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SOME SYNTHETIC STUDIES IN THE ISOQUINOLINE SERIES

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Abstract—The synthesis of some new phenolic N-acyl-1-benzyl-1,2,3,4-tetrahydroisoquinolines (**18**, **20**, **21**, and **27**) is described; oxidation of the latter compounds under various conditions afforded no isolable products. The structures of doryafranine (**8**) and doryanine (**33**), alkaloids from *Doryphora sassafras*, are confirmed by synthesis. The advantageous use of the N-carbethoxy group as the precursor of the N-methyl group of N-methyl-1,2,3,4-tetrahydroisoquinolines is illustrated in new syntheses of the alkaloids armepavine (**5**) and N-methylcoclaurine (**6**).

THE oxidation of a simple phenolic benzyltetrahydroisoquinoline has been recognized as the key step in the biogenesis of more complex alkaloid types,[2] including the bisbenzylisoquinolines, the aporphines, and the recently discovered proaporphines.[3] Since 1962, examples of successful oxidative laboratory syntheses of all three of the latter alkaloid types have been reported. [4] Although phenolic precursors containing a basic nitrogen have been employed, the best results were obtained when the nitrogen atom was protected from oxidation by quaternization. We now report some attempts to synthesize compounds of the bisbenzylisoquinoline, aporphine, and proaporphine groups by the oxidation of appropriate phenolic benzylisoquinolines in which the nitrogen atom has been protected by acylation. Our three synthetic goals were the proaporphine derivative N-acetylstepharine (**4**), the bisbenzylisoquinoline base dauricine (**1**) and the aporphine base isoboldine (**2**).

Although our oxidation experiments were unsuccessful, we found that the N-carbethoxy derivatives of 1-benzyl-1,2,3,4-tetrahydroisoquinolines are usually highly crystalline intermediates which can be used to advantage in the synthesis of the corresponding N-methyl bases. In this way, improved practical syntheses of the alkaloids armepavine (**5**) and N-methylcoclaurine (**6**) were devised, as well as an unambiguous synthesis of doryafranine (**8**). The structure of the simple isoquinolone alkaloid doryanine (**33**) was also confirmed by synthesis.

Synthesis and oxidation of some phenolic N-*acyl*-1-*benzyl*-1,2,3,4-*tetrahydroisoquinolines*. Sodium borohydride reduction of the known[5] 1-(*p*- benzyloxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride (**11**) gave the corresponding crystalline tetrahydroisoquinoline (**14**), m.p. 94–95°. Reaction of **14** with ethyl chloroformate in pyridine gave the N-carbethoxy derivative **15** (m.p. 97–99°), hydrogenolysis of which yielded N-carbethoxy-N-norarmepavine (**21**, m.p. 170–171°). Potassium ferricyanide oxidation of **21** was carried out, followed by lithium aluminum

hydride reduction of the crude oxidation product. Thin layer examination of the resulting base mixture gave no indication of the presence of dauricine (**1**). It may be concluded, therefore, that no appreciable dimeric C—O coupling to give an *o*-hydroxydiphenyl ether took place in the oxidation of **21** under the conditions employed.

Sodium borohydride reduction of the known[6] 1-(*p*-benzyoxybenzyl)-6-methoxy-7-benzyloxy-3,4-dihydroisoquinoline hydrochloride (**12**) gave the corresponding oily tetrahydro base (**24**), converted by acetic anhydride into its crystalline N-acetyl derivative (**19**), m.p. 133–135°. Hydrogenolysis of **19** afforded N-acetylcoclaurine (**20**), m.p. 237–239°. Oxidation of **19** with lead tetraacetate or ferric chloride in chloroform, followed by methylation of the crude product, gave a mixture which was examined carefully for the presence of N-acetylstepharine (**3**).[7] It was found that authentic **4** was readily detected in very small amounts by thin layer chromatography, followed by development of an orange spot by spraying with acidic 2,4-dinitrophenylhydrazine solution. It was readily determined that the methylated oxidation products derived from **19** contained no detectable quantity of **4**.

A second approach to N-acetylstepharine involved the synthesis of 1-(*p*-hydroxybenzyl)-2-acetyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (**18**), which was obtained in the following manner. 3,4-Dibenzyloxybenzaldehyde[8] was condensed with nitromethane in acetic acid in the presence of ammonium acetate to give 3,4-dibenzyloxy-β-nitrostyrene (**37**), m.p. 117–118°, in 74% yield. Reduction of **37** with LAH gave (90%) the oily 3,4-dibenzyloxy-β-phenylethylamine (**38**), characterized as its crystalline N-acetyl derivative (**39**), m.p. 110–111°. Reaction of amine **38** with the acid chloride of *p*-benzyloxyphenylacetic acid gave, in 62% yield, amide **40**, m.p. 122–124°. Cyclization of amide **40** with phosphorus pentachloride in chloroform gave, in 72% yield, the dihydroisoquinoline hydrochloride **13**, m.p. 154–160°. Sodium borohydride reduction of **13** gave the corresponding oily tetrahydroisoquinoline, which was acetylated directly to give the crystalline N-acetyl derivative **17**, m.p. 143–144°, in 72% overall yield. Hydrogenolysis of **17** gave the desired triol **18** in 93% yield as an amorphous glass. Following the procedure of Robinson and Sugasawa in the oxidation of laudanosoline,[9] triol **18** was reacted with chloranil in the hope that oxidation to an *o*-quinone (**34**) would take place, followed by an internal Michael addition to give dienone **35**. Methylation of the crude product gave no material, however, which corresponded to N-acetylstepharine (**4**) by thin layer analysis.

In view of the recent successful oxidation of reticuline methochloride (**28**) to laurifoline chloride (**3**),[4c] it was of interest to examine the oxidation of N-carbethoxy-N-norreticuline (**27**). Sodium borohydride reduction of the known 1-(3)-benzyloxy-4-methoxybenzyl)-6-methoxy-7-benzyloxy-3,4-dihydroisoquinoline hydrochloride (**36**)[10] gave the corresponding oily tetrahydroisoquinoline (**25**) which was acylated directly with ethyl chloroformate to give the crystalline N-carbethoxy derivative (**26**), m.p. 134–135°; in 67% overall yield. Hydrogenolysis of **26** yielded the desired dihydric phenol (**27**) as a colorless gum. Compound **27** was subjected to alkaline ferricyanide oxidation and the resulting product was reduced directly by LAH. The basic reduction product showed no UV absorption band around 300 mμ, indicating the absence of any appreciable yield of the desired aporphine isoboldine (**2**). An authentic comparison sample of **2** was, unfortunately, not available to us at the time of this work so that it is not possible to state unambiguously that **2** was not present in low yield.

