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IMPROVED PREPARATION OF 5-HYDROXYPROTOBERBERINE DERIVATIVES *VIA* 3-ARYLTETRAHYDROISOQUINOLINES

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Abstract- A regioselective synthetic pathway is reported to prepare 5-hydroxytetrahydroprotoberberines, starting from readily available isoquinoline derivatives. Bromoacetaldehyde diethyl acetal is found to be an effective and convenient reagent for *N*-alkylation of the latter derivatives, and subsequent acidic cyclization afforded the corresponding tetracyclic berbines in excellent overall yield. Stereochemical assignments were made on the basis of ^{1}H NMR data supported by decoupling experiments and difference NOE measurements.

The protoberberine system has been synthesized in many different ways and several reviews outline the various approaches to this class of alkaloids.[1] Naturally occurring and modified berbine derivatives have shown hypotensive activity,[2] and the use of tetrahydropalmatine as an antipsychotic drug[3] has increased interest in this class of compounds. Owing chiefly to this interesting biological activity, we have concentrated on the problem of berbine synthesis. Thus, in a recent paper[4] we described the preparation and stereochemistry of a series of novel tetrahydroprotoberberines starting from appropriate 3-aryltetrahydroisoquinolines, which were allowed to react with glycidol (2,3-epoxy-1-propanol), to attain addition of a two-carbon unit.

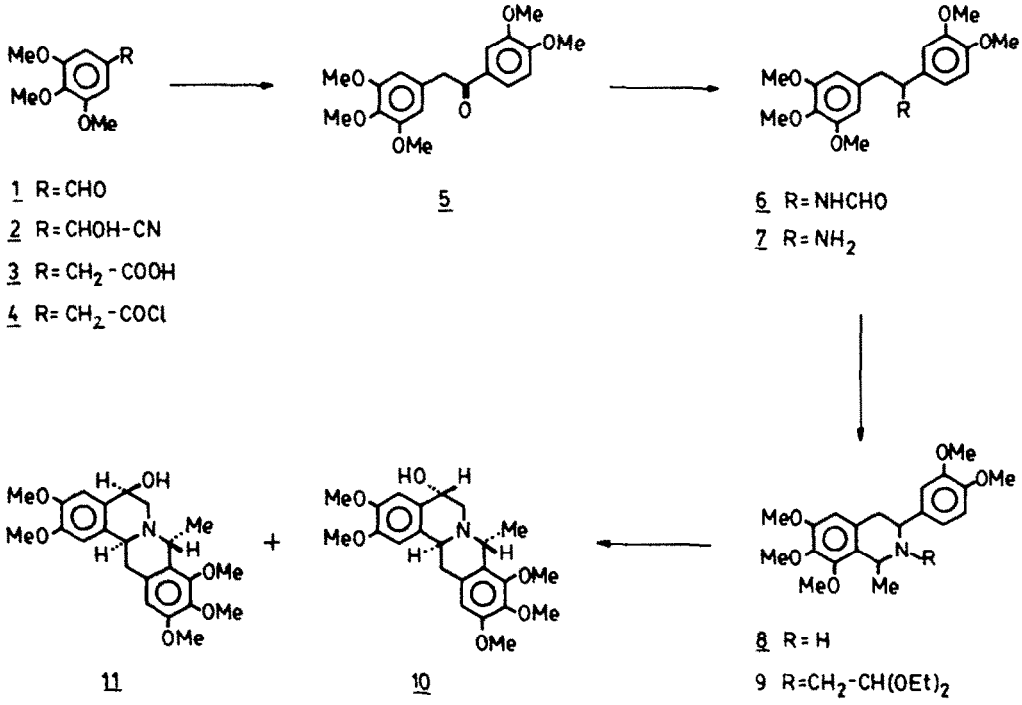
The purpose of this paper is to report an improved method using 3-arylisoquinoline derivatives in the preparation of tetrahydroprotoberberines, which entails reaction of the former compounds with bromoacetaldehyde diethyl acetal,[5] followed by one-pot hydrolysis and subsequent ring closure, thereby affording the tetracyclic protoberberine system. The advantage of the present approach lies in the improved overall yield, as only two-steps are required starting from the appropriate 3-aryltetrahydroisoquinoline.

In addition, the stereochemistry of the tetrahydroisoquinoline 8 and protoberberines 10 and 11 has been unambiguously assigned on the basis of ^{1}H NMR data supported by measurements of the difference Nuclear Overhauser Effect (NOE)[6] and selective ^{1}H-^{1}H decoupling experiments.

