Tetrahedron Vol. 39, No. 12, pp. 1975 to 1982, 1983
Printed in Great Britain.

0040–4020/83 $3.00 + .00

SYNTHETIC APPLICATION OF LITHIATION REACTIONS—XVI

SYNTHESES OF (±) TETRAHYDROPALMATINE, (±) CANADINE, (±) STYLOPINE AND (±) SINACTINE

N. S. NARASIMHAN,* R. S. MALI and B. K. KULKARNI
Department of Chemistry, University of Poona, Pune 411 007, India

(*Received in USA* 10 *June* 1982)

Abstract—N,N-Dimethyl-3,4-dimethoxy- and methylenedioxybenzylamines were lithiated and the organolithium intermediates treated with paraformaldehyde to give the 2-hydroxymethyl derivatives. The latter were converted to 7,8-dimethoxy- and methylenedioxyisochroman-3-ones through successive reaction with ClCOOEt, KCN and KOH. The isochromanones on condensation with homoveratrylamine or homopiperonylamine, followed by cyclisation and reduction furnished the protoberberine alkaloids.

Acid-catalysed aromatic electrophilic substitution reactions occur more at *para* than *ortho* positions with respect to electron donor groups (such as OMe). When the *ortho* position is between two substituents the reaction proceeds almost exclusively at the *para* position. For this reason, quite often, benzene-fused heterocyclic compounds, with a specific OMe substitution pattern are either not synthesized or synthesized only through lengthy routes by the usual acid-catalysed methods. Thus 5-methoxycoumarin is not available by Pechmann condensation[1] and 8-methoxyisoquinoline by Bischler–Napieralsky reaction[2] (Chart 1).

In contrast to the acid-catalysed aromatic substitution reactions, aromatic lithiation reactions[3], where an aromatic H is replaced by Li when the aromatic substrate is treated with an alkyl lithium reagent (RLi), occur exclusively at *ortho* position with respect to the electron donor group (such as OMe). The preferential ortho lithiation is explained by a mechanism[4] (Chart 2), where in the first step, the RLi reagent complexes with the heteroatom present in the group (i.e. O in OMe). The complexed RLi reagent then abstracts an aromatic proton from the substrate, which can be only from the ortho position. Li then enters that position.

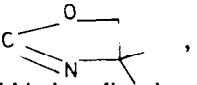
The orientation observed in aromatic lithiation reactions is interesting. But there are several other features of the lithiation reaction, which are also in accord with the above mechanism, which make it even more interesting. Thus

(i) lithiation occurs not only at the *ortho* position but also at other sterically close positions with respect to the electron donor group[5] (Chart 3);

(ii) lithiation is also directed by groups in which the electron donor atom is not directly attached to the aromatic ring but is one or two atoms away[6] (Chart 4);

(iii) even groups, which as a whole are electron withdrawing, direct lithiation *only* to *ortho* or other sterically close positions with respect to themselves, provided they have a heteroatom with unshared electron pair (electron donor atom)[7] (Chart 5); and finally

(iv) when two groups carrying electron donor atoms are present, lithiation is directed by the group which complexes better with the RLi reagent[8] (Chart 6).

Typically the groups which direct lithiation are[3] OH, OMe, OCH_2OMe, OTHP, NH_2, NMe_2, NHCOBu-t, CH_2OH, CH_2NMe_2, $CH_2CH_2NMe_2$, $CONHCH_3$, CONHPh, $CONEt_2$,  , SCH_3, SO_2NHCH_3, F etc. The lithiation directing ability decreases[3] in the order

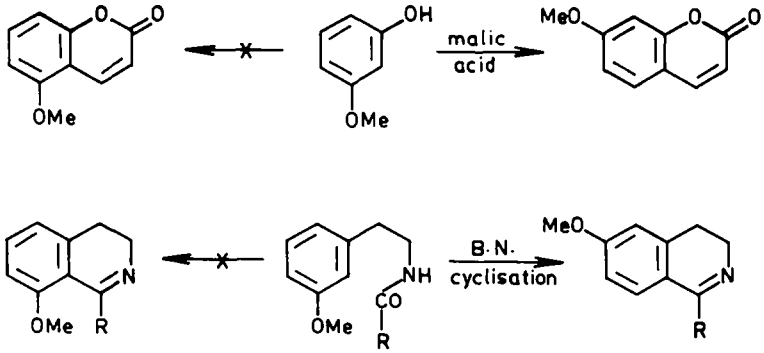


Chart 1.

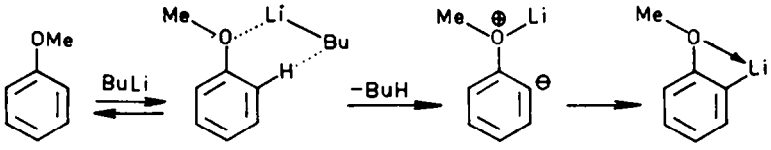


Chart 2.

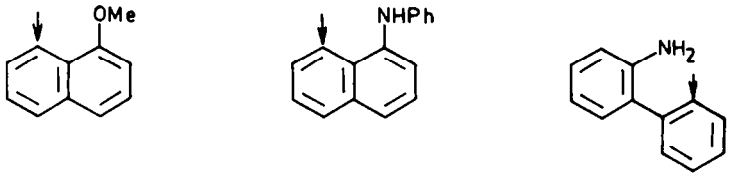


Chart 3.

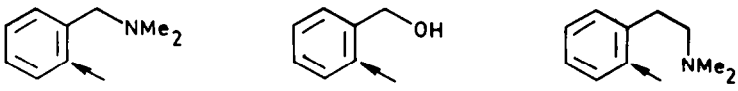


Chart 4.

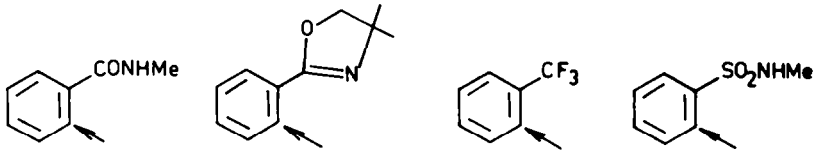


Chart 5.

