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TOTAL SYNTHESES OF (±)-PRONUCIFERINE, (±)-O-METHYLORIENTALINONE, AND (±)-O-METHYLKREYSIGINONE[1,2]

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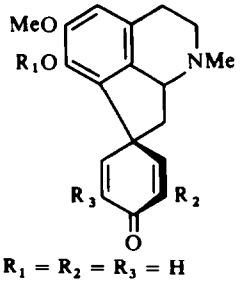
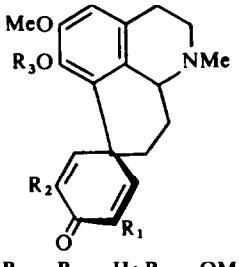
Abstract—Photolysis of 8-bromo-1,2,3,4-tetrahydro-1-(4-hydroxybenzyl)-6,7-dimethoxy-2-methylisoquinoline (**21**) gave (±)-pronuciferine (**2**). The same reaction of the phenolic bromoisoquinoline (**20** and **23**) afforded (±)-O-methylorientalinone (**3a** or **3b**) and (±)-O-methylisoorientalinone (**3b** or **3a**). and (±)-O-methylkreysiginone (**5a** or **5b**).

PREVIOUSLY, we reported the syntheses of (±)-glaziovine (**1**)[3] and of the homoproaporphines (**4a** and **4b**)[4] by phenolic oxidative coupling from the corresponding diphenolic isoquinolines. This type of proaporphines (**2** and **3a, b**) was synthesized by the Pschorr reaction.[5,6] Furthermore. we recently achieved the photolytic conversion of the bromoisoquinoline (**6**) to the morphinandienone (**7**) in addition to the aporphine (**8**).[7] We have successively investigated the general synthetic method of the proaporphine and homoproaporphine type compounds by photolytic cyclization reactions. Herein we wish to report these results.

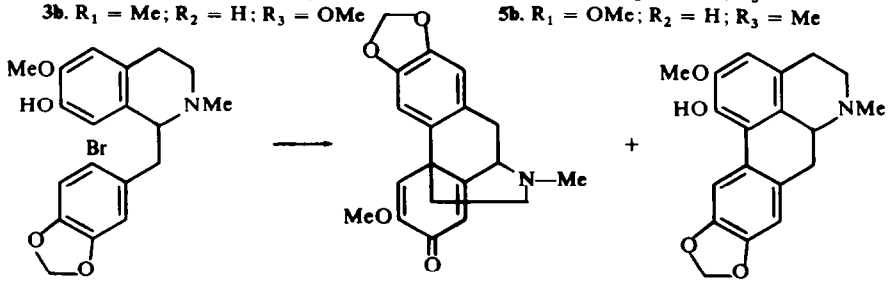
SCHEME 1



1. $R_1 = R_2 = R_3 = H$
2. $R_1 = Me; R_2 = R_3 = H$
3a. $R_1 = Me; R_2 = OMe; R_3 = H$
3b. $R_1 = Me; R_2 = H; R_3 = OMe$



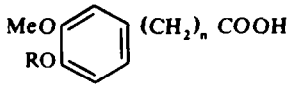
4a. $R_1 = R_3 = H; R_2 = OMe$
4b. $R_1 = OMe; R_2 = R_3 = H$
5a. $R_1 = H; R_2 = OMe; R_3 = Me$
5b. $R_1 = OMe; R_2 = H; R_3 = Me$



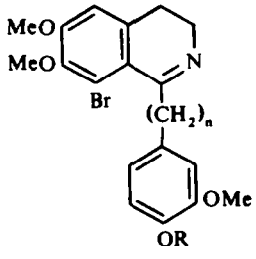
6 **7** **8**

First, 8-bromo-1,2,3,4-tetrahydro-1-(4-hydroxybenzyl)-6,7-dimethoxy-2-methylisoquinoline (**21**)[8] was irradiated for 7 hr in the presence of NaOH with a Hanovia 450 W mercury lamp using a pyrex filter to give (±)-pronuciferine (**2**),[3,5,6,9] an alkaloid from *Papaver* species, in 10% yield. The structure was assigned by direct comparison of IR (1660, 1620 cm^{-1}), and NMR spectra [τ 7·59 (NMe), 6·43 (OMe), 6·22 (OMe), 3·90–3·50 (α,α'-olefinic protons), 3·30–2·90 (β,β'-olefinic protons), 6·58 (aromatic proton)] with those of an authentic sample.[3] In this reaction when the above photolysis was performed in an ethanolic NaOH solution in the presence of Cu powder, the yield increased to 17%. Thus we developed a new synthetic route to the proaporphine type compound which has the basic skeleton of the alkaloids found in *Papaver* species.[10]

