridine (**4**) and sinoacutine (**5**)[9]. The other one was a photolytic decomposition of the diazonium salts[15,16] which was also used for a total synthesis of O-methylandrocymbine (**6**).[14] an alkaloid from *Colchicum autumnale*. In this paper. we report a comparison of the merits of

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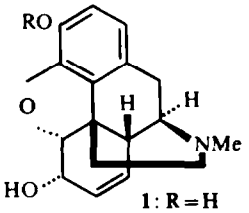
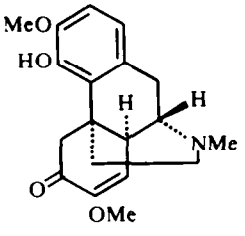


1: R = H
7: R = Me



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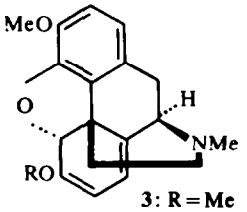
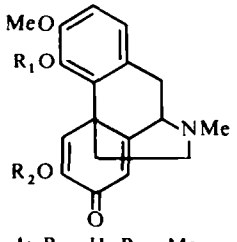
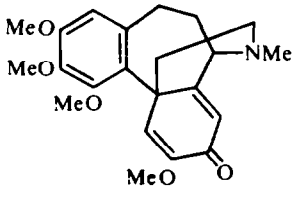


3: R = Me
32: R = CH_2Ph



4: R_1 = H; R_2 = Me
5: enantiomer of **4**
23: R_1 = H; R_2 = CH_2Ph
27: R_1 = R_2 = CH_2Ph
29: R_1 = R_2 = H



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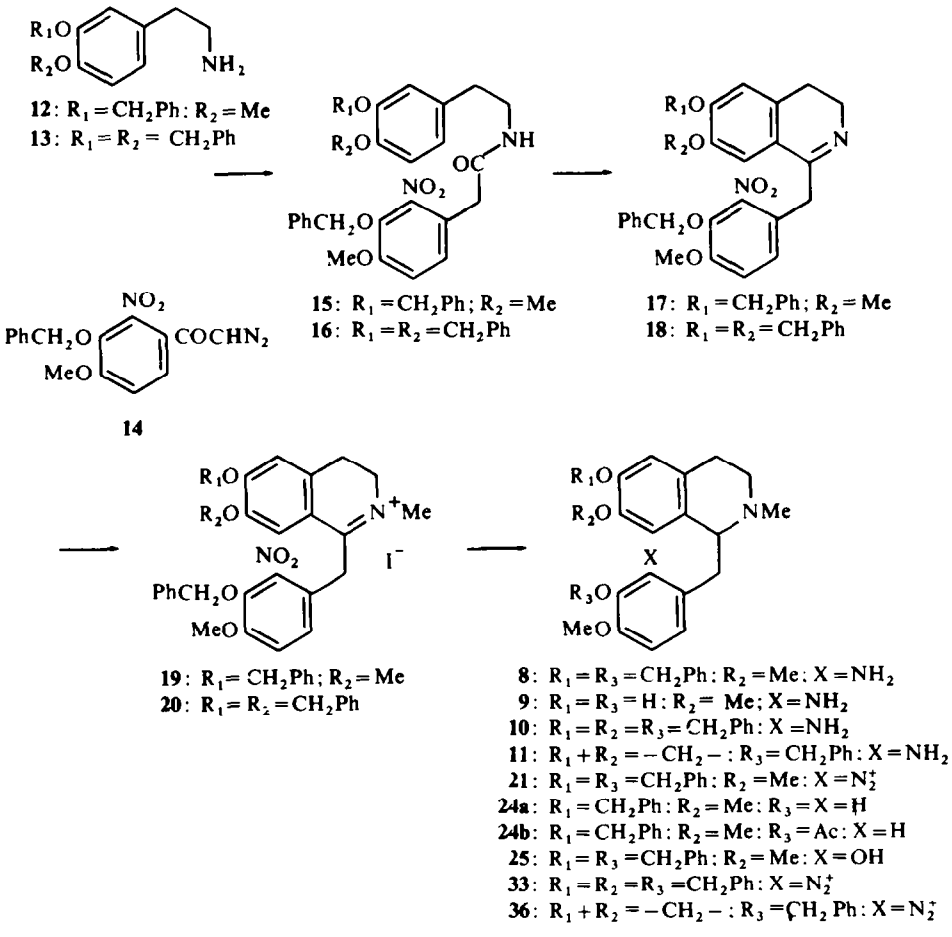
each method and also a synthesis of several aporphine alkaloids by the second method and. the synthetic approach to sinomenine (2) and codeine (7).

The starting aminoisoquinolines (8. 9. 10. and 11[16]) were synthesized by a standard method[16]: an Arndt–Eistert reaction of the β-phenethylamines (12 and 13) with the diazoketone (14) gave the amides (15 and 16). which *via* a Bischler–Napieralski reaction afforded the 3.4-dihydroisoquinolines (17 and 18). The methiodides (19 and and 20) from the corresponding 3.4-dihydroisoquinolines were reduced to the starting 1-(2-aminobenzyl)isoquinolines. The phenolic aminoisoquinoline (9) was synthesized by the debenzylation of 8.