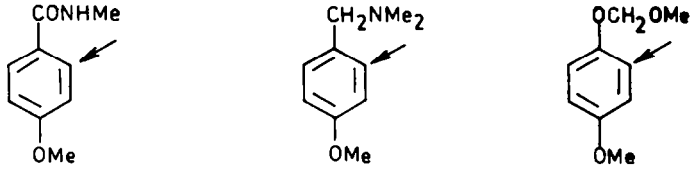
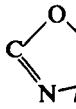


Chart 6.

$SO_2NHCH_3 >$  $> CONHMe > CH_2NMe_2 > OCH_3 > NMe_2$.

Position-selectivity in aromatic lithiation is also determined[3] by the acidity of the hydrogen atom replaced by Li. Here it is found that the hydrogen preferentially replaced by Li is the one which is most acidic from among those which are *ortho* or sterically close with respect to the lithiation directing group. Thus N,N-dimethyl-4-methoxybenzylamine is lithiated at 2- (or 6-) position.[8c]. This is because the aminomethyl group, which would complex better with the RLi reagent, would be the lithiation directing group and would direct lithiation *ortho* to itself. In N,N-dimethyl-3-methoxybenzylamine, lithiation occurs only at the 2- and not 6-position.[8c]. This is because, the H atom at 2-position is more acidic than that at 6-position due to the presence of an O atom at 3-position (Chart 7).

Aromatic lithiation can be further manipulated and the yield and position-selectivity improved to make lithiation synthetically very useful. Thus the reactivity of RLi can be improved by complexation with chelating agents like TMEDA.[3] On the other hand substrate reactivity can be improved by com-

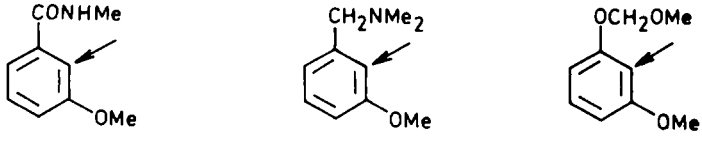
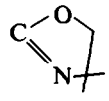


Chart 7.

plexing with $Cr(CO)_6$.[9] In both cases, presumably, it is the proton abstraction process which is facilitated, in the first case because of the increased basicity of the RLi reagent and in the second because of increased acidity of the aromatic H atom.

The lithiation directing ability of groups can be improved by proper derivatization; thus the *ortho* directing effect of the phenolic OH group (which is very poor) can be increased considerably by converting it into an OCH_3 group or still better into a OCH_2OMe or OTHP group.[8d] In specific cases, such derivatisation also leads to a further position-selectivity. Thus while 1-naphthol is lithiated exclusively at 8-position (not in good yield), its methoxymethyl ether is lithiated exclusively at 2-position (in excellent yield.[8d] Similarly the COOH group is rendered into a better lithiation directing group by derivatisation into a CONHMe, CONHPh, $CONEt_2$ or  group.[3] In the case of $CONEt_2$, sec-BuLi is the lithiating agent.

Yet another dimension, which is as yet not investigated in any depth, is the possibility of replacing Li in organolithium compounds with other metals and thereby obtaining other organometallic intermediates which can show differences in reactivity towards different electrophilic reagents.

Considerable position selectivity and yield improvement, thus, can be achieved in aromatic lithiation. The most important feature, however, is that lithiation occurs at positions which are generally not favored in acid catalysed aromatic electrophilic substitution reactions. Since the aromatic lithio derivatives would react readily with a variety of electrophilic reagents, aromatic lithiation would be useful to effect substitutions at positions not normally favored in the usual acid catalysed reactions. By proper choice of the lithiation directing group and the electrophilic reagents, disubstituted aromatic compounds can be obtained, which can be converted to benzene-fused heterocyclic compounds. Indeed aromatic lithiation reactions have been used by us to develop new syntheses of several benzene-fused heterocyclic compounds[5b,c,6c,10] (Chart 8).

The superiority of the new syntheses has been

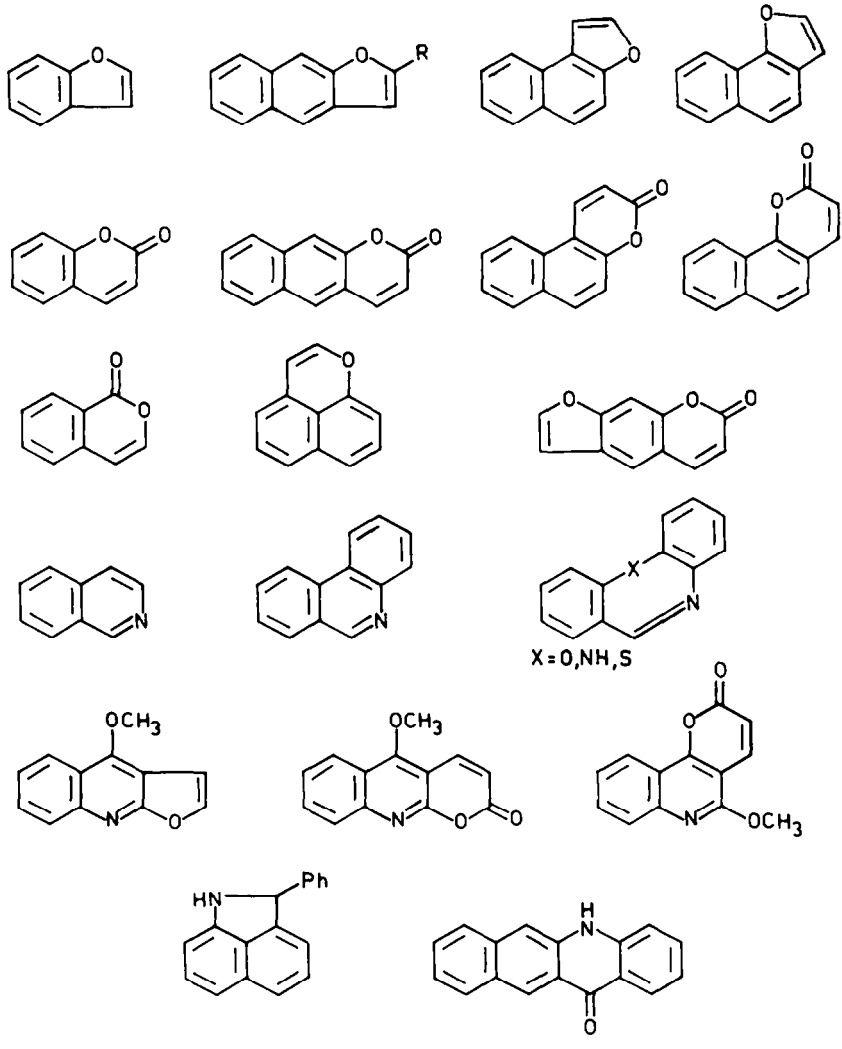
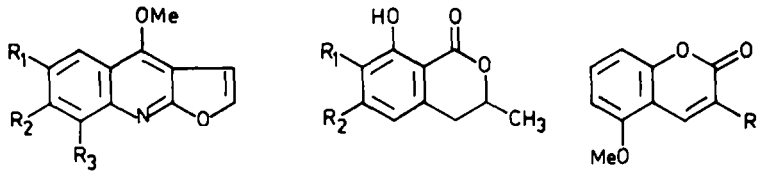