It is of interest to note that the synthesis and oxidation of a number of phenolic N-formyl-1-benzyl-1,2,3,4-tetrahydroisoquinolines was reported recently in an independent study by other investigators.[11] The oxidative aspects of this work were as unsuccessful as those of our work with related N-acetyl and N-carbethoxy compounds.

The synthesis of some alkaloids from Doryphora sassafras. A phytochemical study of the Australian tree *Doryphora sassafras* Endlicher (Monimiaceae) resulted in the isolation of the new alkaloids (+)-doryafranine and doryanine; analytical and spectral data suggested that these bases probably had structures **8** and **33**, respectively.*[12] We now offer synthetic confirmation of the assigned structures of these natural bases.

Previous to the isolation of the crystalline (+)-doryafranine, the literature records three claims for the synthesis of the racemic form of **8**; in all three cases the compound was reported as an oil. In the first reported synthesis, Bischler-Napieralski cyclization of crystalline amide **29** gave the oily dihydroisoquinoline **30**; reaction of **30** with methyl iodide gave a crystalline methiodide, which was reduced catalytically to **8**.[14] Some years later, **8** was prepared by formic acid formaldehyde methylation of the amorphous secondary base **10**;[15] the sample of **10** used was regenerated from its hydrochloride (**9**), which in turn was obtained by reduction of the originally prepared sample of **31**.[14] More recently still, a sample of **8** was isolated as a deaminative by-product of a diazonium salt during a Pschorr ring closure; it was characterized only as its methiodide.[16] In the present study, phosphorus pentachloride cyclization of amide **29** gave, in 63% yield, the crystalline dihydroisoquinoline hydrochloride (**31**), m.p. 200–203°; sodium borohydride reduction of **31** gave the oily tetrahydroisoquinoline **10**, isolated in 88% yield as the hydrate of its hydrochloride (**9**), m.p. 115–118°. Acylation of **9** with ethyl chloroformate in pyridine gave, in 74% yield, the crystalline N-carbethoxy derivative **7**, m.p. 113–114°. Lithium aluminum hydride reduction of **7** afforded, in 83% yield, (±)-doryafranine (**8**) as colorless prismatic needles, m.p. 76–78°. The IR and NMR spectra of the synthetic racemate were identical with those of natural (+)-doryafranine, m.p. 92–94. Doryafranine represents the first *simple* benzyltetrahydroisoquinoline alkaloid which contains the methylenedioxy group.[17]

The spectral data for the alkaloid doryanine were in accord with either the isoquinolone structure **33** or with the isomeric quinolone structures **42** and **43**.[12] Structure **33** seemed more likely in view of the isolation of other isoquinoline alkaloids (i.e., doryafranine and liriodenine) from the same plant source. In our first attempt to synthesize **33**, the dihydroisoquinolone **44** was chosen as a likely intermediate, since dehydrogenation of **44** should give the aromatic isoquinoline **45**. An uncuccessful attempt to cyclize the styryl urethane **41** to **45** has been described, although the same report describes the reduction of **41** to the dihydro derivative **46**, followed by cyclization of the latter to **44**.[18] In the present study, compound **44** was more conveniently prepared by the phosphorus oxychloride cyclization of the ethyl urethane **47**, obtained by the action of ethyl chloroformate on 3,4-methylenedioxy-β-phenylethylamine. Several attempts to dehydrogenate **44** to **45** using either palladium catalyst or chloranil led to negative results. The desired goal was attained, however, by subjecting the known 6,7-methylenedioxyisoquinoline methiodide (**32**)[19] to alkaline ferricyanide

* The stereochemistry of natural (+)-doryafranine was not discussed in Ref. 12. One may confidently assign to it the L (or S) configuration at C-1, since the similarly substituted (−)-armepavine has been shown to have D (or R) configuration at C-1.[13]

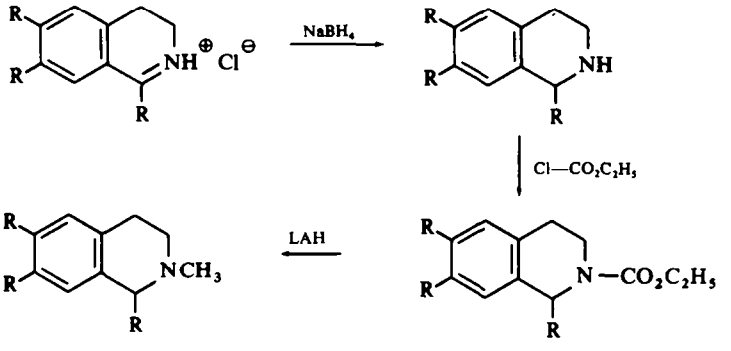
oxidation. The resulting N-methyl-6,7-methylenedioxyisoquinolone (**33**), m.p. 165–167°, was identical with natural doryanine. Doryanine represents the first example of the natural occurrence of a simple aromatic isoquinolone.*

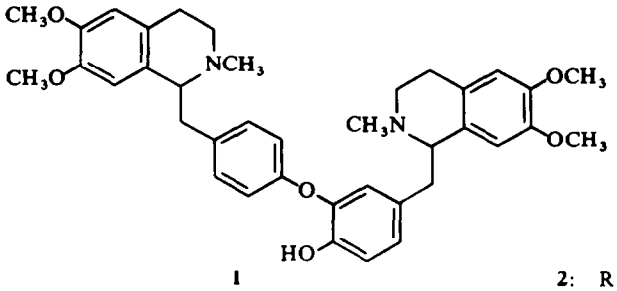
New syntheses of armepavine and N-*methylcoclaurine*. The ease of preparation and purification of the crystalline urethane **15** made this substance an excellent starting material for a new practical synthesis of armepavine (**5**). Thus, lithium aluminum hydride reduction of **15** afforded the oily *o*-benzylarmepavine, isolated in 80% yield as its hydrochloride (**16**), m.p. 192–196°. Hydrogenolysis of **16** gave, in 77% yield, (±)-armepavine (**5**), m.p. 166–167°.