SCHEME II



The diazotized isoquinoline (21) prepared from the first aminoisoquinoline (8) by a standard method was decomposed at 70° in dilute sulfuric acid to give three compounds after separation by chromatography.

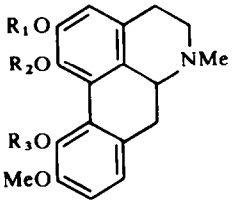
The first compound, $C_{26}H_{27}O_4N$, m.p. 167–168°, obtained in 9·1% yield, was

assigned as 2-benzyloxy-11-hydroxy-1.10-dimethoxyaporphine (**22**). the IR (3500 cm^{-1}) and UV (266 and 304 mμ) spectra of which showed this to have a 1.2.10.11-oxygenated aporphine system. The NMR spectrum supported this and. furthermore. the methylene of the O-benzyl group resonanced at the usual position (4·93).[17] which revealed that an OH group is located at the C_{11}-position. confirming the structure **22**. The IR (3450. 1660. 1645 and 1618 cm^{-1}) and UV (236 mμ) spectra of the second product. $C_{25}H_{25}O_4N$. m.p. 188–192°. obtained in 2% yield. showed the presence of a cross-conjugated α-alkoxylated cyclohexadienone system.[11] The NMR and mass spectra also supported this assignment. Moreover. a chemical shift of an olefinic proton (2·50 τ) revealed this morphinandienone to be the salutaridine type.[18] Therefore. the second compound was assigned as 6-benzyloxy-4-hydroxy-3-methoxy-morphinandienone (**23**). The last compound was assigned to the deamination product **24a**. This conclusion was based on microanalysis and spectral consideration.

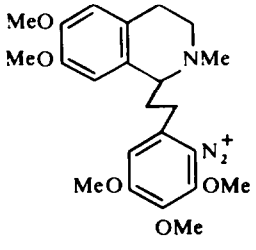
By the second method. the photolytic decomposition of the diazonium salt (**21**). also yielded three products. The first one. obtained in 27·2% yield. was assigned as the hydroxylated isoquinoline **25** by NMR and IR determinations. The second product. which was obtained in 15·2% yield and characterized as its methiodide. $C_{34}H_{36}O_4NI$. m.p. 208–211° (dec). was assigned as the aporphine **26** by UV and NMR spectra. The third component in 1·1% yield was found to be the morphinandienone (**27**) by the spectral considerations described in the Experimental.

A comparison of the above two methods showed clearly that photolysis is more suitable to prepare the aporphine than the thermal decomposition method. but

SCHEME III



22: $R_1 = CH_2Ph$: $R_2 = Me$: $R_3 = H$
26: $R_1 = R_3 = CH_2Ph$: $R_2 = Me$
28: $R_1 = R_3 = H$: $R_2 = Me$
31: $R_1 = R_2 = Me$: $R_3 = H$
35: $R_1 = R_2 = CH_2Ph$: $R_3 = H$
37: $R_1 + R_2 = -CH_2-$: $R_3 = H$



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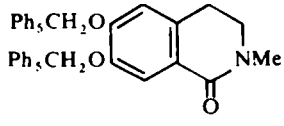

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that the latter method is preferable to photolysis in the synthesis of the morphinandienone. Moreover although the protecting group was removed under the thermal method, this group was retained under the photolytic method. In the thermal method, the deamination product was the main product; whereas in photolysis, the hydroxylated compound was obtained in greater yield. A typical example of these results was obtained in a photolytic decomposition of the diphenolic isoquinoline (**9**), which gave the aporphine corresponding to N-methyllindecarpine (**28**) in 21% yield but no morphinandienone (**29**). However, it is interesting that the photolysis of the diazotized phenethylisoquinoline (**30**) gave the homomorphinandienone (**6**) as the main product, which result could not be obtained by the thermal decomposition of **30**.[14,19]

Debenzylation of the aporphines (**22** and **26**) with hydrochloric acid also gave N-methyllindecarpine (**28**) which was converted into isocorydine (**31**). In order to synthesize codeine (**7**) *via* the thebaine-analog (**32**) from the morphinandienone (**23**), the preparation of **23** was examined. The diazotized isoquinoline (**33**) from the aminoisoquinoline (**10**) was heated at 70° to afford morphinandienone (**23**) in addition to the isocarbostyril (**34**)[20] and the aporphine (**35**). The morphinandienone (**23**) was reduced to the dienol, which was treated with hydrochloric acid to give the non-phenolic base (*m/e*. M^+ 387) showing a UV spectrum similar to that of thebaine (**3**).[9] Thus, we tentatively assigned this the structure **32**, the debenzylation of which under several conditions into codeinone ended in failure.

Secondly, we attempted to convert the morphinandienone (**23**) into sinomenine (**2**) by a route described.[8] The debenzylation of **23** was examined under a variety of conditions by hydrogenolysis or acidic hydrolysis, but dehydrodiosphenol (**29**) could not be obtained. Therefore, a direct synthesis of **29**[10] from the aminoisoquinoline (**11**)[16] was investigated. The thermal decomposition of the diazotized isoquinoline (**36**) of **11** gave bulbocapnine (**37**)[16] but no morphinandione (**29**). During our investigation, Fleischhacker[21] reported that the hydrogenation of the dehydrodiosphenol did not proceed under a variety of conditions, so, we abandoned the synthesis of sinomenine *via* this route.