RESULTS AND DISCUSSION

For this study, we started with 3,4,5-trimethoxyphenylacetyl chloride which reacted under Friedel-Crafts conditions with 3,4-dimethoxybenzene to give the

deoxybenzoin 5 in 77% yield. Leuckart reductive amination of 5 followed by basic hydrolysis produced 1,2-diarylethylamine 7 in 71% overall yield. The diastereoselective cyclization reaction, carried out under classical Pictet-Spengler conditions, gave rise to the isoquinoline derivative 8 (75% yield).



1 R=CHO
2 R=CHOH-CN
3 R=CH_2-COOH
4 R=CH_2-COCl

5

6 R=NHCHO
7 R=NH_2

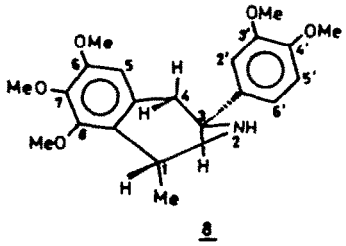
8 R=H
9 R=CH_2-CH(OEt)$_2$

11 + 10

The relative stereochemistry of compound 8 was established by different NOE measurements. Thus the signal due to H-1 was unaffected when that at H-3 was irradiated and vice versa. An increase in the intensity of the resonance of the methyl group at C-1 upon irradiation of the signal due to H-3 is consistent with pseudo-axial and axial orientations for the methyl group and H-3 respectively (Figure 1).

The above stereochemical assignment proves that the Pictet-Spengler cyclization reaction is not only highly diastereoselective, but also a thermodynamically controlled process, as we have previously reported.[8] For tetrahydroisoquinoline 8, the proposed *trans* configuration is the most stable because of the substitution at C-1 and C-8.

With the latter derivative in hand, the crucial two-step sequence for the generation of the protoberberine nucleus was achieved in 74% yield, as follows: (i) *N*-alkylation of the isoquinoline 8 with bromoacetaldehyde diethyl acetal in dry dioxane/NaH yielded regioselectively the corresponding *N*-alkyl intermediate 9 in 77% yield. (ii) One-pot removal of the acetals followed by cyclization (6M HCl) afforded diastereomeric 5-hydroxytetrahydroprotoberberines 10 and 11 in a 3:2 ratio. The separation of these epimers was best achieved by column chromatography.



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This sequence of reactions has also afforded tetracyclic compounds 10 and 11 from 3-arylisoquinoline 8 in good overall yield (74%). It is noteworthy that the use of 2,3-epoxi-1-propanol instead of bromoacetaldehyde diethyl acetal for the same purpose, gives an overall yield of only 46%[4] and 32% in similar derivatives.[9]

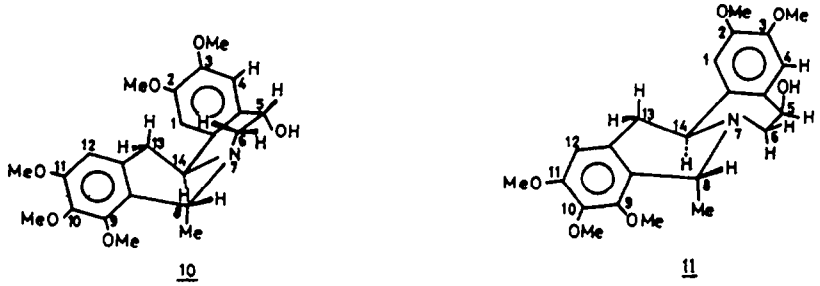
The stereochemical assignment of the above obtained derivatives was established by spectroscopy (IR, ^{1}H NMR), assuming the same configur-

ation for ring C. Thus, H-13 and H-14 show a typical ABX system in both protoberberines, with coupling constants (J_{AX}=11, J_{BX}=3 Hz), revealing the axial coupling between the sole H-14 proton and the corresponding pseudoaxial H-13 proton. An NOE between H-14 and the methyl protons at C-8 was observed, indicating the expected pseudoaxial position for the methyl group. Furthermore, no NOE was observed between H-14 and H-8 (Table 2 and Figure 2).