A similar new practical synthesis of N-methylcoclaurine (**6**) was readily devised from the known dihydroisoquinoline hydrochloride **12**.[6] Reduction of **12** with sodium borohydride and direct acylation of the resulting oily base (**24**) with ethyl chloroformate gave, in 74% yield, the crystalline urethane **22**, m.p. 105–107°. LAH reduction of **22** gave, in 79% yield, O, O-dibenzyl-N-methylcoclaurine, isolated as its hydrochloride (**23**), m.p. 173–175°. Hydrogenolysis of **23** gave crystalline (±)-N-methylcoclaurine (**6**), m.p. 161–163°, in 83% yield.

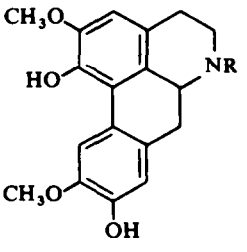
The simple synthetic sequence drawn below (Scheme 1) would seem to be worthy of further application in the area of benzylisoquinoline alkaloid synthesis on the basis of the examples described in this paper.

SCHEME 1



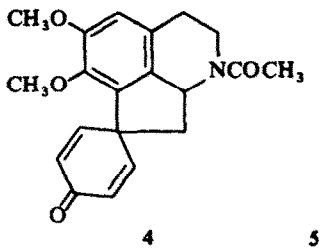


1



2: R = CH_3
3: R = $(CH_3)_2Cl$

* The isolation of a second simple isoquinolone alkaloid from natural sources was reported recently.[20] It should be pointed out that a double bond was inadvertently omitted from the structure of this base (N-methyl-6,7-dimethoxyisoquinolone) in the above cited communication.



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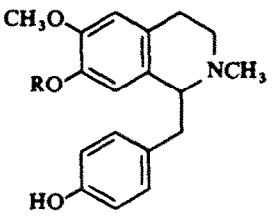
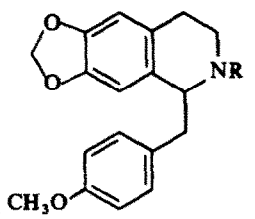
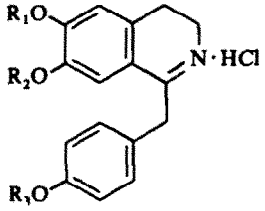


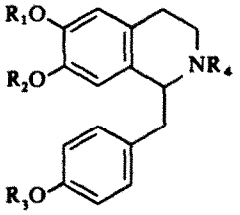
5: R = CH_3
6: R = H



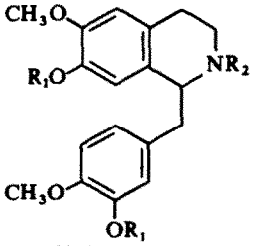
7: R = $CO_2C_2H_5$
8: R = CH_3
9: R = H·HCl
10: R = H



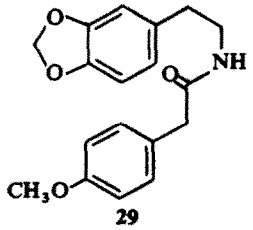
11: $R_1 = R_2 = CH_3$; $R_3 = CH_2C_6H_5$
12: $R_1 = CH_3$; $R_2 = R_3 = CH_2C_6H_5$
13: $R_1 = R_2 = R_3 = CH_2C_6H_5$



14: $R_1 = R_2 = CH_3$; $R_3 = CH_2C_6H_5$; $R_4 = H$
15: $R_1 = R_2 = CH_3$; $R_3 = CH_2C_6H_5$; $R_4 = CO_2C_2H_5$
16: $R_1 = R_2 = CH_3$; $R_3 = CH_2C_6H_5$; $R_4 = CH_3$·HCl
17: $R_1 = R_2 = R_3 = CH_2C_6H_5$; $R_4 = COCH_3$
18: $R_1 = R_2 = R_3 = H$; $R_4 = COCH_3$
19: $R_1 = CH_3$; $R_2 = R_3 = CH_2C_6H_5$; $R_4 = COCH_3$
20: $R_1 = CH_3$; $R_2 = R_3 = H$; $R_4 = COCH_3$
21: $R_1 = R_2 = CH_3$; $R_3 = H$; $R_4 = CO_2C_2H_5$
22: $R_1 = CH_3$; $R_2 = R_3 = CH_2C_6H_5$; $R_4 = CO_2C_2H_5$
23: $R_1 = CH_3$; $R_2 = R_3 = CH_2C_6H_5$; $R_4 = CH_3$·HCl
24: $R_1 = CH_3$; $R_2 = R_3 = CH_2C_6H_5$; $R_4 = H$



25: $R_1 = CH_2C_6H_5$; $R_2 = H$
26: $R_1 = CH_2C_6H_5$; $R_2 = CO_2C_2H_5$
27: $R_1 = H$; $R_2 = CO_2C_2H_5$
28: $R_1 = H$; $R_2 = (CH_3)_2Cl$



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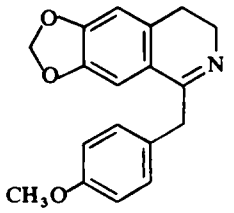

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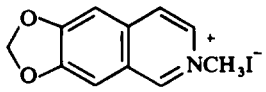

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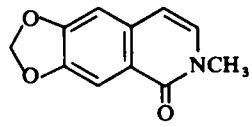
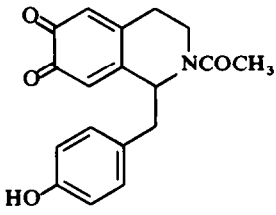


33

31: HCl salt of **30**



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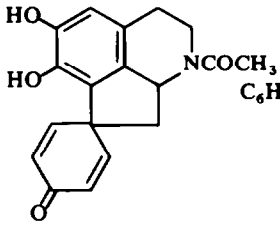

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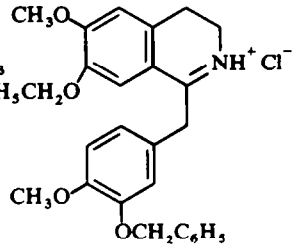

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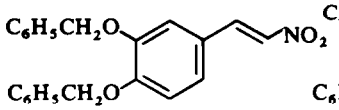

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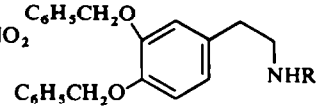
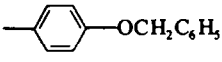
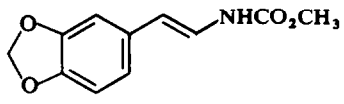