Thus, we developed a new synthetic method of the aporphine by photo-Pschorr reaction, and obtained isocorydine in good yield.

EXPERIMENTAL

Melting pts are uncorrected. The IR spectra were taken in $CHCl_3$ soln with a Hitachi EPI-S_2 spectrometer. UV spectra were taken in MeOH soln on a Hitachi 124 double beam recording spectrophotometer. Mass spectra were measured on a Hitachi RMU-7 mass spectrometer. NMR spectra were measured on a Hitachi R-20 in $CDCl_3$ soln using TMS as an internal standard.

N-(3-Benzyloxy-4-methoxyphenethyl)-3-benzyloxy-4-methoxy-2-nitrophenylacetamide (**15**). To a soln of **14** (41 g) in 600 ml dry dioxane, **12** (38·7 g) was added at 60–65° with stirring and 7 g of Ag_2O was then added in small portions. The stirring was continued for 2 hr at 65–70° and an additional 6 g of Ag_2O was added and the mixture refluxed for 1 hr. After the mixture had been treated with charcoal, the solvent was removed by distillation to give 78 g of a dark reddish oil, which was chromatographed on 220 g silica gel. Evaporation of the chloroform eluant gave 63 g of **15** as a pale yellow syrup. The mass spectrum showed the molecular ion at *m/e* 556; ν_{max} 3360 (NH), 1665 cm^{-1} (amide C=O); NMR τ 6·31 ($O-CH_3$, 3H, s), 6·27 ($O-CH_3$, 3H, s), 5·02 ($OC\underline{H}_2Ph$, 2H, s), 5·00 ($OC\underline{H}_2Ph$, 2H, s), 3·40 (aromatic protons, 2H, s), 3·28 (aromatic proton, 1H, s), 3·18 (aromatic protons, 2H, s), 2·78 (2 × $OCH_2C_6\underline{H}_5$, 10H, s).

6-Benzyloxy-1-(3-benzyloxy-4-methoxy-2-nitrobenzyl)-3,4-dihydro-7-methoxyisoquinoline (**17**) *hydrochloride* and *methiodide* (**19**). A mixture of **15** (60 g), 550 ml dry $CHCl_3$ and 55 ml $POCl_3$ was refluxed on a water-bath for 1·5 hr. After reaction, the $CHCl_3$ layer was removed by distillation *in vacuo*, and the resulting syrup

was mixed with an excess of cold hexane and kept overnight. The hexane layer was then removed by decantation to give a syrup, to which was added an excess of ether to precipitate 40 g of **17**. Recrystallization from MeOH gave colorless needles. mp 192–195°. ν_{max} 1645 cm^{-1} (C=N). (Found: C, 65·01; H, 5·25; N, 4·81. Calcd for $C_{32}H_{31}O_6NCl.H_2O$: C, 64·80; H, 5·61; N, 4·72%).

A soln of 37 g of the above hydrochloride in 60 ml MeOH was neutralized with 10% ammonia and extracted with chloroform. The dried extract was concentrated to afford a syrup, which was dissolved in 60 ml $CHCl_3$ together with an excess MeI. After the mixture had been refluxed for 2 hr, the $CHCl_3$ layer was evaporated and the resulting methiodide was recrystallized from MeOH to give 41 g of **19** as yellow needles. m.p. 163–165°. ν_{max} 1625 cm^{-1} (shoulder) (C=N). (Found: C, 56·16; H, 5·10; N, 3·54. Calcd for $C_{33}H_{33}O_6N_2I.1/2H_2O$: C, 56·01; H, 5·31; N, 3·96%).

1-(2-Amino-3-benzyloxy-4-methoxybenzyl)-6-benzyloxy-1.2.3.4-tetrahydro-7-methoxy-2-methylisoquinoline (8). Zn (225 g) powder was added in portions to a soln of 30 g of the above methiodide in 7·50 ml AcOH, 125 ml water and 750 ml conc HCl at 0° with stirring. The stirring was continued for 7 hr at 0–10°, and the soln was filtered in order to remove an inorganic substance. The filtrate was poured into ammonia cooled with ice. The mixture was extracted with $CHCl_3$, and the extract was washed with water, dried over Na_2SO_4, and evaporated to give 21 g of **8** as a pale yellow oil. ν_{max} 3340 cm^{-1} (NH_2).