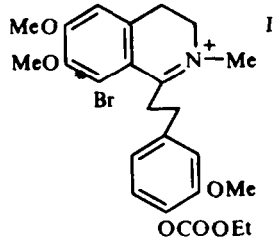
SCHEME 2



9. R = CH_2Ph; n = 1
10. R = H; n = 2



15. R = CH_2Ph; n = 1
16. R = COOEt; n = 2



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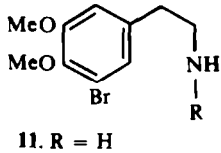
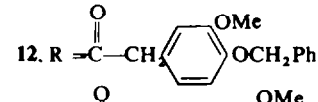
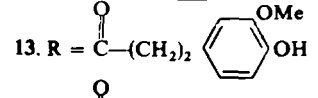


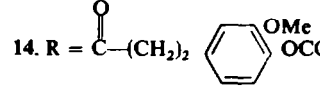
11. R = H



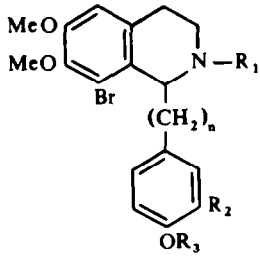
12. R = $-C(=O)-CH_2$



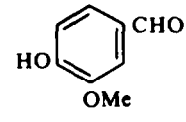
13. R = $-C(=O)-(CH_2)_2$



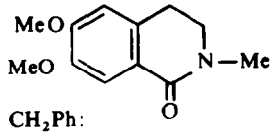
14. R = $-C(=O)-(CH_2)_2$



18. R_1 = H; R_2 = OMe; R_3 = MeO
19. R_1 = Me; R_2 = OMe; R_3 = CH_2Ph; n = 1
20. R_1 = Me; R_2 = OMe; R_3 = H; n = 1
21. R_1 = Me; R_2 = R_3 = H; n = 1
22. R_1 = Me; R_2 = OMe; R_3 = COOEt; n = 2
23. R_1 = Me; R_2 = OMe; R_3 = H; n = 2



24



25

Secondly, photolysis of phenolic 8-bromoisoquinoline (**20**) was examined under the same conditions. The isoquinoline (**20**) was synthesized as follows. Fusion of the amine (**11**) with 4-benzyloxy-3-methoxyphenylacetic acid (**9**) gave the corresponding amide (**12**). Ring-closure of this amide (**12**) was accomplished with $POCl_3$ in boiling benzene. The 3,4-dihydroisoquinoline (**15**) so obtained was reduced with $NaBH_4$ to give 1,2,3,4-tetrahydroisoquinoline (**18**). Reductive *N*-methylation, followed

by debenzylation with ethanolic HCl, gave the phenolic isoquinoline (**20**). Photolysis of **20**, under conditions similar to those of the reaction of **21**, yielded three compounds in addition to the starting material. The first and second ones were identical with vanillin (**24**) and the 3,4-dihydroisocarbostyril (**25**)[11], respectively, according to spectroscopic comparisons. The last one was a mixture of *O*-methylorientalinone (**3a** or **3b**) and *O*-methylisoorientalinone (**3b** or **3a**) that differed in configuration at the spiro center. These were separated by fractional recrystallization of the picrolonate.[5] The physical and spectroscopic data of both compounds are described in the experimental section.

Finally, photolysis of the phenolic bromophenethylisoquinoline (**23**) was examined. The isoquinoline (**23**) was synthesised as follows. Fusion of the amine (**11**) with the acid (**10**) afforded the corresponding amide (**13**). Treatment of **13** with ethyl chloroformate, followed by ring closure of the amide (**14**), afforded the 3,4-dihydroisoquinoline (**16**), which was converted to the methiodide (**17**). Reduction of **17** with $NaBH_4$ afforded the expected isoquinoline (**23**) through **22**. The phenolic isoquinoline, thus obtained was irradiated under the same conditions as in the case of **20**. A work-up similar to that of **20** afforded a mixture of *O*-methylkreysiginone (**5a** or **5b**) and its spiro isomer (**5b** or **5a**), which could not be separated, showing a ratio of 1:1 by NMR spectral analysis.[4]

As mentioned above, the photolysis of the phenolic 8-bromoisoquinolines under alkaline conditions was found to be a useful method for synthesising the proaporphines and homoproaporphines.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were taken in $CHCl_3$ solution unless otherwise noted with a Hitachi EPI-S_2 spectrophotometer. NMR spectra were measured on a Hitachi R-20 in $CDCl_3$ solution using TMS as internal reference.