38: R = H
39: R = $COCH_3$
40: R = $COCH_2$ — 



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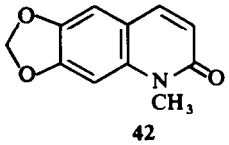

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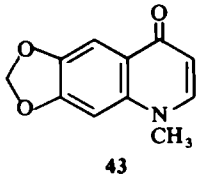

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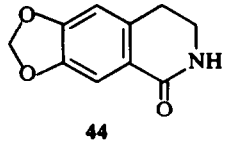

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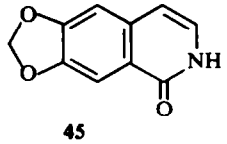

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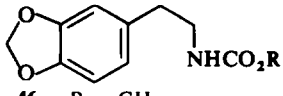

46: R = CH_3
47: R = C_2H_5

EXPERIMENTAL

M.p. were determined on a Fisher m.p. block and are uncorrected. Analyses were carried out by Dr. A. Bernhardt, Mulheim, Germany and by Midwest Microlab, Inc., Indianapolis, Indiana.

1-(p-*Methoxybenzyl*)-6,7-*methylenedioxy*-3,4-*dihydroisoquinoline hydrochloride* (**31**). A solution of **29**[14]. (3·0 g) in $CHCl_3$ (25 ml) was cooled in a dry ice–acetone bath and P_2O_5 PCl_5 (3·0g) was added. The reaction was allowed to stand at room temp for 24 hr and then EtOH (10 ml) was added dropwise with stirring. The $CHCl_3$ was evaporated, water (10 ml) was added and the resulting soln was extracted twice with ether (200 ml portions) to remove unreacted starting material. The aqueous layer was extracted twice

with $CHCl_3$ (100 ml portions) and the combined $CHCl_3$ extracts were dried (Na_2SO_4) and evaporated. The residual oil gave yellow crystals (2·0 g, 63%), m.p. 192–195° (dec), from ether-EtOH. The analytical sample, m.p. 200–203° (dec), was recrystallized from a small amount of absolute EtOH. (Found: C, 64·76; H, 5·57; N, 4·28. Calc. for $C_{18}H_{18}NO_3Cl$: C, 65·16; H, 5·47; N, 4·22%).

1-(p-*Methoxybenzyl*)-6,7-*methylenedioxy*-1,2,3,4-*tetrahydroisoquinoline hydrochloride* (**9**). Sodium borohydride (0·3 g) was added in portions with stirring to a soln of **31** (1·6 g) in MeOH (10 ml). As soon as the reaction subsided, water (50 ml) was added and the mixture was extracted twice with ether (50 ml portions). The extracts were dried ($MgSO_4$) and the solvent was evaporated to give an almost colorless oil. Treatment of the oil with 10% HCl (10 ml) gave colorless crystals of **9** (1·5 g, 88%), m.p. 117–122°. The analytical sample was recrystallized from water and had m.p. 115–118°, lit.[14] 105°. (Found: C, 61·68; H, 6·39; N, 4·15. Calc. for $C_{18}H_{20}NO_3Cl \cdot H_2O$: C, 61·45; H, 6·30; N, 3·98%).

1-(p-*Methoxybenzyl*)-2-*carbethoxy*-6,7-*methylenedioxy*-1,2,3,4-*tetrahydroisoquinoline* (**7**). A stirred soln of **9** (1·0 g) in $CHCl_3$ (20 ml) and pyridine (3 ml) was cooled in an ice bath and ethyl chloroformate (2 ml) was added dropwise. The soln was then warmed for 5 min on the steam bath. The $CHCl_3$ was evaporated, water (20 ml) was added and the mixture was extracted twice with ether (50 ml portions). The combined ether extracts were washed successively with 10% HCl, 10% $NaHCO_3$ aq and water. Removal of the solvent, followed by crystallization from cyclohexane, gave colorless microcrystals (0·82 g, 74%), m.p. 110–113°. The analytical sample crystallized from cyclohexane as star-shaped clusters of platelets, m.p. 113–114°. (Found: C, 68·28; H, 6·28; N, 4·05. Calc. for $C_{21}H_{23}NO_5$: C, 68·18; H, 6·22; N, 4·23%).

The urethane (**7**) was also prepared from amide **29**, in overall 43% yield, without characterization or purification of the intermediates.

1-(p-*Methoxybenzyl*-2-*methyl*-6,7-*methylenedioxy*-1,2,3,4-*tetrahydroisoquinoline* (**8**): (±)-*doryafranine*. LAH (1·0 g) was added to a soln of **7** (3·0 g) in THF (150 ml). The reaction mixture was refluxed for 2 hr, cooled to room temp, and sat Na_2SO_4 aq was added dropwise with stirring to decompose excess hydride. The inorganic ppt was removed by filtration and washed with THF. Evaporation of the THF gave a light yellow oil which was crystallized from cyclohexane as colorless prismatic needles (2·1 g, 83%), m.p. 77–81°. Recrystallization from cyclohexane gave the analytical sample, m.p. 76–78°. (Found: C, 73·08; H, 6·80; N, 4·60. Calc. for $C_{19}H_{21}NO_3$: C, 73·29; H, 6·80; N, 4·50%).

The soln IR and NMR spectra of **8** were identical to those of natural (+)-doryafranine.[12] The picrate of **8** crystallized from acetone–ether as yellow microcrystals, m.p. 160–162° (lit.,[14] orange-red, m.p. 179–180°). (Found: C, 55·26; H, 4·46; N, 10·46. Calc. for $C_{25}H_{24}N_4O_{10}$: C, 55·55; H, 4·48; N, 10·37%).

The methiodide of **8** was prepared in acetone soln and formed colorless prisms, m.p. 177–179° (lit., 184°[14] and 187–189°[16]). The analytical sample was recrystallized twice from 95% EtOH. (Found: C, 51·33; H, 5·50; N, 2·83. Calc. for $C_{20}H_{24}NO_3I$: C, 51·71; H, 5·48; N, 3·17%).