Chart 8.



Dictamine
Pteleine
γ-fagarine
Evolitrine
Kokusaginine

mellein
kigeline

R = H
= Ph

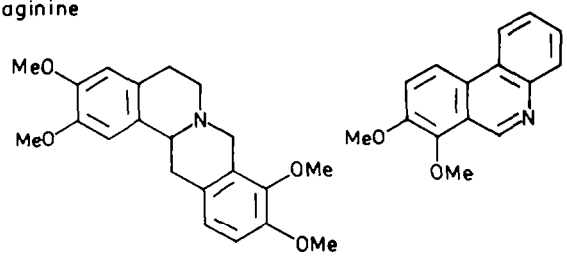
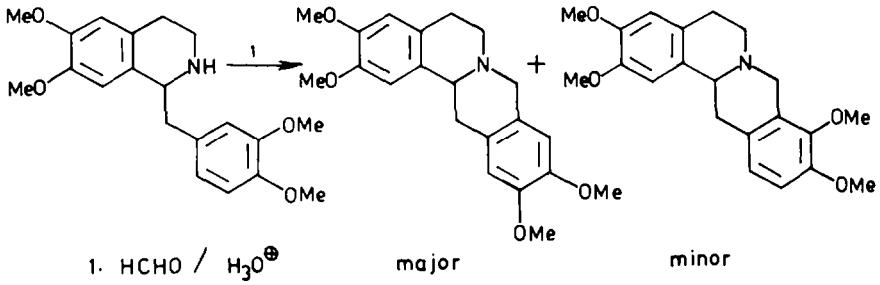


Chart 9.



1. HCHO / $H_3O^{\oplus}$ major minor

Chart 10.

demonstrated by the syntheses of several natural products and other compounds, not available readily by the usual methods, in fewer steps and good yields[5c,8a,10b,11] (Chart 9).

In the present paper we describe the application of aromatic lithiation to the synthesis of four protoberberine alkaloids, which are obtained with difficulty by the usual methods. These protoberberine alkaloids have oxygen functions at the 9, 10 positions and can pose problems in their synthesis.[12] For example a direct synthesis of tetrahydropalmatine, an alkaloid belonging to this class, through Mannich reaction on 1-(3′,4′-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline gives the 9,10-dioxygenated compound in a very minor yield. The major product is the 10,11-dioxygenated compound[13] (Chart 10). This is because of the greater electrophilic reactivity of the substrate at the 6′- rather than the 2′-position in the acid catalysed reaction.

When an OH group is present at 3′-position, by adjusting the pH of the reaction medium, it is possible to get some 2′-hydroxymethyl derivative,[14] which can be cyclised to give the 9,10-dioxygenated compound. However, in this reaction, the 6′-hydroxymethyl derivative is also obtained.

For reasons similar to the above, the synthesis of tetrahydropalmatine through the Bischler-Napieralsky reaction on the formyl derivative of 1-(3′,4′-dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydro isoquinoline does not cyclize to the 2′-position, but only to 6′-position[15] (Chart 11).

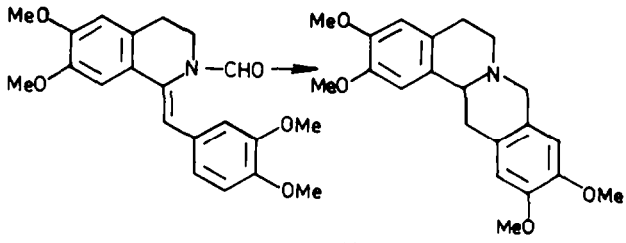
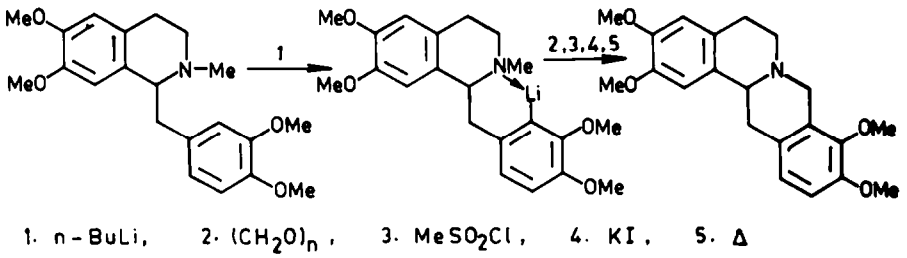


Chart 11.



1. n-BuLi, 2. $(CH_2O)_n$, 3. $MeSO_2Cl$, 4. KI, 5. Δ

Chart 12.

To achieve the desired cyclisation, the more active 6′-position is blocked[16] by incorporation of a Br atom, then cyclisation proceeds to 2′-position. The Br blocking group is subsequently removed and the 9,10-dioxygenated protoberberine alkaloid is obtained.