Photolysis of **21**. (a) A mixture of the isoquinoline (**21**) (2·0 g), NaOH (1 g), MeOH (600 ml), and water (400 ml) was irradiated with a 450 W Hanovia mercury lamp using a pyrex filter for 7 hr with water-cooling. After evaporation of MeOH, excess crystalline NH_4Cl was added to the remaining aqueous solution and extracted with $CHCl_3$. The extract was washed with water and dried (Na_2SO_4). Removal of solvent gave a brownish syrup (1·2 g) which was chromatographed on silica gel (35 g). Elution with $CHCl_3$ (fractions 1–13; each of 70 ml) and elution with MeOH–$CHCl_3$ (1:99) (fractions 14–15) were discarded. Evaporation of MeOH–$CHCl_3$ (1:99) fractions (16–22) afforded the dienone fraction (410 mg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1660, 1620. This was rechromatographed on silica gel (15 g). After the $CHCl_3$ eluate was discarded, elution with MeOH–$CHCl_3$ (1:99) yielded the dienone (200 mg). Further rechromatography on neutral alumina (10 g) was carried out using $CHCl_3$ as eluant. Removal of the appropriate fraction gave (±)-pronuciferine (150 mg), m.p. 145–147° (lit.,[3] 147–150°), the spectroscopic data of which were identical with those of the authentic sample.

(b) A mixture of the isoquinoline (**21**) (1 g), NaOH (0·7 g), EtOH (600 ml), Cu powder (0·7 g) and water (400 ml), was irradiated for 7 hr under conditions as above. After removal of Cu powder, the mixture was worked up as above to give (±)-pronuciferine (**2**) (140 mg) in IR spectroscopic pure state, m.p. 145–148°, identical with the above authentic sample.

N-(5-Bromo-3,4-dimethoxyphenethyl)-4-benzyloxy-3-methoxyphenylacetamide (**12**). A mixture of 5-bromo-3,4-dimethoxyphenethylamine (**11**) (8 g) and 4-benzyloxy-3-methoxyphenylacetic acid (**9**) (7 g) was heated for 1·5 hr in a current of N_2. After cooling, the mixture was extracted with $CHCl_3$ (50 ml), washed with 5% $NaHCO_3$, 10% HCl, and water, dried (Na_2SO_4), and evaporated. Recrystallization of resulting solid from EtOH afforded **12** (9 g) as colourless needles, m.p. 113–113·5°. (Found: C, 60·82; H, 5·59; N, 2·75. $C_{26}H_{28}BrNO_5$ requires: C, 60·70; H, 5·49; N, 2·72%). IR $\nu_{max}^{CHCl_3}$: 3370 (NH), 1655 (C=O); NMR ($CDCl_3$) τ: 6·32 (3H, s, $OC\underline{H}_3$), 6·28 (6H, s, 2 × $OC\underline{H}_3$), 5·01 (2H, s, $OC\underline{H}_2Ph$), 3·23–3·59 (5H, m, aromatic protons), 2·79 (5H, s, aromatic protons).

1-(4-*Benzyloxy*-3-*methoxybenzyl*)-8-*bromo*-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (**18**). A mixture of the amide (**12**) (8·5 g), dry benzene (85 ml) and $POCl_3$ (7 ml) was refluxed for 1·5 hr. The mixture was poured into excess *n*-hexane (1 l) and allowed to stand overnight. The precipitate was washed with ether to give the 3,4-dihydroisoquinoline (**15**) hydrochloride (7 g). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1640 (C=N^+<). To a cooled solution of the hydrochloride (7 g) was added in small portions $NaBH_4$ (5 g) within 0·5 hr under stirring. After the addition, the mixture was stirred for a further 0·5 hr at room temp and refluxed for 0·5 hr. The solvent was evaporated and the remaining residue diluted with water and extracted with Et_2O. The extract was washed with water, dried (K_2CO_3) and evaporated to leave a pale yellowish caramel (5·5 g), which was chromatographed on silica gel (60 g). Evaporation of the elution with MeOH–$CHCl_3$ (1:200) afforded the 1,2,3,4-tetrahydroisoquinoline (**18**) (4·8 g), m.p. 121–123° (from EtOH). (Found: C, 62·84; H, 5·74; N, 2·77. $C_{26}H_{28}BrNO_4$ requires: C, 62·55; H, 5·66; N, 2·81%). NMR ($CDCl_3$) τ: 6·29 (3H, s, $OC\underline{H}_3$), 6·26 (3H, s, $OC\underline{H}_3$), 6·23 (3H. s, $OC\underline{H}_3$), 5·08 (2H, s, $OC\underline{H}_2Ph$), 3·55 (1H, s, aromatic proton), 3·31 (2H, s, aromatic protons), 3·24 (1H, s, aromatic proton), 2·73 (5H, s, aromatic protons).