Pschorr reaction of 8

(a) *Thermal decomposition of aminoisoquinoline* (8). To a soln of **8** (8 g), 40 ml AcOH and 200 ml 5% H_2SO_4 13 ml of 10% $NaNO_2$ aq was added dropwise at 0° with stirring, and the resulting diazonium soln was kept at the same temp for 1 hr with stirring. The mixture was then heated at 70° for 2 hr, then cooled, made basic with ammonia, and extracted with $CHCl_3$. Evaporation of the dried extract gave 7·5 g of a reddish oil, which was chromatographed on 200 g of silica gel using $CHCl_3$ and MeOH as eluants; $CHCl_3$ (each Fr. 300 ml, Fr 1–6), $CHCl_3$–MeOH (99:1; Fr 7–11), $CHCl_3$–MeOH (98:2; Fr 12–15), and $CHCl_3$–MeOH (94:5; Fr 16–25). Evaporation of Fr 5–8 gave 780 mg of yellow oil (**22**), which was recrystallized from EtOH to give 730 mg (9·1%) of colorless needles. m.p. 167–168°. λ_{max} 266 (log ε 4·143), 304 mμ (log ε 3·718); ν_{max} 3500, 3130 cm^{-1} (OH); NMR τ 7·50 (N–CH_3, 3H, s), 6·31 (O–CH_3, 3H, s), 6·15 (O–CH_3, 3H, s), 4·93 ($OC\underline{H}_2$Ph, 2H, s), 3·31 (aromatic proton, 1H, s), 3·25 (aromatic protons, 2H, s), 2·69 ($OCH_2C_6\underline{H}_5$, 5H, s), 12·8 (OH 1H, s, exchangeable with D_2O). Gibbs' test was positive. (Found: C, 74·39; H, 6·29; N, 3·56. Calcd for $C_{26}H_{27}ON_4$: C, 74·80; H, 6·52; N, 3·36%).

Secondly, evaporation of Fr 13–14 gave 600 mg of a crude cyclohexadienone as a yellow oil, which was rechromatographed on 15 g silicic acid using $CHCl_3$. Evaporation of the $CHCl_3$ eluate gave 220 mg of a morphinandienone type compound **23** as a pale yellow syrup, which was recrystallized from benzene to give 160 mg (2%) of colorless needles, m.p. 188–192°; λ_{max} 236, 282 mμ; ν_{max} 3450 (OH), 1660, 1645, 1618 cm^{-1} (cyclohexadienone system); NMR τ 7·61 (N–CH_3, 3H, s), 6·22 (O–CH_3, 3H, s), 5·05 ($OC\underline{H}_2$Ph, 2H, s), 3·78 (olefinic proton, 1H, s), 3·41 (aromatic protons, 2H, s), 2·50 (olefinic proton, 1H, s). The mass spectrum showed the peaks at *m/e* 403 (M^+), 375 ($M^+ - 28$), 312 ($M^+ - 91$), and 284 ($M^+ - 91 - 28$). (Found: C, 74·89; H, 6·41; N, 3·29. Calcd for $C_{25}H_{25}ON_4$: C, 74·42; H, 6·25; N, 3·47%).

Evaporation of Fr 15–20 gave 1·6 g of a dark oil, which was rechromatographed on 45 g silicic acid using $CHCl_3$ and MeOH as eluants. Evaporation of $CHCl_3$–MeOH (99:1) eluate gave 1·3 g of **24a**, which was recrystallized from MeOH to give colorless needles (16·3%), m.p. 119–119·5°; Gibbs' test was positive; ν_{max} 3500, 3150 cm^{-1} (OH); NMR τ 7·5 (N-CH_3, 3H, s), 6·43 (O-CH_3, 3H, s), 6·19 (O-CH_3, 3H, s), 4·95 ($OC\underline{H}_2$Ph, 2H, s), 4·61 (OH, 1H, broad signal, exchangeable with D_2O), 3·90 (C_8-aromatic proton, 1H, s), 3·56–3·15 ($C_{2'}$, $C_{5'}$, and $C_{6'}$-aromatic protons, 3H, m), 3·42 (C_5-aromatic proton, 1H, s), 2·65 ($OCH_2C_6\underline{H}_5$, 5H, s). (Found: C, 74·37; H, 7·39; N, 3·45. Calcd for $C_{26}H_{29}O_4N$: C, 74·44; H, 6·97; N, 3·34%).

Acetylation of 24a. A mixture of **24a** (40 mg), 1 ml Ac_2O, and 2 drops pyridine was allowed to stand at room temp overnight, and then poured into ice-water. After standing for 5 hr, the mixture was basified with ammonia, and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated to give **24b** as a reddish viscous syrup. ν_{max} 1760 cm^{-1} (C=O); NMR τ 7·72 (OCO-CH_3, 3H, s), 7·50 (N-CH_3, 3H, s), 6·41 (O-CH_3, 3H, s), 6·23 (O-CH_3, 3H, s), 4·93 ($OC\underline{H}_2$Ph, 2H, s), 3·90 (C_8-aromatic proton, 1H, s), 3·42 (C_5-aromatic proton, 1H, s), 3·18 ($C_{2'}$, $C_{5'}$, and $C_{6'}$-aromatic protons, 3H, s), 2·65 ($OCH_2C_6\underline{H}_5$, 5H, s).