There are alternate syntheses of the 9,10-dioxygenated protoberberine alkaloids.[17] The starting compounds in these cases, which are 1,2,3,4-tetrasubstituted benzenes, are not readily accessible.

Earlier, we described a direct synthesis of a 9,10-dioxygenated protoberberine alkaloid, tetrahydropalmatine. The starting compound was the readily accessible N-methyl-1-(3′,4′-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4 tetrahydroisoquinoline. Aromatic lithiation was the crucial step in the synthesis and this resulted in the desired orientation of the OMe groups[11d] (Chart 12). Although the work-up procedure was clean, the yields were poor.

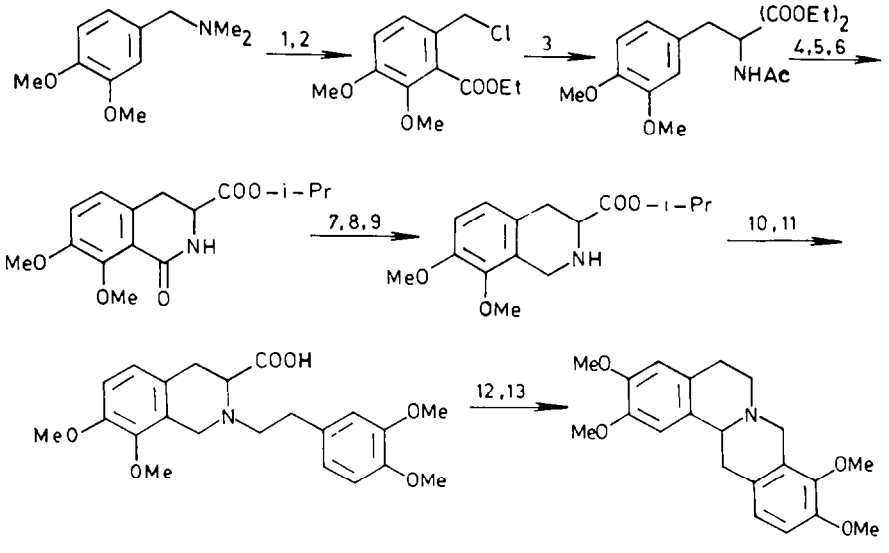
Recently Rapoport *et al.* described another synthesis of tetrahydropalmatine, through a 1,2,3,4-tetrasubstituted benzene intermediate, which was obtained by aromatic lithiation reaction[18] (Chart 13). The synthesis involved numerous steps.

We now describe new syntheses of four of the protoberberine alkaloids oxygenated at 9,10-positions, i.e., tetrahydropalmatine, canadine, stylopine, and sinactine, which proceed in good overall yields. The syntheses are based on the well known[19] method of conversion of an isochroman-3-one into a protoberberine alkaloid structure. The key step in our syntheses is to obtain the difficultly accessible 7,8-dimethoxy- and methylenedioxy isochroman-3-ones.

The general method for obtaining 7,8-dioxygenated isochroman-3-ones by acid-catalysed methods are not satisfactory.[19a]

A high yield synthesis of 7,8-dimethoxyisochroman-3-one, through a route involving reaction of 3-hydroxy-4-methoxyphenyl acetic acid and phenylboronic acid is known.[19c] Synthesis of 7,8 methylenedioxyisochroman-3-one, however, is not yet reported.

In the present work, the 7,8-dioxygenated isochroman-3-ones were obtained in excellent yield



1. n-BuLi, 2. ClCOOEt, 3 Sodium diethyl acetamido malonate
4. KOH/EtOH, 5. HCl, 6 i-PrOH/H^+, 7. Ag_2O, MeI, 8. P_2S_5,
9. Raney Ni, 10 β-(3,4-dimethoxy phenyl) etnyl bromide,
11 Hydrolysis, 12. $POCl_3$, 13 H^+/Δ.

Chart 13.

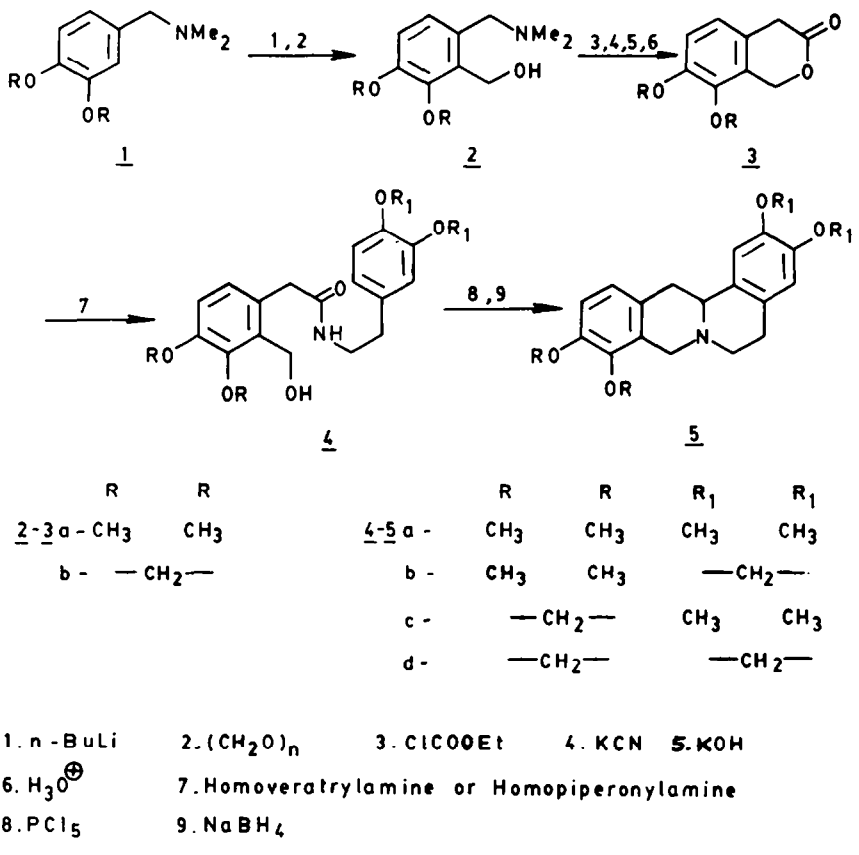


Chart 14.

by a sequence where aromatic lithiation was the crucial step (Chart 14).