Table 2. Selected 250 MHz ^{1}H NMR Data and Proton Configuration Assignments of Protoberberines 10 and 11

Protons	δ (ppm)		Multiplicity[1]		J (Hz)		Observed NOE		Configuration[2]	
	10	11	10	11	10	11	10	11	10	11
CH_3	1.46	1.31	d	d	6.7	6.5	H-8 H-14	H-8 H-14 H-6[3]	a(α)	a(α)
H-13β	2.79	2.76	dd	dd	J_{AX}=10.7 J_{AB}=16.8	J_{AX}=11.1 J_{AB}=16.4	—	H-13α H-12	a(β)	a(β)
H-13α	2.88	3.22	dd	dd	J_{BX}= 5.9 J_{AB}=16.8	J_{BX}= 4.3 J_{AB}=16.4	—	H-13β H-14 H-12 H-1	e(α)	e(α)
H-6α	2.83		dd		J_{AX}= 3.6 J_{AB}=11.8		—		e(α)	
		3.08[3]		m		—		CH_3 H-8 H-5 H-14		e(β) a(α)
H-6β	3.21		dd		J_{BX}= 3.0 J_{AB}=11.8		H-5 H-6α H-13β		a(β)	
H-14	4.35	4.20	dd	dd	J_{AX}=10.7 J_{BX}= 5.9	J_{AX}=11.1 J_{BX}= 4.3	CH_3 H-13α H-13β H-1	CH_3 H-13α H-6 H-1	-(α)[4]	a(α)
H-8	4.09	4.25	q	q	6.7	6.5	CH_3 H-6α	—	e(β)	e(β)
H-5	4.58	4.55	m	m	—	—	H-6α H-6β H-4	H-6 H-4	e(β)	e(α)

[1] d: doublet, dd: doublet of doublets, q: quartet, m: multiplet. [2] a: axial, e: equatorial, β: above the plane containing the ring, α: below the same plane. [3] H-6 protons in compound 11 were indistinguishable. [4] The position of H-14 is axial towards ring C and equatorial towards ring B.



10 11

Figure 2

Compound 10 presents a *cis*-fused quinolizidine conformation as deduced from the following: the observed NOE between one H-6 proton and the axial H-13 proton implies that the nitrogen lone pair and the angular proton H-14 require a *cis*-juncture of ring B/C. To support the above conclusion, no NOE is observed between the methyl group and the H-6 protons or between the latter protons and H-14. In agreement with the proposed *cis* B/C juncture for compound 10 no Bohlmann bands[10] were found in the expected region (2700-2800 cm^{-1}). The same spectrophotometric behaviour for C-8 substituted protoberberine derivatives has been reported.[11]

In contrast, diastereoisomeric compound 11 presents a *trans*-fused quinolizidine conformation. Thus, it shows an NOE between the axial H-6 proton and the protons of the methyl group and H-14, respectively (Figure 2), while no NOE is observed between H-6 and H-13, as expected. The IR spectrum of this compound does not show Bohlmann bands either,[11] though we have already demonstrated it has a *trans* B/C juncture. This exception to Bohlmann's rule has also been reported in the case of 4-methyl quinolizidines.[12]

Therefore, we conclude that the presence of Bohlmann bands is not a necessary condition for a *trans* B/C juncture of the C-8 substituted quinolizidine system and we have demonstrated that difference NOE measurements are an accurate technique to establish unambiguously the correct conformation for the above mentioned quinolizidine system.

Finally, the signal due to H-5 in the epimeric compound 11 when irradiated causes enhancements in the resonance of both H-6 protons and also that of H-4. Moreover, analysis of the coupling constants of the above mentioned aliphatic protons (J_{ea}=3.0, J_{ee}=3.5 Hz) indicates a pseudoequatorial position for H-5, implying a *cis* relationship between H-5 and H-14 (Figure 2 and Table 2). In agreement with this, the infrared spectrum of compound 11 exhibits a broad hydroxylic absorption at 3500-3300 cm^{-1}, which proved to be concentration independent in chloroform solution over the range 10^{-3}-10^{-4} *M* and was thus in keeping with an intramolecular OH-N hydrogen bond.[13]

Similar spectroscopic behaviour (^{1}H NMR) regarding these protons allows us to propose a pseudoaxial conformation for the OH group in compound 10, implying a *trans* relationship between H-5 and H-14 (Figure 2 and Table 2). The IR spectrum for this compound ($CHCl_3$) shows the existence of a free OH band (3620 cm^{-1}) and an associate OH band (3560-3400 cm^{-1}). Therefore, we are able now using difference NOE measurements to correct the stereochemical assignment first proposed for the epimeric C-5 compounds 10 and 11.[4]

EXPERIMENTAL

Melting points were determined on either Electrothermal 1A 6304 or Büchi apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1430 spectrophotometer and only noteworthy absorptions (cm^{-1}) are reported. The 250 MHz ^{1}H NMR spectra were performed on a Bruker WM-250 spectrometer at ambient temperature. ^{1}H-{^{1}H} NOE experiments were carried out in the difference mode.[6] Chemical shifts are reported in parts per million (ppm) downfield (δ) from internal tetramethylsilane; the solvent for NMR spectra was deuteriochloroform unless otherwise stated. Routine mass spectra were obtained using a Hewlett-Packard HP-5970 instrument. Combustion analyses were performed with a Perkin-Elmer model 240 B.