N-3,4-*Methylenedioxy*-β-*phenylethylurethane* (**47**). A soln for 3,4-methylenedioxy-β-phenylethylamine (10 g) in $CHCl_3$ (100 ml) was cooled in ice and ethyl chloroformate (10 ml) followed by pyridine (10 ml) was added slowly. The reaction was warmed 5 min on the steam bath and then the solvent was evaporated and water (100 ml) was added to the residue. Work-up of the neutral product in the usual manner, followed by crystallization from cyclohexane–benzene (charcoal decolorization), gave colorless leaflets (4·5 g, 33%), m.p. 38–39°. The analytical sample was recrystallized from benzene–cyclohexane. (Found: C, 60·79; H, 6·42; N, 6·11. Calc. for $C_{12}H_{15}NO_4$: C, 60·75; H, 6·37; N, 5·90%).

6,7-*Methylenedioxy*-3,4-*dihydroisoquinolone* (**44**). A soln of urethane **47** (8·5 g) in $CHCl_3$ (15 ml) and $POCl_3$ (24 ml) was refluxed gently for 48 hr. $CHCl_3$ and some of the $POCl_3$ were removed on a rotary evaporator, the dark brown residue was dissolved in water (50 ml) and the soln was extracted twice with ether (50 ml portions). The aqueous soln was basified with NH_4OH and cooled in an ice bath. The product which separated was filtered and washed with water to give light tan plates (4·5 g, 66%), m.p. 180–185°. Recrystallization of a small sample from benzene–skellysolve B gave colorless plates, m.p. 185–186° (lit.,[18] 182–183°).

Attempted dehydrogenation of the dihydroisoquinolone (**44**). Heating **44** in a salt bath at 300° for 45 min with an equal weight of 5% Pd–C and extraction of the mixture with MeOH gave a very small yield of an oil which did not crystallize.

Refluxing **44** with chloranil (2·2 equiv) in xylene for 72 hr followed by evaporation of the solvent, extraction of the residue with 10% NaOH and dilution with water gave a small amount of black gum which could not be purified.

N-*Methyl*-6,7-*methylenedioxyisoquinolone* (*doryanine*) (**33**). KOH (200 mg) and $K_3Fe(CN)_6$ (200 mg) were added to a soln **32**[19] (100 mg) in water (5 ml) and the reaction mixture was refluxed 30 min. After

cooling, the mixture was extracted twice with ether (25 ml portions). Evaporation of the dried ($MgSO_4$) extracts, followed by crystallization from cyclohexane gave almost colorless plates (20 mg, 31%), m.p. 165–167°. The m.p. and IR spectrum of **33** were identical to those of a purified sample of doryanine.[12]

1-(p-*Benzyloxybenzyl*)-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline* (**14**). Sodium borohydride (0·25 g) was added in small portions with stirring to a soln of **11**[5] (1·0 g) in MeOH (10 ml). The reaction mixture was stirred an additional 30 min at room temp and then water (30 ml) was added. Work-up in the usual manner, followed by crystallization from EtOH–water gave almost colorless crystals (0·74 g, 81%). The analytical sample was recrystallized twice from EtOH–water to give colorless leaflets, m.p. 94–95°. (Found: C, 77·03; H, 6·82; N, 3·87. Calc. for $C_{25}H_{27}NO_3$: C, 77·09; H, 6·99; N, 3·60%).

1-(p-*Benzyloxybenzyl*)-2-*carbethoxy*-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline* (**15**). Sodium borohydride (1·2 g) was added in small portions to a stirred solution of **11**[5] (5·0 g) in MeOH (50 ml). After 30 min at room temp, the soln was diluted with water (150 ml) and the precipitated oil was extracted twice with ether (250 ml portions). The combined organic layers were dried (Na_2SO_4) and evaporated. The residual oil was dissolved in $CHCl_3$ (50 ml), the soln was cooled in ice and pyridine (5 ml), followed by ethyl chloroformate (5 ml) were added with stirring. The mixture was then warmed 5 min on the steam bath. Work-up in the usual manner, followed by crystallization from MeOH–water gave colorless prismatic needles (4·2 g, 77%), m.p. 95–98°. The analytical sample, m.p. 97–99°, was recrystallized twice from EtOH. (Found: C, 72·74; H, 6·85; N, 3·42. Calc. for $C_{28}H_{31}NO_5$: C, 72·86; H, 6·77; N, 3·04%).

1-(p-*Hydroxybenzyl*)-2-*carbethoxy*-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline* (**21**). To a soln of **15** (3·00 g) in MeOH (170 nl) was added 5% Pd–C (750 mg) and the mixture was hydrogenated for 16 hr at 40 pounds press. Evaporation of the filtered soln, followed by crystallization from MeOH–water gave colorless plates (2·02 g, 84%), which melted at 84–87° with loss of solvent of crystallization. The analytical sample, m.p. 170–171°, was recrystallized twice from absolute EtOH. (Found: C, 68·02; H, 6·84; N, 3·93. Calc. for $C_{21}H_{25}NO_5$: C, 67·90; H, 6·78; N, 3·77).

1-(p-*Benzyloxybenzyl*)-2-*methyl*-6,7-dimethoxy-1,2,3,4-*tetrahydroisoquinoline hydrochloride* (**16**). LAH (0·10 g) was added to to a soln of **15** (300 mg) in THF (15 ml). The reaction mixture was refluxed for 4 hr, cooled to room temp, and excess hydride decomposed by added satd Na_2SO_4 aq. The ppt of inorganic salts was removed by filtration and washed well with THF. Evaporation of the solvent gave an oil which was treated with 10% HCl aq (2 ml). Colorless plates of the amine hydrochloride (271 mg, 80%), m.p. 192–196°, separated rapidly. The analytical sample was recrystallized twice from absolute EtOH. (Found: C, 71·27; H, 6·63; N, 3·26. Calc. for $C_{26}H_{30}NO_3Cl$: C, 70·97; H, 6·87; N, 3·18%).

1-(p-*Hydroxybenzyl*)-2-*methyl*-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline*: (±)-*armepavine* (**5**). To a soln of **16** (8·4 g) in MeOH (250 ml) was added 5% Pd–C (1 g) and the mixture was hydrogenated at 40 pounds press. The reaction was complete within 5 hr. Evaporation of the filtered soln gave a colorless oil which was converted to the free base by treatment with NH_4OH. The product crystallized on scratching and was filtered and washed with a small amount of water. Recrystallization from acetone–ether gave colorless microcrystals (4·6 g, 77%), m.p. 166–167° (lit.. 166°[5,21]).