Thus lithiation of N,N-dimethyl-3,4-dimethoxy- or methylenedioxybenzylamine (**1**) proceeded exclusively at 2-position. The organolithium intermediate, on treatment with paraformaldehyde, furnished the 2-hydroxymethyl derivatives **2**, in 92% yield in the case of the dimethoxy compound and in 65% yield in the case of the methylenedioxy compound. To convert the hydroxymethyl derivative into the isochroman-3-one, it was necessary to replace the NMe_2 group with the COOH group. In earlier experiments this was achieved by quaternization of the amino group with MeI, treatment of the quaternary compound with KCN to get the nitrile and finally hydrolysis to the COOH group. The isochroman-3-one was directly obtained, however, in poor yield (12%). In later experiments the transformation was achieved by direct replacement of the NMe_2 group with Cl by reaction with ClCOOEt, followed by treatment with KCN to get the nitrile and finally hydrolysis to the isochroman-3-ones (**3**). The yields from the carbinols were 53% in the case of the dimethoxy compound and 67% in the case of methylenedioxy.

The isochroman-3-ones were converted into the alkaloids by first reacting with homoveratrylamine or homopiperonylamine in refluxing alcohol to get the phenylacetamides **4**, followed by cyclisation with PCl_5 to obtain the dihydro compounds. The latter were then reduced with sodium borohydride to give the alkaloids **5** (Chart 14). The yields of the alkaloids from the isochromanones were 50–70%. It may be mentioned here that for cyclization, PCl_5 was found to be a better reagent than $POCl_3$.

In the present paper the 7,8-dioxygenated isochroman-3-ones, now readily available through aromatic lithiation, have been converted to the protoberberine alkaloids oxygenated at 9,10-positions. The isochroman-3-ones can be also used to obtain the corresponding benzocyclobutenes,[20] useful for the synthesis of a variety of compounds.[20]

EXPERIMENTAL

N,N - *Dimethyl* - 3,4 - *dimethoxy* - 2 - *hydroxymethylbenzylamine* (**2a**). A soln of N,N - dimethyl - 3,4 - dimethoxybenzylamine (3.90 g, 0.02 mol) in ether (30 ml) was stirred and cooled to 0°. n-BuLi (0.08 mol, prepared from 1.2 g Li and 8.8 ml of BuBr in 100 ml of ether) was added over 10 min at an even rate.

The white ppt was stirred for one hr and paraformaldehyde (4 g) was added. Stirring was continued for 8 hr and the mixture decomposed with water (100 ml). The organic phase was separated and the aqueous layer extracted with ether (2 × 50 ml). The combined ether extract was treated with 1:1 HCl (2 × 30 ml). The acidic layer was basified with 2 N NaOH and extracted with ether. The ether layer was dried (Na_2SO_4) and evaporated *in vacuo* gave an oil, which was distilled *in vacuo* to give **2a**: 4.15 g (92%); b.p. 123°/0.5 mm; IR (film): 3150 cm^{-1}; PMR (CCl_4): δ 2.16 (s, 6H, $-NMe_2$), 3.33 (s, 2H, $ArCH_2-N$), 3.77 (s, 6H, 2 × OMe), 4.43 (s, 2H, $ArCH_2O-$), 6.60 (s, 1H, Ar–H), 6.67 (s, 1H, Ar–H). (Found: C, 63.80, H, 8.82%. Calc. ($C_{12}H_{19}NO_3$): C, 63.97; H, 8.50%).

N,N-*Dimethyl*-2-*hydroxymethyl*-3,4-*methylenedioxybenzylamine* (**2b**). N,N-Dimethyl-3,4-methylenedioxybenzylamine

(2.70 g, 0.015 mol) in ether (25 ml) was lithiated using n-BuLi (0.06 mol, prepared from 0.84 g of Li and 6.5 ml of BuBr in 100 ml ether) as above. The metallated mixture was stirred for 2 hr at room temp then a green color developed, paraformaldehyde (3 g) was added and stirring was continued over a period of 12 hr. The mixture was worked up as in the case of **2a**. The final ether extract was evaporated to obtain crystals, which were washed with 20 ml of pet-ether to give **2b**: 2.00 g (65%); m.p. 85°; IR (Nujol): 3100–3150 cm^{-1} br; PMR (CCl_4): δ 2.22 (s, 6H, NMe_2), 3.38 (s, 2H, $ArCH_2N$), 4.50 (s, 2H, $ArCH_2O$), 5.78 (bs, exchangeable with D_2O, 1H, –OH), 5.95 (s, 2H, $-OCH_2O-$), 6.60 (s, 2H, Ar–H). (Found: C, 62.99; H, 7.25%. Calc ($C_{11}H_{15}NO_3$): C, 63.17; H, 7.18%).

7,8-*Dimethoxyisochroman-3-one* (**3a**). To a vigorously stirred soln of N,N-dimethyl-3,4-dimethoxy-2-hydroxymethylbenzylamine (0.670 g, 0.003 mol) in benzene (20 ml), containing $NaHCO_3$ (2.5 g), a soln of ethyl chloroformate (5 ml) in benzene (10 ml) was added. Stirring was further continued over a period of 15 min. Filtration and removal of the solvent at low pressure left the crude chlorocompound, as a thick liquid, which was dissolved in DMF (10 ml). KCN (1 g) was added to the solution and stirred vigorously for 20 hr. The mixture was poured into water (50 ml) and extracted with ether (3 × 50 ml). The combined ether extract was washed with water (50 ml). Drying (Na_2SO_4) and evaporation afforded the crude nitrile, as a viscous liquid, which was dissolved in methanol (5 ml) and an alcoholic soln of KOH (10 ml, 10% in 50–50 aqueous MeOH) was added to the solution, then refluxed on a water bath for 1.5 hr. MeOH was removed *in vacuo*. Water (50 ml) was added to the oily residue and extracted with ether. The aqueous layer was acidified with 1:1 HCl. On standing for 2 hr, a crystalline mass separated, which was filtered and dried to give 260 mg of **3a**. The filtrate was extracted with ether (50 ml). Drying (Na_2SO_4) and removal of the solvent gave an additional 60 mg of the product. (Total yield, 53%), m.p. 95° (lit.[19c] m.p. 98–100°); IR (Nujol): 1750 cm^{-1}; PMR ($CDCl_3$): δ 3.77 (s, 2H, $ArCH_2CO$), 4.03 (s, 6H, 2 × OMe), 5.57 (s, 2H, $ArCH_2O$), 7.03 (s, 2H, Ar–H). (Found: C, 63.44; H, 6.01%. Calc ($C_{11}H_{12}O_4$): C, 63.45; H, 5.81%).