(b) *Photolysis of aminoisoquinoline* (8). 10% $NaNO_2$ aq (4·8 ml) was added dropwise during 15 min to a stirred and cooled (0°) soln of 3 g of **8** in 75 ml 5% H_2SO_4 and 30 ml AcOH. The stirring was continued at 0–5° for 1 hr and then water (1 l) was added to the above mixture. The mixture was irradiated, with a Hanovia 450 W mercury lamp using a pyrex filter, at 5–15° for 4 hr, during which an evolution of N_2 was observed. The resulting mixture was made basic with ammonia and extracted with $CHCl_3$. The extract

was washed with sat NaCl aq and dried over Na_2SO_4. Evaporation of the solvent gave 3 g of a reddish oil, which was chromatographed on 90 g of silica gel with $CHCl_3$ and $CHCl_3$–MeOH as eluants; $CHCl_3$ (each Fr 200 ml, Fr 1–5), $CHCl_3$–MeOH (99:1, Fr 6–10), $CHCl_3$–MeOH (99:2, Fr 11–17), and $CHCl_3$–MeOH (99:3, Fr 18–25). Evaporation of Fr 7–9 gave 1·2 g of a yellow oil, which was again chromatographed on 15 g silicic acid with $CHCl_3$. Evaporation of $CHCl_3$ gave 816 mg (27·2%) of **25** as a brownish syrup. ν_{max} 2400–2600, 1700–1900 cm^{-1} (betaine). NMR τ 7·5 (N-CH_3, 3H, s), 6·39 (O-CH_3, 3H, s), 6·29 (O-CH_3, 3H, s), 5·15 (O$C\underline{H}_2$Ph, 2H, s), 5·18 (O$C\underline{H}_2$Ph, 2H, s), 4·0 and 3·69 (aromatic protons, 2H, a pair of d, J = 9 cs), 3·67 (aromatic proton, 1H, s), 3·58 (aromatic proton, 1H, s), 2·81 (2 × $OCH_2C_6\underline{H}_5$, 10H broad singlet). λ_{max} 280 mμ. This was characterized as methiodide, m.p. 98–101°, as an amorphous powder. (Found: C, 59·90; H, 5·77. Calcd for $C_{34}H_{38}O_5NI \cdot 1{\cdot}2H_2O$: C, 60·35; H, 5·81%).

Secondly, evaporation of Fr 10–16 gave 650 mg of a reddish oil, which was again chromatographed on silicic acid (15 g) with $CHCl_3$. Evaporation of $CHCl_3$ gave 460 mg (15·3%) of **26**, τ_{max} 272, 300 mμ; NMR τ 7·63 (N-CH_3, 3H, s), 6·40 (O-CH_3, 3H, s), 6·20 (O-CH_3, 3H, s), 5·34 and 5·12 (O$C\underline{H}_2$Ph, 2H, a pair of d, J = 12 cs), 5·08 (O$C\underline{H}_2$Ph, 2H, s), 3·30 (aromatic protons, 2H, s), 3·0 ($OCH_2C_6\underline{H}_5$, 5H, s), 2·75 ($OCH_2C_6\underline{H}_5$, 5H, s). Recrystallization of the methiodide from MeOH gave colorless needles, m.p. 208–211° dec. (Found: C, 58·80; H, 5·37. Calcd for $C_{34}H_{36}O_4NI \cdot 2{\cdot}5H_2O$: C, 58·79; H, 5·95%).

Evaporation of the successive Fr 21 gave 0·2 g of a reddish oil, which was again chromatographed on 6 g of silicic acid with $CHCl_3$. Evaporation of the $CHCl_3$ eluate gave 33 mg (1·1%) of **27** as a pale yellow syrup. λ_{max} 280, 232 mμ; ν_{max} 1665, 1640, 1615 cm^{-1} (cyclohexadienone system); NMR τ 7·60 (N-CH_3, 3H, s), 6·20 (O-CH_3, 3H, s), 5·04 (O$C\underline{H}_2$Ph, 2H, s), 4·93 (O$C\underline{H}_2$Ph, 2H, s), 3·80 (C_8-olefinic proton, 1H, s), 3·22 (aromatic protons 2H, s), 2·86 ($OCH_2C_6\underline{H}_5$, 5H, s), 2·71 (olefinic proton and $OCH_2C_6\underline{H}_5$, 6H, broad s). Mass spectrum showed the peaks at *m/e* 493 (M^+), 402 ($M^+ - 91$), 374 ($M^+ - 91 - 28$), 311 ($M^+ - 91 - 91$), 283 ($M^+ - 91 - 91 - 28$).

1-(2-*Amino*-3-*hydroxy*-4-*methoxybenzyl*)-1,2,3,4-*tetrahydro*-6-*hydroxy*-7-*methoxy*-2-*methylisoquinoline*(9) A mixture of **8** (4·7 g) of 45 ml conc HCl, and 45 ml EtOH was refluxed on a water-bath for 2·5 hr. After the removal of the EtOH, the residue was washed with ether several times to give 4 g of **9** as a reddish oil, ν_{max} 3500 cm^{-1} (OH).