1-(p-*Benzyloxybenzyl*)-2-*acetyl*-6-*methoxy*-7-*benzyloxy*-1,2,3,4-*tetrahydroisoquinoline* (**19**). Sodium borohydride (1·3 g) was added slowly with stirring to a soln of **12**[6] (5·0 g) in MeOH (50 ml). The usual work up afforded a gum which was dissolved in pyridine (10 ml) and Ac_2O (10 ml). After warming 15 min on the steam bath, the reaction mixture was diluted with water (100 ml). The neutral product crystallized from EtOH–water as colorless matted needles (2·8 g, 55%), m.p. 133–135°, The analytical sample was recrystallized from absolute EtOH. (Found: C, 77·97; H, 6·59; N, 2·83. Calc. for $C_{33}H_{33}NO_4$: C, 78·08; H, 6·55; N, 2·77%).

1-(p-*Hydroxybenzyl*)-2-*acetyl*-6-*methoxy*-7-*hydroxy*-1,2,3,4-*tetrahydroisoquinoline* (**20**). To a soln of **19** (2·0 g) in acetone (200 ml) was added 5% Pd–C (1·0 g) and the mixture was hydrogenated 15 hr at 40 pounds press. Evaporation of the filtered soln followed by crystallization from MeOH–water gave colorless microcrystals (0·67 g, 52%), m.p. 237–239°. The analytical sample crystallized from acetone as colorless plates. (Found: C, 69·47; H, 6·39; N, 4·58. Calc. for $C_{19}H_{21}NO_4$: C, 69·70; H, 6·47; N, 4·28%).

1-(3-*Benzyloxy*-4-*methoxybenzyl*)-2-*carbethoxy*-6-*methoxy*-7-*benzyloxy*-1,2,3,4-*tetrahydroisoquinoline* (**26**). Sodium borohydride (1·0 g) was added in small portions with stirring to a soln of **36**[10] (5·0 g) in MeOH (50 ml). The reaction mixture was stirred an additional 15 min at room temp, water (150 ml) was added, and the product was extracted into ether. Evaporation of the dried extracts gave a residue which was dissolved in $CHCl_3$ (50 ml), and pyridine (5 ml) and then ethyl chloroformate (5 ml) was added with

cooling and stirring. The mixture was warmed 5 min on the steam bath and the solvent was then removed on a rotary evaporator. Work-up of the neutral product in the usual manner, followed by crystallization from MeOH containing a small amount of $CHCl_3$ gave colorless microcrystals (3·6 g, 67%), m.p. 136–138°. The analytical sample, m.p. 134–135°, was recrystallized twice from benzene–cyclohexane. (Found: C, 74·02; H, 6·70; N, 2·44. Calc. for $C_{35}H_{37}NO_6$: C, 74·05; H, 6·57; N, 2·47%).

1-(p-*Benzyloxybenzyl*)-2-*carbethoxy*-6-*methoxy*-7-*benzyloxy*-1,2,3,4-*tetrahydroisoquinoline* (**22**). Sodium borohydride (0·8 g) was added slowly with stirring to a soln of **12** (3·00 g) in MeOH (30 ml). After stirring an additional 5 min, isolation of the basic product gave a gum which was dissolved in a mixture of $CHCl_3$ (75 ml) and pyridine (6 ml), to which ethyl chloroformate (6 ml) was added cautiously with stirring. The mixture was warmed 5 min on the steam bath and the $CHCl_3$ was than evaporated. Work-up of the neutral product in the usual manner gave an oil which crystallized from 95% EtOH as almost colorless microcrystals (2·39 g, 74%), m.p. 102–105°. The analytical sample, m.p. 105–107°, was recrystallized twice from 95% EtOH. (Found: C, 75·99; H, 6·55; N, 2·95. Calc. for $C_{34}H_{35}NO_5$: C, 75·95; H, 6·56; N, 2·61%).

1-(p-*Benzyloxybenzyl*)-2-*methyl*-6-*methoxy*-7-*benzyloxy*-1,2,3,4-*tetrahydroisoquinoline hydrochloride* (**23**). LAH (0·20 g) was added to a soln of **22** (300 mg) in THF (15 ml). The reaction mixture was refluxed for 2 hr. Isolation of the resulting base in the usual manner gave a gum which was treated with 10% HCl aq (5 ml). Crystals of the amine hydrochloride separated rapidly in the form of colorless needles (228 mg, 79%), m.p. 170–174°. Two recrystallizations from water gave the analytical sample as colorless microcrystals, m.p. 173–175°. (Found: C, 73·20; H, 6·72; N, 2·80. Calc. for $C_{32}H_{34}NO_3Cl \cdot \frac{1}{2} H_2O$: C, 73·20; H, 6·72; N, 2·67%).

1-(p-*Hydroxybenzyl*)-2-*methyl*-6-*methyl*-7-*hydroxy*-1,2,3,4-*tetrahydroisoquinoline* (±)-N-*methyl-coclaurine* (**6**). To a soln of **23** (300 mg) in MeOH (30 ml was added 5% Pd—C (100 mg) and the mixture was hydrogenated for 16 hr at 40 pounds press. Evaporation of the filtered soln gave a yellow gum. After addition of NH_4OH (0·5 ml), the free base crystallized on rubbing and was recrystallized from acetone and washed with ether to give almost colorless microcrystals (145 mg, 83%), m.p. 161–163° (lit.[23] 161–162°).

3,4-*Dibenzyloxy*-β-*nitrostyrene* (**37**). A soln of **8** (32 g), nitromethane (50 ml) and ammonium acetate (20 g) in glacial AcOH (200 ml) was refluxed for 1 hr. On cooling to room temp, the reaction mixture deposited crystals which were filtered and washed with a small amount of ether to give yellow needles (27 g, 74%), m.p. 117–118°. The analytical sample was recrystallized twice from 95% EtOH. (Found: C, 73·15; H, 5·43; N, 3·75. Calc. for $C_{22}H_{19}NO_4$: C, 73·11; H, 5·30; N, 3·88%).

3,4-*Dibenzyloxy*-β-*phenylethylamine* (**38**). To a stirred soln of LAH (8 g) in THF (270 ml) was added slowly solid **37**, (40 g). The reaction mixture was stirred and refluxed for 1 hr, then cooled to room temp and excess hydride decomposed by the addition of sat Na_2SO_4 aq. Evaporation of the filtered solvent gave a light brown oil (33 g, 90%) which was used without further purification.