7,8-*Methylenedioxyisochroman-3-one* (**3b**). The reaction between N,N-dimethyl-2-hydroxymethyl-3,4-methylenedioxybenzylamine (1.1 g, 0.0053 mol) and ethyl chloroformate, as above, gave the crude chlorocompound, which was dissolved in DMF (10 ml) and KCN (1.5 g) added. The mixture was stirred for 8 hr at room temp and worked up as in the previous case to obtain the crude nitrile, which was hydrolyzed with alcoholic KOH at reflux for 3.5 hr and work up as above furnished the crystalline **3b**: 0.725 g (67%); m.p. 131° (from EtOH); IR (Nujol): 1730 cm^{-1}; PMR (CCl_4): δ 3.54 (s, 2H, $ArCH_2CO$), 5.22 (s, 2H, $ArCH_2O$), 5.95 (s, 2H, $-OCH_2O-$), 6.57 (d, J = 8 Hz, 1H, Ar–H), 6.73 (d, J = 8 Hz, 1H, Ar–H). (Found: C, 62.77; H, 4.29. Calc ($C_{10}H_8O_4$): C, 62.50, H, 4.20%).

N-[2-(3,4-*Dimethoxyphenyl*) *ethyl*] (3,4-*dimethoxy*-2-*hydroxymethyl*)-*phenylacetamide* (**4a**). A soln of **3a** (0.1 g, 0.0005 mol) and homoveratryl amine (0.15 ml) in abs EtOH (10 ml) was stirred for 4.5 hr at room temp. After completion (monitored by TLC), EtOH was removed *in vacuo* and dry ether (5 ml) was added to the semisolid and scratched until the gummy mass became powdery. Ether was decanted and the solid recrystallised from benzene to give **4a**: 0.130 g (70%); m.p. 104–5°; UV (MeOH): 223 nm (log ϵ 5.17), 275 (4.67); IR (Nujol): 1640, 3070, 3180, 3250 cm^{-1}; PMR ($CDCl_3$): δ 2.67 (t, 2H, $ArCH_2CH_2N$), 3.20 (bs, exchangeable with D_2O, 1H), 3.40 (t, 2H, $ArCH_2CH_2N$), 3.52 (s, 2H, $ArCH_2CO$), 3.80, 3.81, 3.83, 3.85 (s, 3H each, 4 × –OMe), 4.70 (s, 2H, $ArCH_2O$), 6.37 (bs, exchangeable with D_2O, 1H), 6.55–6.90 (m, 5H, Ar–H). (Found: C, 64.60; H, 6.97. Calc ($C_{21}H_{27}NO_6$): C, 64.76; H, 6.99%).

N-[2-(3,4-*Methylenedioxyphenyl*)*ethyl*](3,4-*dimethoxy*-2-*hydroxymethyl*)*phenylacetamide* (**4b**). Condensation of **3a** (0.1 g, 0.0005 mol) with homopiperonylamine (0.15 ml) in refluxing EtOH for 6 hr and work up as above gave **4b**: 0.15 g (84%); m.p. 156° (benzene); UV (MeOH): 225 nm (log ϵ 4.98), 280 (4.69); IR (Nujol): 1650, 3100, 3170, 3200, 3270 cm^{-1}; PMR ($CDCl_3$–DMSO-d_6): δ 2.66 (t, 2H, $ArCH_2CH_2N$), 3.36 (t, 2H, $ArCH_2CH_2N$), 3.52 (s, 2H, $ArCH_2CO$), 3.82 (s, 6H, 2 × –OMe), 4.65 (d, J = 2.5 Hz, 2H, singlet on D_2O exchange $ArCH_2O$), 4.90 (bs, exchangeable with D_2O, 1H), 5.88 (s, 2H, $-OCH_2O$), 6.52–7.05 (m, 5H, Ar–H), 7.32 (bs, exchangeable with D_2O, 1H). (Found: C, 64.35; H, 6.09%. Calc ($C_{20}H_{23}NO_6$): C, 64.33; H, 6.21%).

N-[2-(3,4-*Dimethoxyphenyl*)*ethyl*](3,4-*methylenedioxy*-2-*hydroxymethyl*)*phenylacetamide* (**4c**). Condensation of **3b** (0.02 g, 1.04 mmol) with homoveratylamine (0.3 ml) in refluxing EtOH soln for 3.5 hr and concentration and cooling of the EtOH soln gave **4c**: 340 mg (87.5%); m.p. 158°; UV (MeOH): 220 nm (log ϵ 5.07) 278 (4.73); IR (Nujol): 1645, 3083, 3167, 3275, 3320 cm^{-1}; PMR ($CDCl_3$–DMSO-d_6): δ 2.66 (t, 2H, $ArCH_2CH_2N$), 3.30 (t, 2H, $ArCH_2CH_2N$), 3.48 (s, 2H, $ArCH_2CO$), 3.75 (s, 6H, 2 × –OMe), 4.52 (d, J = 2.5 Hz, singlet on D_2O exchange, 2H, $ArCH_2O$–), 5.38 (bs, exchangeable with D_2O, 1H), 5.92 (s, 2H, $-OCH_2O-$), 6.62–6.80 (m, 5H, Ar–H), 7.90 (bs, exchangeable with D_2O, 1H). (Found: C, 64.69; H, 6.36%. Calc ($C_{20}H_{23}NO_6$): C, 64.33; H, 6.21%).