1-(4-*Benzyloxy*-3-*methoxybenzyl*)-8-*bromo*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-2-*methylisoquinoline* (**19**). A mixture of **18** (4·5 g), MeOH (100 ml), and 37% HCHO (10 ml) was stirred for 1 hr at room temp, and refluxed for 0·5 hr. After cooling, to the above stirred mixture was added $NaBH_4$ (5 g) in portions within 1·5 hr. After addition, the mixture was stirred for a further 1·5 hr at room temp and refluxed for 0·5 hr. Solvent was evaporated and the remaining residue diluted with water and extracted with $CHCl_3$. The extract was washed with water and dried (K_2CO_3). The resulting yellowish syrup (43 g) was chromatographed on silica gel (500 g) using $CHCl_3$. Removal of solvent afforded **19** (3·8 g) as a pale yellowish syrup, used for the following reaction without further purification. NMR ($CDCl_3$) τ: 7·62 (3H, s, N–$C\underline{H}_3$), 6·21 (9H, s, 3 × $OC\underline{H}_3$), 4·96 (2H, s, $OC\underline{H}_2Ph$), 3·11–3·50 (4H, m, aromatic protons), 2·72 (5H, s, aromatic protons).

8-*Bromo*-1,2.3.4-*tetrahydro*-1-(4-*hydroxy*-3-*methoxybenzyl*)-6,7-*dimethoxy*-2-*methylisoquinoline* (**20**). A mixture of **19** (3·8 g), conc HCl (30 ml), and EtOH (30 ml) was refluxed for 1·5 hr. After removal of solvent, the residue was made basic with 10% NH_4OH and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4) and evaporated. Recrystallization of the resulting residue from EtOH gave **20** (3·0 g) as colourless prisms, m.p. 136–136·5°. (Found: C, 56·67; H, 5·49; N, 3·64. $C_{20}H_{24}BrNO_4$ requires: C, 56·88; H, 5·73; N, 3·32%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH); NMR ($CDCl_3$) τ: 7·69 (3H, s, N–$C\underline{H}_3$), 6·22 (9H, s, 3 × OCH_3), 3·51 (1H, s, C_5–H), 3·35 (3H, s, aromatic protons).