For characterization, the acetyl derivative (**39**) was prepared. Ac_2O (1 ml) was added to a soln of **38** (0·5 ml) in pyridine (1 ml) and the mixture was warmed 10 min on the steam bath. Water (10 ml) was added and the neutral product was isolated in the usual manner. Crystallization from benzene–cyclohexane gave the pure **39** as colorless needles, m.p. 110–111°. (Found: C, 76·84; H, 6·90; N, 3·86. Calc. for $C_{24}H_{25}NO_3$: C, 76·77; H, 6·71; N, 3·73%).

N-(3,4-*Dibenzyloxy*-β-*phenylethyl*)-p-*benzyloxyphenylacetamide* (**40**). To a soln of *p*-benzyloxyphenylacetic acid (26 g) in abs ether (80 ml) was added $SOCl_2$ (7·5 ml) and one drop of pyridine. After 24 hr standing at room temp, the ether was removed on a rotary evaporator and the residual acid chloride was dissolved in $CHCl_3$ (100 ml). This soln was added dropwise, with vigorous stirring, to a mixture of crude **38** (33 g), $CHCl_3$ (100 ml), Na_2CO_3 (20 g) and water (100 ml). After stirring an additional 30 min, the neutral product was isolated in the usual manner. Crystallization from abs EtOH gave colorless microcrystals (34·4 g, 62%), m.p. 122–124°. The analytical sample was recrystallized twice from 95% EtOH. (Found: C, 79·37; H, 6·07; N, 2·77. Calc. for $C_{37}H_{35}NO_4$: C, 79·68; H, 6·33; N, 2·51%).

1-(p-*Benzyloxybenzyl*)-6,7-*dibenzyloxy*-3,4-*dihydroisoquinoline hydrochloride* (**13**). A soln of **40** (28 g) in $CHCl_3$ (250 ml) was cooled in a dry ice–acetone bath and PCl_5 (25 g) was added. The mixture was allowed to stand at room temp for 24 hr and was then poured into anhyd ether (2000 ml). After standing in the refrigerator for 12 hr, the product was filtered, washed with ether and immediately dissolved in abs MeOH (100 ml). On standing in the refrigerator, the soln deposited yellow microcrystals, which were filtered and washed with ether to give the product (14·9 g, 53%), m.p. 154–160°. The analytical sample

was recrystallized twice from abs EtOH. Found: C, 76·35; H, 6·15; N, 2·58. Calc. for $C_{37}H_{34}NO_3Cl \cdot \frac{1}{2}C_2H_5OH$: C, 76·17; H, 6·22; N, 2·34%).

1-(p-*Benzyloxybenzyl*)-2-*acetyl*-6,7-*dibenzyloxy*-1,2,3,4-*tetrahydroisoquinoline* (**17**). Sodium borohydride (1·0 g) was added slowly with stirring to a soln of **13** (4·0 g) in MeOH (40 ml). After 5 min of additional stirring, the mixture was diluted with water (120 ml). The usual isolation procedure gave the tetrahydro base as a light yellow gum which was dissolved in pyridine (8 ml) and Ac_2O (8 ml). The mixture was warmed 15 min on the steam bath and then water (80 ml) was added. Isolation of the neutral product in the usual manner gave a solid which crystallized from benzene-cyclohexane as colorless platelets (2·9 g, 72%), m.p. 143–144°. The analytical sample was recrystallized twice from abs EtOH. (Found: C, 79·87; H, 6·36; N, 2·73. Calc. for $C_{39}H_{37}NO_4$: C, 80·25; H, 6·39; N, 2·40%).

1-(p-*Hydroxybenzyl*)-2-*acetyl*-6,7-*dihydroxy*-1,2,3,4-*tetrahydroisoquinoline* (**18**). To a soln of **17** (2·0 g) in MeOH (200 ml) was added 5% PdC (0·5 g) and the mixture was hydrogenated for 16 hr at 40 pounds press. The catalyst was removed by filtration and the solvent was evaporated to give **18** as a colorless puffed glass (1·0 g, 93%). This material, which could not be crystallized, was used directly in various oxidation experiments.

Oxidation of 1-(p-*hydroxybenzyl*)-2-*carbethoxy*-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline* (**21**). Potassium ferricyanide (1·6 g) was dissolved in water (20 ml). In another flask, **21** (800 mg) was dissolved in 5% NaOH aq (80 ml) at room temp and the previously prepared ferricyanide soln was immediately added with vigorous stirring. The resulting ppt was reduced with LAH to give a basic oil (432 mg).

The above oil (20 mg) was subjected to TLC on silica gel G with MeOH containing 1% conc NH_4OH. Comparison samples of **1** and **5** were run on the same plate and the band (1 mg) corresponding most closely to dauricine was scraped off the plate and rechromatographed on silica gel H using the same solvent system. The product gave one spot of R_f 0·34. On the same plate, armepavine showed R_f 0·48 and dauricine showed R_f 0·23. The result was reproducible.

Attempted oxidation of **21** with aqueous $K_3Fe(CN)_6$ in ammonium acetate buffer gave a 90% recovery of starting material. Oxidation of **21** with one equivalent of $K_3Fe(CN)_6$ in a MeOH–water soln of Na_2CO_3 followed by reduction with LAH in THF gave a yellow oil, TLC of which showed that it was mostly armepavine; no dauricine spot was observed.

Oxidation of 1-(p-*hydroxybenzyl*)-2-*acetyl*-6-*methoxy*-7-*hydroxy*-1,2,3,4-*tetrahydroisoquinoline* (**19**). To a soln of **19** (100 mg) in EtOH-free reagent $CHCl_3$ (50 ml) was added with stirring at room temp lead tetraacetate (135 mg) in purified $CHCl_3$ (10 ml). Work-up after 5 min gave a yellow gum, which was dissolved in anhyd acetone (20 ml) and refluxed for 10 hr with anhyd K_2CO_3 (1 g) and Me_2SO_4 (0·4 ml). The usual work-up afforded a light brown oil (75 mg).

This oil (38 mg) was subjected to TLC on silica gel G with EtOAc, N-acetylstepharine (**4**) being run on the same plate. The bands were developed by spraying a small area of the plate with a 1% soln of 2,4-dinitrophenylhydrazine in 95% EtOH containing 1% conc H_2SO_4. The dienone **4** gave an orange spot. The corresponding product band, which did not give a noticeable dienone test, was scraped off and extracted with MeOH. Evaporation of the MeOH gave a colorless oil (0·5 mg). Chromatography of this on silica gel H with EtOAc gave no spot with 2,4-dinitrophenylhydrazine solution. In this system, N-acetylstepharine had R_f 0·12.