Modified Photo-Pschorr reaction of 9. To a soln of **9** (3 g) in 84 ml 5% H_2SO_4, 10% $NaNO_2$ aq (7·2 ml) was added at 0° with stirring within 20 min, and the stirring continued for 1 hr at the same temp. After the reaction, 700 mg urea was added with stirring for 15 min and then water (1 l) was added. A soln of the resulting diazonium salt was irradiated, with a Hanovia 450 W mercury lamp using a pyrex filter, at 5–15° for 4 hr. The mixture was made basic with ammonia and extracted with $CHCl_3$. The extract was washed with NaCl aq, dried over Na_2SO_4 and evaporated to give reddish crystals, which were washed with MeOH. Recrystallization from MeOH gave 630 mg (21%) of the aporphine which correspond to **28** as colorless needles, m.p. 211–214°; λ_{max} 267 (log ε 4·143), 305 mμ (log ε 3·827); ν_{max} 3500, 3350 cm^{-1} (OH); NMR τ 7·49 (N-CH_3, 3H, s), 6·39 (O-CH_3, 3H, s), 6·12 (O-CH_3, 3H, s), 3·32 (aromatic proton, 1H, s), 3·21 (aromatic protons, 2H, s), 1·71 (2 × OH, 2H, s, exchangeable with D_2O). Gibbs' test was positive. (Found: C, 67·81; H, 6·17; N, 4·42. Calcd for $C_{19}H_{21}ON_4 \cdot 1{\cdot}2H_2O$: C, 67·84; H, 6·59; N, 4·16%).

N-(3,4-*Dibenzyloxyphenethyl*)-3-*benzyloxy*-4-*methoxy*-2-*nitrophenylacetamide* (16). To a stirred soln of **14** (35 g) in 500 ml dry dioxane, a mixture of **13** (36 g), 80 ml dry dioxane and 6 g freshly prepared Ag_2O was added at 55–60°. After 2 hr stirring, an additional 6 g Ag_2O was added and the mixture refluxed for 45 min. After treatment with charcoal, the mixture was filtered and the solvent was removed by distillation *in vacuo* leaving 65 g of a dark-reddish oil, which was chromatographed on silica gel (300 g). Evaporation of the $CHCl_3$ eluant gave 53 g **16**, which was recrystallized from EtOAc-hexane as colorless needles, m.p. 75–77°; ν_{max} 3400 (NH), 1665 cm^{-1} (C=O); NMR τ 6·41 (O-CH_3, 3H, s), 5·12 and 5·09 (3 × O$C\underline{H}_2$Ph, 6H, d), 3·25–3·62 (aromatic protons, 5H, m), 2·80 (3 × $OCH_2C_6\underline{H}_5$, 15H, s). (Found: C, 72·22; H, 5·74; N, 4·87. Calcd for $C_{38}H_{36}O_7N_2$: C, 72·17; H, 5·74; N, 4·43%).

6,7-*Dibenzyloxy*-1-(3-*benzyloxy*-4-*methoxy*-2-*nitrobenzyl*)-3,4-*dihydroisoquinoline* (18) *hydrochloride*. A mixture of **16** (50 g), 500 ml dry $CHCl_3$ and 50 ml $POCl_3$ was refluxed on a water bath for 1·5 hr. After removal of the solvent, the residue was poured into an excess of cold hexane, and the mixture was allowed to stand at room temp overnight. The excess hexane was removed by decantation, and the resulting reddish gum was washed with ether several times and recrystallized from MeOH to give 34 g of **18** as colorless needles, m.p. 205–210° dec; ν_{max} 1645 cm^{-1} (C=N). (Found: C, 69·51; H, 5·56. Calcd for $C_{38}H_{35}O_6N_2Cl$: C, 70·9; H, 5·42%).

6,7-*Dibenzyloxy*-1-(3-*benzyloxy*-4-*methoxy*-2-*nitrobenzyl*)-3,4-*dihydroisoquinoline methiodide* (20). A soln of the above hydrochloride (33 g) in 60 ml MeOH was neutralized with 10% ammonia and extracted with $CHCl_3$. The dried extract was concentrated to give the residue, which was dissolved in 60 ml $CHCl_3$. The

mixture was then refluxed with an excess MeI for 2 hr. After removal of the solvent and excess reagent, the resulting methiodide was recrystallized from MeOH to give 31 g of **20** as yellow needles, m.p. 185–189°; ν_{max} 1625 cm^{-1} (C=N). (Found: C, 62·04; H, 4·99; N, 4·20. Calcd for $C_{39}H_{37}O_6N_2I$: C, 61·91; H, 4·93; N, 3·70%).

1-(2-*Amino*-3-*benzyloxy*-4-*methoxybenzyl*)-6,7-*dibenzyloxy*-1,2,3,4-*tetrahydro*-2-*methylisoquinoline* (10). Zn powder (120 g) was added in portions to a soln of the above methiodide (20 g) in 600 ml AcOH, 120 ml water and 600 ml conc HCl at 0° with stirring. The stirring was continued for 7 hr at 0–10°, and the mixture was filtered. The filtrate was poured into cooled ammonia with ice. The mixture was extracted with $CHCl_3$, and the extract was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave 13 g of a reddish oil (**10**). ν_{max} 3400 cm^{-1} (NH); NMR τ 7·61 (N-CH_3, 3H, s), 6·30 (O-CH_3, 3H, s), 5·16 (2 × $OC\underline{H}_2Ph$, 4H, s), 5·08 ($OC\underline{H}_2Ph$, 2H, s), 4·01 and 3·75 (aromatic protons, 2H, a pair of d, J = 9 cs), 3·74 (aromatic proton, 1H, s), 3·56 (aromatic proton, 1H, s), 2·78 (3 × $OCH_2C_6\underline{H}_5$, 15 H, s).