All reactions were monitored by thin-layer chromatography (tlc) carried out on 0.2 mm silica gel 60 GF-254 (Merck) plates using UV light and Dragendorff's reagent[14] as the developing agent. Column chromatography was conducted with silica gel 60, 0.040-0.063 nm, 230-400 mesh (Merck).

3,4,5-trimethoxybenzyl 3,4-dimethoxyphenyl ketone 5.

Thionyl chloride (11.6 ml) was added to a solution of 3,4,5-trimethoxyphenyl acetic acid 3 (18.1 g, 0.08 mol) prepared from 3,4,5-trimethoxybenzaldehyde 1 following Baker's procedure[15] in dry benzene (250 ml) at 30°C and allowed to stand for 3/4 h, then heated under reflux for 3 h. Solvent and excess of thionyl chloride were evaporated under reduced pressure, thus obtaining 3,4,5-trimethoxyphenylacetyl chloride 4 as a yellow oil. To a solution of this chloride and 1,2-dimethoxy-

benzene (13.8 g, 0.1 mol) in dry dichloromethane (150 ml), anhydrous $AlCl_3$ (16 g, 0.12 mol) was added and the mixture was heated under reflux for 3 h. The cooled solution was poured into a stirred mixture of water (30 ml), 6M HCl (66 ml), and ice (90 g). The organic phase was separated, and the aqueous phase was extracted with dichloromethane (3x50 ml). The combined extracts were dried ($MgSO_4$) and filtered. Removal of solvents *in vacuo* afforded a residue that was flash chromatographed[16] (eluent: CH_2Cl_2/EtOAc, 8:2), to give ketone 5 (21.2 g, 77%), which crystallized from ethanol as colourless needles, mp 156-158°C (lit.[17] mp 151-152°C).

N-1-(3,4-dimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethylformamide 6.

A mixture of ketone 5 (15 g, 0.043 mol), ammonium formate (27 g, 0.43 mol), 90% formic acid (8.6 ml, 0.21 mol), and formamide (8.3 ml, 0.21 mol) was heated at 185-190°C for 3.5 h. After cooling to room temperature the reaction mixture was poured into water and an abundant precipitate was produced. The so-obtained solid crystallized from ethanol to afford formamide 6 as a white solid (13.7 g, 88%), mp 167-169°C (lit.[17] mp 164-165°C).

1-(3,4-dimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethylamine 7.

To a well stirred solution of ethylformamide 6 (9.75 g, 26 mmol) in ethanol (100 ml), a solution (20 ml) of aqueous NaOH (40%) was added. The mixture was heated under reflux for 2 h, the solvent was evaporated, water was added, and then extracted with chloroform (3x100 ml). Evaporation of the solvent from the combined dried extracts afforded a white solid, which crystallized from ethanol to give ethylamine 7 (7.2 g, 80%), mp 70-72°C (lit.[17] mp 71-72°C).

trans-3-(3,4-dimethoxyphenyl)-6,7,8-trimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline 8.

To a stirred solution of ethylamine 7 (5.6 g, 17 mmol) in 12M H_2SO_4 (200 ml), acetaldehyde (0.8 ml, 17 mmol) was added and the mixture was stirred under reflux for 1.5 h. Then, a second portion of acetaldehyde (0.8 ml) was added and the mixture stirred at room temperature overnight. After addition of a third portion of acetaldehyde (0.8 ml), the solution was refluxed for 5 h. The reaction mixture was cooled, extracted with ether (3x50 ml), and basified to pH 9 with NaOH (20%). The resulting aqueous layer was extracted with ether (3x50 ml) and dried (Na_2SO_4). Removal of the solvent afforded a brown syrup, which on crystallization from methanol gave tetrahydroisoquinoline 8 (4.7 g, 75%), mp 85-87°C. IR (KBr) ν_{max} 3315 (NH). ^{1}H NMR δ 7.03 (1H, d, J_{meta}= 1.9, H-2'), 6.96 (1H, dd, J_{ortho}= 8.2, J_{meta}= 1.9, H-6'), 6.85 (1H, d, J_{ortho}= 8.2, H-5'), 6.39 (1H, s, H-5), 4.46 (1H, q, J= 6.5, H-1), 4.23 (1H, t, J= 7.5, H-3), 3.93 (3H, s, OMe), 3.89 (3H, s, OMe), 3.87 (3H, s, OMe), 3.84 (3H, s, OMe), 3.81 (3H, s, OMe), 2.85 (2H, d, J= 7.5, 2H 2H-4), 2.28 (1H, broad s, NH), 1.52 (3H, d, J= 6.5, Me). MS, *m/e* 373 (M^+, 4), 358 (100), 208 (25), 193 (29). Anal. Calcd. for $C_{21}H_{27}NO_5$: C, 67.56; H, 7.24; N, 3.75. Found: C, 67.88; H, 7.23; N, 3.75..

trans-*N*-(2,2-Diethoxyethyl)-3-(3,4-dimethoxyphenyl)-6,7,8-trimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline 9.