Photolysis of **20**. A stirred mixture of **20** (1·5 g), NaOH (0·6 g), EtOH (200 ml) and water (800 ml) was irradiated for 7 hr with a 450 W Hanovia mercury lamp equipped with a pyrex filter. After removal of EtOH, to the remaining aqueous solution was added an excess of crystalline NH_4Cl and the mixture was extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4) and evaporated to leave a brownish oil (1·2 g), chromatographed on silica gel (35 g). After the elution with $CHCl_3$ (fractions 1–7: each fraction, 100 ml) had been discarded, evaporation of the elution with the same solvent (fractions 8 and 9) yielded vanillin (33 mg), the spectroscopic data and m.p. of which were identical with those of an authentic sample. Evaporation of the elution with MeOH–$CHCl_3$ (0·5:99·5) (fraction 10) gave a pale yellowish oil, which was further rechromatographed on silica gel (0·5 g) using $CHCl_3$ as eluant. Removal of solvent afforded isocarbostyril (**25**) (10 mg) as pale yellowish needles, m.p. 123–124°, the spectroscopic data of which were identical with those of the authentic sample. The elution with MeOH–$CHCl_3$ (fraction 13) gave isoquinoline **20** (140 mg), and evaporation of the elution with MeOH–$CHCl_3$ (1:99) (fractions 14–18) and MeOH-$CHCl_3$ (2:98) (fractions 19–23) gave a brownish oil (460 mg), which showed dienone absorption bands in the IR spectrum; this was further chromatographed on neutral alumina (20 g) using benzene-$CHCl_3$ (80:20) as eluant. The solvent was removed to leave a mixture of the dienones (**3a** and **3b**) (156 mg; 10·5%). The picrolonate prepared as usual was recrystallized from THF to yield (**3a** or **3b**) as yellowish prisms (75 mg), m.p. 214–217° (decomp.) [lit.,[5] m.p. 215–217° (decomp.)]. (Found: C, 57·21; H, 5·19; N, 11·24. $C_{20}H_{23}NO_4 \cdot C_{10}H_8N_4O_5 \cdot 1·5H_2O$ requires: C, 56·95; H, 5·42; N, 10·07%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1660, 1637, 1609, NMR ($CDCl_3$) τ: 7·59 (3H, s, $NC\underline{H}_3$), 6·49, 6·43, 6·26 (9H, each s, 3 × $OC\underline{H}_3$), 4·15 (1H, d, J = 3 Hz, $\underline{H}_\alpha$-proton adjacent to OMe group), 3·71 (1H, d, J = 10 Hz, $\underline{H}_\alpha$), 3·47 (1H, s, aromatic proton), 3·21 (1H, d, d, J = 3 and 10 Hz, $\underline{H}_\beta$). After removal of the dienone isomer (**3a** or **3b**) the filtrate was treated with EtOH-THF to give yellowish plates (**3b** or **3a**) (68 mg), m.p. 195–199° (decomp.). (Found: C, 59·96; H, 5·61; N, 11·24. $C_{20}H_{23}NO_4 \cdot C_{10}H_8N_4O_5$ requires: C, 59·50; H, 5·16; N, 11·57%). [lit.,[5] 199–201° (decomp.)] IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1656, 1634, 1606, NMR ($CDCl_3$) τ: 7·63 (3H, s, N–$C\underline{H}_3$), 6·46, 6·41, 6·25 (9H, each s, 3 × $OC\underline{H}_3$), 4·10 (1H, d, J = 3 Hz, $\underline{H}_\alpha$-proton adjacent to OMe group), 3·68 (1H, d, J = 10 Hz, $\underline{H}_\alpha$), 3·45 (1H, s, aromatic proton), 3·19 (1H, d, d, J = 3 Hz, and 10 Hz, $\underline{H}_\beta$).

N-(5-*Bromo*-3.4-*dimethoxyphenethyl*)-4-*hydroxy*-3-*methoxyphenylpropionamide* (**13**). A mixture of the

amine (**11**) (6·6 g) and 4-hydroxy-3-methoxyphenylpropionic acid (**10**) (7 g) was heated at 180° in a current of N_2 for 1 hr. After cooling, the mixture was extracted with $CHCl_3$. The extract was washed with 10% HCl, saturated $NaHCO_3$ and water, and dried (K_2CO_3). Removal of solvent afforded a brownish oil (11 g), which was chromatographed on silica gel (150 g) using $CHCl_3$ as eluant. Evaporation of solvent gave the amide (**13**) (9·5 g) as a pale brownish oil, used for the following reaction without purification. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH), 3400 (NH), 1655 (C=O); NMR ($CDCl_3$) τ: 6·23 (9H, s, 3 × $OC\underline{H}_3$), 3·39 (3H, s, aromatic protons), 3·31 (1H, s, aromatic proton), 3·15 (1H, s, aromatic proton).

N-(*5-Bromo-3.4-dimethoxyphenethyl*)-*4-ethoxycarbonyloxy-3-methoxyphenylpropionamide* (**14**). To a stirred mixture of the amide (**13**) (9·5 g), Et_3N (3·0 g), and $CHCl_3$ (80 ml) was added dropwise ethyl chlorocarbonate (3·0 g) within 0·5 hr under ice-cooling. After the stirring had been continued for 40 min, the mixture was washed with 10% HCl and H_2O, and dried over Na_2SO_4. Removal of solvent afforded a brownish oil (11 g), chromatographed on silica gel (150 g) using $CHCl_3$ as an eluant. Evaporation of solvent gave the amide (**14**) (10·5 g), used for the following reaction. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (NH), 1752 (OCOOEt), 1655 (amide CO). NMR ($CDCl_3$) τ: 8·71 (3H, t, J = 7 Hz, $CH_2C\underline{H}_3$), 6·36 (9H, s, 3 × $OC\underline{H}_3$), 5·9 (2H, q, J = 7 Hz, $-C\underline{H}_2CH_3$).