Modified Pschorr reaction of 1-(2-*amino*-3-*benzyloxy*-4-*methoxybenzyl*)-6,7-*dibenzyloxy*-1,2,3,4-*tetrahydro*-2-*methylisoquinoline* (10). To a soln of **10** (6 g) 30 ml AcOH and 150 ml 5% H_2SO_4 aq, 10 ml 10% $NaNO_2$ aq was added dropwise at 0° with stirring, and a soln of the resulting diazonium salt was stirring at the same temp for 1 hr. The mixture was then heated at 70° for 2 hr, and then cooled. The resulting aqueous soln was made basic with ammonia and extracted with $CHCl_3$. Evaporation of the dried extract gave 6 g of a reddish oil, which was chromatographed on silica gel (200 g) using $CHCl_3$ and MeOH as eluants: $CHCl_3$ (each Fr 300 ml, Fr 1–5), $CHCl_3$–MeOH (99:1, Fr 6–10), $CHCl_3$–MeOH (98:2, Fr 11–17), $CHCl_3$–MeOH (97:3, Fr 18–25).

Evaporation of Fr 4–6 gave 200 mg of a yellow oil, which was again chromatographed on Al_2O_3 (16 g) using benzene-$CHCl_3$. Evaporation of benzene-$CHCl_3$ (1:1) eluant gave **34** as a pale yellow syrup, which was recrystallized from EtOAc to give 35 mg (0·6%) of colorless needles, m.p. 117–118°; λ_{max} 295 mμ; ν_{max} 1635 cm^{-1} (C=O); NMR τ 7·06 (N-CH_3, 3H, s), 5·06 ($OC\underline{H}_2Ph$, 2H, s), 5·00 ($OC\underline{H}_2Ph$, 2H, s), 3·56 (aromatic proton, 1H, s), 2·47 (aromatic proton 1H, s), 2·79 (2 × $OCH_2C_6\underline{H}_5$, 10H, s). (Found: C, 77·04; H, 6·03; N, 3·82. Calcd for $C_{24}H_{23}O_3N$: C, 77·19; H, 6·21; N, 3·75%).

Secondly, evaporation of Fr 7–10 gave 850 mg of a reddish oil, which was again chromatographed on silica gel (25 g) using $CHCl_3$. Evaporation of $CHCl_3$ gave 600 mg of **35** as a yellow syrup. λ_{max} 268, 305 mμ; ν_{max} 3200 cm^{-1} (OH); NMR τ 7·52 (N-CH_3, 3H, s), 6·18 (O-CH_3, 3H, s), 5·34 and 5·08 ($OC\underline{H}_2Ph$, 2H, a pair of d, J = 11 cs), 4·98 ($OC\underline{H}_2Ph$, 2H, s), 3·31 (aromatic protons, 3H, s), 3·02 ($OCH_2C_6\underline{H}_5$, 5H, s), 2·70 ($OCH_2C_6\underline{H}_5$, 5H, s). Gibbs' test was positive (blue-green). The methiodide formed colorless needles, m.p. 204–208° dec (from MeOH). (Found: C, 62·63; H, 5·32. Calcd for $C_{33}H_{34}O_4NI$: C, 62·36; H, 5·30%).

Finally, evaporation of Fr 16–17 gave 200 mg of a reddish syrup, which was again chromatographed on silic acid (8 g) using $CHCl_3$. Evaporation of $CHCl_3$ gave **23** as a pale yellow syrup, which was recrystallized from benzene to give 78 mg (1·3%) of colorless needles, m.p. 188–192°, identical with the authentic morphinandienone.

6-O-*Benzylthebaine* (32). Compound **23** (120 mg) in 30 ml MeOH was treated with 1 g $NaBH_4$ at 0° with stirring. After stirring for 2 hr at 0° and then for 1 hr at room temp, the solvent was evaporated to leave a residue, which was shaken with 10% NH_4Cl aq and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over Na_2SO_4 and evaporated to give the epimeric alcohol as a pale yellow syrup [ν_{max} 3500 (OH), 1665 cm^{-1} (C=C)]. Without separation, the mixture was treated with 1N HCl (25 ml) at room temp for 1 hr, then made basic with 10% NaOH aq and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated to give a pale yellow oil, which was chromatographed on silicic acid (1·5 g). Evaporation of the $CHCl_3$ eluate gave 18 mg of **32**. Mass spectrum showed the peaks at *m/e* 387 (M^+), 297 ($M^+ - 90$); λ_{max} 285 mμ.

Debenzylation of 2-*benzyloxy*-N-*methyllindecarpine* (22). A mixture of **22** (40 mg) 2 ml of conc HCl and 2 ml EtOH was refluxed on a water-bath for 2·5 hr. After removal of the EtOH, the residue was basified with 10% ammonia and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated to give 30 mg of **28** which corresponded to N-methyllindecarpine. The IR and NMR spectra were superimposable on an authentic sample.