N-[2-(3,4-*Methylenedioxyphenyl*)*ethyl*](3,4-*methylenedioxy*-2-*hydroxymethyl*)*phenylacetamide* (**4d**). Condensation of **3b** (85 mg, 0.44 mmol) with homopiperonylamine (0.13 ml) as in the case of **4b** gave the amide **4d** 140 mg (91%); m.p. 189° (benzene); UV (MeOH): 232 nm (log ϵ 4.85) 283 (4.84); IR (Nujol): 1610, 3070, 3150, 3250 cm^{-1}. (Found: C, 64.18; H, 5.75%. Calc ($C_{19}H_{19}NO_6$): C, 63.86; H, 5.36%).

General procedure for conversion of the amides **4** *into the alkaloids* **5**. The amide (0.05 g) was dissolved in $CHCl_3$ (10 ml). PCl_5 (0.1 g) was added with stirring and, if necessary, cooling. The mixture was stirred at room temp for a further period of 20 min. The solvent was removed *in vacuo* and crushed ice was added to the residue. It was extracted with ether. A sat $NaHCO_3$ aq was added till basic and the mixture extracted with CH_2Cl_2 (2 × 10 ml). Drying (Na_2SO_4) and evaporation of the solvent gave a yellow, syrupy liquid or a solid (in last three cases), which was dissolved in MeOH (25 ml) and reduced with $NaBH_4$ (0.5 g, added in lots, with stirring, over a period of 1.5 hr). MeOH was removed at low pressure. Water (15 ml) was added and the mixture was extracted with ether (2 × 25 ml). Drying (Na_2SO_4) and evaporation of the solvent gave the alkaloids.

(±) *Tetrahydropalmatine* (**5a**) (yield 77%) m.p. 147°; mmp undepressed. IR superposable with an authentic sample.[11d]

(±) *Canadine* (**5b**) light yellow needles from ethanol (yield 62%) m.p. 167–8° (lit.[21] m.p. 163–5°); UV[22]; PMR[21] and mass[23] spectral values were in agreement with the reported values; UV (MeOH): 225 (sh) nm (log ϵ 4.25), 284 (3.88), λ_{max} 250 (3.14); IR ($CHCl_3$): 2835, 2800, 2770, 2750 cm^{-1}; PMR ($CDCl_3$): δ 2.50–3.36 (m, 7H, methylene and methine protons), 3.50 (d, J = 16 Hz, 1H, C_8–H), 381 (s, 6H, 2 × –OMe), 4.24 (d, J = 16 Hz, 1H, C_8–H), 5.88 (s, 2H, $-OCH_2O-$), 6.56 (s, 1H, Ar–H), 6.70 (s, 1H, Ar–H), 6.80 (d, J = 2 Hz, 2H, ArH); MS *m/e* (rel. intensity): 339 (M^+, metastable, 97.6), 338 (100), 308 (26.8), 176 (8.8), 174 (28.6), 165 (34.8), 164 (metastable, 98.3), 149 (99.4).

(±) *Sinactine* (**5c**) (yield 66%) m.p. 163–5° (ether–pet. ether, lit.[24] m.p. 167–8°); UV (MeOH): 230 nm (log ϵ 3.01), 282 (2.89); IR ($CHCl_3$): 2840, 2810, 2780, 2760 cm^{-1}; PMR ($CDCl_3$): δ 2.42–3.24 (m, 7H, methylene and methine protons), 3.52 (d, J = 16 Hz, 1H, C_8–H), 3.83 and 3.85 (s, 3H each, 2 × –OMe), 4.08 (d, J = 16 Hz, 1H, C_8–H), 5.90 (s, 2H, $-OCH_2O$), 6.59 (s, 1H, ArH), 6.63 (s, 2H, Ar–H), 6.69 (s, 1H, ArH); MS *m/e* (rel. intensity): 339 (M^+, 49), 338 (32.8), 190 (17.9), 149 (17.9), 148 (100).

(±) *Stylopine* (**5d**) (yield 78%) m.p. 194–5° (ethanol, lit.[24] m.p. 191–2°); UV and mass spectral data[23] were in agreement with the reported. UV (MeOH): 230 nm (log ϵ 3.94),

283 (3.90). IR ($CHCl_3$): 2800, 2770, 2760, 2750 cm^{-1}; PMR ($CDCl_3$): δ 2.46–3.54 (m, 7H, methylene and methine protons), 3.48 (d, J = 16 Hz, 1H, C_8–H), 4.07 (d, J = 16 Hz, 1H, C_8–H), 5.87 (s, 4H, 2 × $-OCH_2O-$), 6.54 (s, 1H, Ar–H) 6.62 (s, 2H, Ar–H), 6.68 (s, 1H, ArH); MS *m/e* (rel. intensity: 323 (48.7), 322 (21.5), 174 (12.8), 149 (16.9), 148 (100).

Acknowledgement—We thank Mr. D. D. Dhavale for microanalysis, UV, IR and NMR spectral data.