8-*Bromo*-1-(*4-ethoxycarbonyloxy-3-methoxyphenethyl*)-3.4-*dihydro*-6.7-*dimethoxyisoquinoline* (**16**). A mixture of **14** (11 g), $POCl_3$ (25 ml), and dry benzene (200 ml) was refluxed for 1·5 hr. The solvent was evaporated, and the remaining residue washed with Et_2O, and extracted with $CHCl_3$. The extract was washed with 10% NH_4OH and water, and dried (Na_2SO_4). Removal of solvent gave a brownish oil (10 g), which was chromatographed on silica gel (180 g) using $CHCl_3$ as an eluant. The solvent was evaporated to leave **16** (9·0 g) as a pale yellowish oil, used for the following reaction without further purification because of difficulty of crystallization. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1755 (OCOOEt). NMR ($CDCl_3$) τ: 8·68 (3H, t, J = 7 Hz, $CH_2C\underline{H}_3$), 6·32, 6·30, 6·23 (9H, each s, 3 × $OC\underline{H}_3$), 5·86 (2H, q, J = 7 Hz, $C\underline{H}_2CH_3$), 3·48 (1H, s, aromatic proton), 3·43 (2H, s, aromatic protons), 3·31 (1H, s, aromatic proton).

8-*Bromo*-1,2,3,4-*tetrahydro*-1-(*4-hydroxy-3-methoxyphenethyl*)-6,7-*dimethoxy*-2-*methylisoquinoline* (**23**). A mixture of **16** (9·0 g), MeI (18 ml) and MeOH (50 ml) was refluxed for 3 hr. Removal of the solvent afforded **17** (9·5 g) as a brownish syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750 (OCOOEt), 1610 (C=N). To a stirred solution of **17** (9·5 g) in MeOH (80 ml) was added in small portions $NaBH_4$ (5·0 g) under ice-cooling within 0·5 hr. After the stirring for an additional 1 hr, the mixture was refluxed for 0·5 hr. Solvent was evaporated and the remaining residue diluted with water. After the addition of an excess of crystalline NH_4Cl the mixture was extracted with $CHCl_3$. The extract was washed with water and dried (Na_2SO_4). Removal of solvent afforded a brownish syrup (8·5 g), chromatographed on silica gel using $CHCl_3$ as eluant. The solvent was removed to leave **22** (7 g) as a pale yellowish oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH). NMR ($CDCl_3$) τ: 7·63 (3H, s, $NC\underline{H}_3$), 6·29, 6·26, 6·21, (9H, each s, 3 × $OC\underline{H}_3$), 4·36 (1H, broad, s, OH, disappeared with D_2O), 3·15 (1H, s, aromatic proton), 3·29 (3H, s, aromatic protons). The hydrochloride prepared as usual was recrystallized from MeOH–Et_2O to give colourless prisms, m.p. 149–155°. (Found: C, 53·74; H, 6·05; N, 2·87. $C_{21}H_{27}BrClNO_4$ requires: C, 53·34; H, 5·76; N, 2·96%).

Photolysis of **23**. A mixture of **23** (4 g), 10% NaOH (20 ml), and EtOH (50 ml) was diluted to 1 l with EtOH–H_2O (1:3). This mixture was irradiated for 7 hr under the same conditions as before. After the usual work-up, the crude product (3·5 g), obtained on evaporation of solvent, was chromotographed on silica gel (90 g). After the elution with $CHCl_3$ (fractions 1–4; each fraction, 200 ml) was discarded, removal of the elution with MeOH–$CHCl_3$ (0·5:99·5) (fractions 5 and 6) and MeOH–$CHCl_3$ (1:99) (fractions 7–12) gave the isoquinoline **23**. After the elution with MeOH–$CHCl_3$ (1:99) (fractions 13–18) and MeOH–$CHCl_3$ (3:97) (fractions 19–20) was discarded, the MeOH–$CHCl_3$ (3:97) (fractions 21–25) and MeOH–$CHCl_3$ (5:45) eluates (fractions 26–32) were evaporated to give the dienones as a brownish syrup (314 mg), further chromatographed on neutral alumina (10 g) using $CHCl_3$-benzene (1:9). Removal of solvent afforded a mixture of dienones (**5a** and **5b**) (140 mg) as a pale yellowish caramel, whose NMR spectra showed a mixture of **5a** and **5b**[4] (1:1). The picrate prepared as usual was recrystallized from Me_2CO–hexane to give yellow plates, m.p. 207–211° (decomp.). (Found: C, 55·48; H, 4·94; N, 9·71. $C_{21}H_{25}NO_4$ requires: C, 55·48; H, 4·83; N, 9·59%). All attempts to separate the isomers resulted in failure.

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