Debenzylation of 2,11-*dibenzyloxyaporphine* (26). A mixture of **26** (30 mg) 2 ml of conc HCl and 2 ml EtOH was refluxed on a water bath for 2·5 hr. The mixture was basified with 10% ammonia and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated to give 20 mg of **28**, the IR and NMR spectra of which were superimposable on an authentic sample.

(±)-*Isocorydine* (31). Excess diazomethane (prepared from 10 g of *p*-toluenesulfonyl-N-methyl-N-nitrosoamide) in ether was added to a soln of **28** (40 mg) in 5 ml MeOH at 0° and the mixture was kept

overnight at room temp. The solvent was evaporated to give 40 mg of **31**. the IR and NMR spectra of which were superimposable on an authentic sample.

Thermal decomposition of diazonium salt of 11. To a soln of **11**[16] (5 g) in 315 ml 5% H_2SO_4. 12 ml 10% $NaNO_2$ aq was added dropwise at 0–5° with stirring. and the stirring was continued at the same temp for 1 hr and then at 70° for 2 hr. The cooled mixture was made basic with 10% ammonia and extracted with $CHCl_3$. The extract was washed with water. dried over K_2CO_3. and evaporated to give 5 g of a dark reddish oil. which was chromatographed on silica gel (150 g) using $CHCl_3$ and MeOH as eluants.

Evaporation of Fr 11–16 (each Fr 200 ml. $CHCl_3$–MeOH. 99:1) gave 900 mg of a brownish yellow oil. which was again chromatographed on silica gel (25 g). Evaporation of the $CHCl_3$ eluate gave 450 mg of a yellowish syrup. which was recrystallized from acetone to give 430 mg (8·3%) of **39** as colorless needles. m.p. 212–215 (lit.[16]. m.p. 213·214°): λ_{max} 268. 303 mμ; ν_{max} 3350 cm^{-1} (OH). the IR and NMR spectra of which were superimposable on an authentic bulbocapine.[16]

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REFERENCES

[1] Part II: T. Kametani, M. Koizumi, and K. Fukumoto, *J. Chem. Soc.* (C), 1792 (1971)
[2] This forms Part CDXXVII of *Studies on the Syntheses of Heterocyclic Compounds* by T. Kametani; Part CDXXVI, T. Kametani, T. Sugahara, H. Sugi, S. Shibuya, and K. Fukumoto, *Chem. Comm.* 724 (1971)
[3] T. Kametani. K. Fukumoto. F. Satoh. and H. Yagi. *Chem. Comm.* 1398 (1968)
[4] T. Kametani. K. Fukumoto. F. Satoh. and H. Yagi. *J. Chem. Soc.* (C). 520 (1969)
[5] T. Kametani. K. Fukumoto. and T. Sugahara. *Tetrahedron Letters* 5459 (1968)
[6] T. Kametani. K. Fukumoto. and T. Sugahara. *J. Chem. Soc.* (C). 801 (1969)
[7] T. Kametani. T. Sugahara. H. Yagi. and K. Fukumoto. *Ibid.* (C). 1063 (1969)
[8] T. Kametani. M. Koizumi. and K. Fukumoto. *Chem. Pharm. Bull. Tokyo* **17**. 2245 (1969)
[9] T. Kametani. M. Ihara. K. Fukumoto. and H. Yagi. *J. Chem. Soc.* (C). 2030 (1969)
[10] T. Kametani. T. Sugahara. and K. Fukumoto. *Chem. and Ind.* 833 (1969)
[11] T. Kametani. T. Sugahara. K. Fukumoto. B. R. Pai. and Charubala. *J. Chem. Soc.* (C). 624 (1970)
[12] T. Kametani. K. Fukumoto. F. Satoh. and H. Yagi. *Chem. Comm.* 1001 (1968)
[13] T. Kametani. K. Fukumoto. F. Satoh. and H. Yagi. *J. Chem. Soc.* (C). 3084 (1968)
[14] T. Kametani. M. Koizumi. and K. Fukumoto. *Chem. Comm.* 1157 (1970)
[15] T. Kametani. K. Fukumoto. and K. Shishido. *Chem. and Ind.*. 1566 (1970)
[16] I. Kikkawa. *J. Pharm. Soc. Japan* **79**. 1244 (1959)
[17] cf. M. Shamma and W. A. Slusarchyk. *Chem. Revs* **64**. 59 (1964)
[18] K. L. Stuart and C. Chambers. *Tetrahedron Letters* 2879 (1967); T. Kametani. K. Takahashi. T. Sugahara. M. Koizumi. and K. Fukumoto. *J. Chem. Soc.* (C). 1032 (1971)
[19] T. Kametani. M. Koizumi. K. Shishido. and K. Fukumoto. *Ibid.* (C). 1923 (1971)
[20] T. Kametani. M. Koizumi. and K. Fukumoto. *J. Pharm. Soc. Japan* **90**. 1331 (1970)
[21] W. V. Fleischhacker and F. Zeidler. *Monatsh.* **101**. 1215 (1970)