Attempts to oxidize **19** with anhyd $FeCl_3$ in $CHCl_3$ gave a 50% recovery of starting material. On methylation of the residues as described above, followed by chromatography of the product on silica gel H with EtOAc, no orange spot was obtained after spraying with 2,4-dinitrophenylhydrazine soln.

Oxidation of 1-(p-*hydroxybenzyl*)-2-*acetyl*-6,7-*dihydroxy*-1,2,3,4-*tetrahydroisoquinoline* (**18**). A mixture of NaOAc (0·5 g), **18** (1·00 g), and abs EtOH (25 ml) was heated on the steam bath to effect soln. After cooling to room temp. a soln of chloranil (480 mg) in abs EtOH (200 ml) was added rapidly. After 12 hr at room temp, the solvent was evaporated and the residual dark oil was methylated by Me_2SO_4 and NaOH in aqueous MeOH. Work-up for neutral material gave a brown gum (1·85 g).

The above gum (20 mg) was subjected to preparative TLC on alumina G with EtOAc. Bands having R_f 0·81, 0·74, 0·68 and 0·48 were observed on development with I_2 vapor. No band was observed corresponding to N-acetylstepharine, R_f 0·39.

Oxidation of **18** was also carried out with K_3FeCN_6. To a solution of **18** (30 mg) in 5% Na_2CO_3 aq (2 ml) and water (2 ml) at room temp was added rapidly, with stirring, a soln of K_3FeCN_6 (30 mg) in water (1 ml). Me_2SO_4 methylation of the product, followed by preparative TLC of this on silica gel G with EtOAc gave no material corresponding to N-acetylstepharine. R_f 0·12.

Preparation and oxidation of 1-(3-*hydroxy*-4-*methoxybenzyl*)-2-*carbethoxy*-6-*methoxy*-7-*hydroxy*-

1,2,3,4-tetrahydroisoquinoline (**27**). To a soln of **26** (100 mg) in acetone (10 ml) was added 5% Pd–C (50 mg) and the mixture was hydrogenated 12 hr at 40 pounds press. The catalyst was removed by filtration and the solvent was evaporated to give **27** as a colorless gum which did not crystallize.

Without further purification, the above phenol was dissolved in a mixture of 10% NaOH aq (1 ml) and water (10 ml). A soln of $K_3Fe(CN)_6$ (116 mg) in water (5 ml) was added dropwise over 5 min with stirring at room temp. Isolation of the product by extraction, followed by LAH reduction afforded a brown oil (32 mg), the UV spectrum of which showed a band at 286 mμ, but no absorption above 300 mμ, indicative of the presence of an aporphine system.

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REFERENCES

[1] To whom all inquiries should be addressed: Department of Chemistry, Wayne State University, Detroit, Michigan 48202.

[2] For a broad discussion of the role of phenolic oxidation in the biogenesis of alkaloids, see D. H. R. Barton and T. Cohen, *Festschr. Arthur Stoll* 117 (1957) and earlier refs cited therein.

[3] The proaporphines have been reviewed recently: K. L. Stuart and M. P. Cava, *Chem. Rev.* **68**, 321 (1968).

[4] For some representative examples, see [a]N. Franck, G. Blaschke and G. Schlingloff, *Tetrahedron Letters* 439 (1962); [b]B. Franck and G. Schlingloff, *Liebigs Ann.* **659**, 123 (1962); [c]S. M. Albonico, A. M. Kuck, and V. Deulofeu, *Chem. & Ind.* 1580 (1964); [d]A. R. Battersby and T. H. Brown, *Proc. Chem. Soc.* **85** (1964); [e]T. Kametani and H. Yagi, *J. Chem. Soc.* C, 2182 (1967); [f]A. H. Jackson and J. A. Martin, *ibid.* 2061 (1966); [g]M. Tomita, Y. Masaki, K. Fujitani, and Y. Sakatani, *Chem. Pharm. Bull. Tokyo* **16**, 688 (1968).

[5] M. Tomita and H. Yamaguchi, *Chem. Pharm. Bull. Tokyo* **1**, 10 (1953).

[6] K. Kratzl and G. Billek, *Monatsh.* **83**, 1045 (1952).

[7] M. P. Cava, K. Nomura, S. K. Talapatra, M. J. Mitchell, R. H. Schlessinger, K. T. Buck, J. L. Beal, B. Douglas, R. F. Raffauf, and J. A. Weisbach, *J. Org. Chem.* **33**, 2785 (1968).

[8] N. W. Bristow, *J. Chem. Soc.* 513 (1957).

[9] R. Robinson and S. Sugasawa, *Ibid.* 789 (1932).

[10] K. W. Gopinath, T. R. Govindachari, and N. Viswanathan, *Chem. Ber.* **92**, 1657 (1959).

[11] I. Baxter, L. T. Allen, and G. A. Swan, *J. Chem. Soc.* 3645 (1965).

[12] S. A. Gharbo, J. L. Beal, R. H. Schlessinger, M. P. Cava, and G. Svoboda, *Lloydia* **28**, 237 (1965).

[13] M. Tomita and J. Kunitomo, *Yakagaku Zasshi* **82**, 734 (1962).

[14] M. Tomita and M. Satomi, *Yakagaku Zasshi* **58**, 617 (1938).

[15] Y. Sasaki, H. Ohnishi, and N. Satoh, *Chem. Pharm. Bull. Tokyo*, **3**, 178 (1955).

[16] K. Ito, *Yakagaku Zasshi* **81**, 703 (1961).

[17] For a recent report of a fully aromatic quaternary benzylisoquinoline alkaloid which contains two methylenedioxy groups (escholamine), see L. Slavikova and J. Slavik, *Coll. Czech. Chem. Comm.* **31**, 3362 (1966).

[18] B. B. Dey and R. Parikshit, *Proc. Natl. Acad. Sci. India*, **11**, 37 (1945).

[19] P. Fritsch, *Liebigs Ann.* **286**, 1 (1895).

[20] M. P. Cava, K. Bessho, B. Douglas, S. Markey, and J. A. Weisbach: *Tetrahedron Letters* 4279 (1966).

[21] L. Marion, L. Lemay and V. Portelance, *J. Org. Chem.* **15**, 216 (1950).

[22] H. Hellmann and W. Elser, *Liebigs Ann.* **639**, 77 (1961).