REFERENCES

[1]S. Sethna and R. Phadke, *Org. React.* **7**, 1 (1953).
[2]W. M. Whaley and T. R. Govindachari, *Ibid.* **6**, 74 (1951).
[3a]H. Gilman, *Ibid.* **8**, 258 (1954); R. G. Jones and H. Gilman, *Ibid.* **6**, 339 (1951); [b]J. M. Mallan and R. L. Bebb, *Chem. Rev.* **69**, 693 (1969); [c]H. W. Gschwend and H. R. Rodriguez, *Org. React.* **26**, 1 (1979); [d]B. J. Wakefield, *The Chemistry of Organolithium Compounds*. Pergamon Press, Oxford (1974).
[4]J. D. Roberts and D. Y. Curtin, *J. Am. Chem. Soc.* **68**, 1658 (1946).
[5a]R. A. Barnes and L. J. Nehmsmann, *J. Org. Chem.* **27**, 1939 (1962); D. A. Shirley and C. F. Cheng, *J. Organometal. Chem.* **20**, 251 (1969); [b]N. S. Narasimhan and A. C. Ranade, *Indian J. Chem.* **7**, 538 (1969); [c]N. S. Narasimhan and R. H. Alurkar, *Ibid.* **7**, 1280 (1969); N. S. Narasimhan and P. S. Chandrachood, *Synthesis* 589 (1979); N. S. Narasimhan, P. S. Chandrachood and N. R. Shete, *Tetrahedron* **37**, 825 (1981).
[6a]F. N. Jones, M. F. Zinn and C. R. Hauser, *J. Org. Chem.* **28**, 663 (1963); [b]M. Uemura, S. Tokuyama and T. Sakan, *Chem. Lett.* 1195 (1975); D. Seebach and N. Mayer, *Chem. Ber.* **113**, 1304 (1980); [c]N. S. Narasimhan and A. C. Ranade, *Tetrahedron Letters* 603 (1966).
[7a]W. H. Puterbaugh and C. R. Hauser, *J. Org. Chem.* **29**, 853 (1964); N. S. Narasimhan and R. S. Mali, *Synthesis* 797 (1975); [b]A. J. Meyers and E. D. Mihelich, *J. Org. Chem.* **40**, 3158 (1975); K. Hantke, Ph.D. Thesis, Univ. of Gottingen (1973), Personal communication from Prof. U. Schollkopf; [c]H. Gilman and T. S. Soddy, *J. Org. Chem.* **22**, 1715 (1957); [d]H. W. Gschwend, Unpublished work, see Ref. 3*a*.
[8a]N. S. Narasimhan and B. H. Bhide, *Tetrahedron* **27**, 6171 (1971); [b]K. P. Klein and C. R. Hauser, *J. Org. Chem.* **32**, 1479 (1967); [c]N. S. Narasimhan and B. H. Bhide, *Tetrahedron Letters* 4159 (1968); [d]N. S. Narasimhan and M. V. Barve, Unpublished results.
[9]M. F. Semmelhack, H. T. Hall, M. Yoshifuji and G. Clark, *J. Am. Chem. Soc.* **97**, 1247 (1975).
[10a]N. S. Narasimhan and M. V. Paradkar, *Chem. & Ind.* 1529 (1963); *Indian J. Chem.* **7**, 536 (1969); [b]N. S. Narasimhan and R. S. Mali, *Tetrahedron Letters* 843 (1973); *Tetrahedron* **30**, 4153 (1974); **31** 1005 (1975); *Synthesis* 796 (1975); [c]N. S. Narasimhan and M. V. Paradkar, *Indian J. Chem.* **7**, 1004 (1969); [d]N. S. Narasimhan and M. V. Paradkar, *Chem. & Ind.* 831 (1967); [e]N. S. Narasimhan and S. P. Bhagwat, *Synthesis* 903 (1979).
[11a]N. S. Narasimhan, M. V. Paradkar and R. H. Alurkar, *Tetrahedron* **27**, 1351 (1971); N. S. Narasimhan, R. S. Mali and A. M. Gokhale, *Indian J. Chem.* **18B**, 115 (1979); [b]N. S. Narasimhan and B. H. Bhide, *Chem. Commun.* 1552 (1970); B. H. Bhide, V. P. Gupta, N. S. Narasimhan and R. S. Mali, *Chem. & Ind.* 519 (1975); [c]N. S. Narasimhan, R.S. Mali and M. V. Barve, *Synthesis* 906 (1979); [d]N. S. Narasimhan and B. H. Bhide, *Chem. & Ind.* 621 (1969); N. S. Narasimhan, A. C. Ranade and B. H. Bhide, *Indian J. Chem.* **20B**, 439 (1981).
[12]M. Shamma, *The Isoquinoline Alkaloids*. Academic Press, New York (1972).
[13a]A. Pictet and A. Gams, *Ber. Dtsch. Chem. Ges.* **44**, 2480 (1911); [b]R. D. Haworth, W. H. Perkin Jr. and J. Rankin, *J. Chem. Soc.* **125**, 1686 (1924).
[14]T. Kametani, K. Fukumoto, H. Agui, H. Yagi, K. Kigasawa, H. Siegahara, M. Hiiragi, T. Hayasaka and H. Ishimaru, *Ibid.* (*C*), 112 (1968).
[15]N. T. Le Quang Thuan and J. Gardent, *Bull. Soc. Chim. Fr.* **5**, 2401 (1966).
[16]H. Suguna and B. R. Pai, *Coll. Czech. Chem. Commun.* **41**, 1219 (1976).
[17a]T. R. Govindachari, S. Rajadurai, M. Subramanian and N. Viswanathan, *J. Chem. Soc.* 2943 (1957); [b]C. K. Bradsher and N. L. Dutta, *J. Am. Chem. Soc.* **82**, 1145 (1960).
[18]R. T. Dean and H. Rapoport, *J. Org. Chem.* **43**, 2115 (1978).
[19a]A. R. Battersby, R. Southgate, J. Staunton and M. Hirst, *J. Chem. Soc.* (C), 1052 (1966); [b]W. Meise and F. Zymalkowski, *Tetrahedron Letters* 1475 (1969); [c]W. Nagata, H. Itazaki, K. Okada, T. Wakabayashi, K. Shibata and N. Tokutake, *Chem. Pharm. Bull. Japan*, **23**, 2867 (1975).
[20]R. J. Spangler and B. G. Beckmann, *Tetrahedron Letters* 2517 (1976) and refs. cited; *J. Org. Chem.* **42**, 2989 (1977).
[21]M. Cushman and F. Dekow, *J. Org. Chem.* **44**, 407 (1979).
[22]A. W. Sangster and K. L. Stuart, *Chem. Rev.* **65**, 69 (1965).
[23]C. Y. Chen and D. B. MacLean, *Can. J. Chem.* **46**, 2501 (1968).
[24]R. Rajaraman, B. R. Pai, M. S. Premila and H. Suguna, *Indian J. Chem.* **15B**, 876 (1977).