A solution of the tetrahydroisoquinoline 8 (3.73 g, 10 mmol) in dry dioxane[18] (20 ml) was added under nitrogen to 0.3 g of sodium hydride (80% suspension in oil) in dry dioxane (10 ml). The resulting suspension was stirred and heated at 110°C under nitrogen for 5 h. Then, the mixture was cooled to room temperature and bromoacetaldehyde diethyl acetal (3 ml, 20 mmol) was added dropwise. The reaction mixture was heated at 110°C under nitrogen for 24 h. The reaction was monitored by tlc ($CHCl_3$/MeOH, 9:1). Excess NaH was decomposed by dropwise addition of methanol and the resulting solution poured into toluene/water. The aqueous phase was extracted with toluene (3x30 ml). Evaporation of the solvent from the combined extracts afforded an oil which crystallized from methanol to give the *N*-alkylated tetrahydroisoquinoline 9 (3.76 g, 77%), mp 90-91°C. IR (KBr) ν_{max} 1287 (OCH_2). ^{1}H NMR δ 7.14 (1H, d, J_{meta}= 1.7, H-2'), 7.00 (1H, dd, J_{ortho}= 8.2, J_{meta}= 1.7, H-6'), 6.84 (1H, d, J_{ortho}= 8.2, H-5'), 6.47 (1H, s, H-5), 4.40 (2H, m, H-1 and $CH(OEt)_2$), 4.30 (1H, dd, J_{AX}= 4.8, J_{BX}= 11.5, H-3), 3.93 (3H, s, OMe), 3.92 (3H, s, OMe), 3.89 (3H, s, OMe), 3.86 (3H, s, OMe), 3.84 (3H, s, OMe), 3.47 (4H, m, OCH_2CH_3), 3.00 (1H, dd, J_{BX}= 11.5, J_{AB}= 16.5, H-4), 2.85 (1H, dd, J_{AX}=4.8, J_{AB}= 16.5, H-4), 2.45 (1H, dd, J_{BX}= 5.9, J_{AB}= 13.6, $CH_2CH(OEt)_2$), 2.29 (1H, dd, J_{AX}= 5.9, J_{AB}= 13.6, $CH_2CH(OEt)_2$), 1.49 (3H, d, J= 6.6, $CHCH_3$), 1.19 (3H, t, J= 7.0, OCH_2CH_3), 1.07 (3H, t, J= 7.0, OCH_2CH_3). Anal. Calcd. for $C_{27}H_{39}NO_7$: C, 66.25; H, 7.97; N, 2.86. Found: C, 65.89; H, 7.72; N, 2.88.

cis-5-hydroxy-2,3,9,10,11-pentamethoxy-8-methyl-5,6,13,14-tetrahydroprotoberberine 10 and *trans*-5-hydroxy-2,3,9,10,11-pentamethoxy-8-methyl-5,6,13,14-tetrahydroprotoberberine 11.

Hydrochloric acid 6M (30 ml) was added dropwise to tetrahydroisoquinoline 9 (3 g, 6 mmol), and the resulting solution was magnetically stirred overnight at room temperature. The reaction mixture was extracted with chloroform and the combined dried extracts were evaporated under reduced pressure to afford a solid residue which on tlc ($CHCl_3$/MeOH, 9:1) showed two spots attributed to the hydrochloride salts of protoberberines 10 and 11. A suspension of this mixture in water was basified (pH 10) by adding 50% aqueous NH_4OH and stirred at room temperature for 6 h. The resulting aqueous solution was extracted with chloroform (3x20 ml) and dried (Na_2SO_4). Removal of the solvent afforded a residue (2.47 g), which was

column chromatographed ($CHCl_3$/MeOH, 100-99.5%) to afford diastereomers 10 and 11 in a 3:2 ratio. R_f 0.8 and 0.7 respectively ($CHCl_3$/MeOH, 9:1). Compound 10, yield: 1.46 g, 57% white crystals of mp 174-176°C from methanol (lit.[4] 174-176°C). Compound 11, yield: 0.97 g, 38%, white crystals of mp 148-150°C from methanol (lit.[4] 148-150°C).

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