CONSTITUENTS OF WEST AFRICAN MEDICINAL PLANTS XXV[1] ISOLATION OF OBLONGINE FROM *TILIACORA DINKLAGEI* AND THE SYNTHESIS OF OBLONGINE AND RELATED BENZYLISOQUINOLINE ALKALOIDS

D. DWUMA-BADU, J. S. K. AYIM, T. T. DABRA

Faculty of Pharmacy, University of Science and Technology, Kumasi, Ghana, West Africa

and M. M. EL-AZIZI,[2] P. L. SCHIFF, JR., D. J. SLATKIN, and J. E. KNAPP*

School of Pharmacy, University of Pittsburgh, Pittsburgh, PA 15261

ABSTRACT.—An investigation of the water-soluble alkaloid fraction of the roots of *T. dinklagei* resulted in the isolation of the novel benzylisoquinoline alkaloid, oblongine (**17**). The identity of the isolated oblongine (**17**) was established by spectral means as well as by synthesis. During the course of the synthesis, several compounds (**11, 12, 13, 15, 16, 18,** and **19**) not previously reported were prepared. Their properties as well as those of certain related compounds are presented.

Tiliacora dinklagei (Menispermaceae), a woody climber indigenous to Ghana and other parts of West Africa, has been the subject of previous investigations in our laboratories (1-4) and has yielded, in addition to several previously described bases, the new bisbenzylisoquinoline biphenyl alkaloids, dinklacorine (**1**) and tiliageine (**2**). Because *T. dinklagei* had proven to be a good source of alkaloids and to complete our investigation, a study of the water-soluble alkaloid fraction of extracts of the roots of this plant was undertaken.

Dried, powdered roots of *T. dinklagei*, after moistening with dilute ammonium hydroxide, were extracted with ethanol and the resulting extract subjected to solvent partitioning as previously described (2). The aqueous ammonium hydroxide fraction remaining after the removal of the chloroform-soluble bases was acidified and treated with an excess of Mayer's reagent (5) to precipitate the water-soluble alkaloids. The resulting precipitate was passed, as a solution in aqueous methanol, through a column of an anion exchange resin (IRA 401S; I^-) to convert the bases into their iodide salts. Chromatography of the crude alkaloid iodide fraction over a column of acid alumina afforded a fraction containing oblongine (**17**). Re-chromatography of the oblongine-containing fraction over a column of silica gel G afforded pure oblogine (**17**), which was identified by comparison of its physical properties with published values (6).

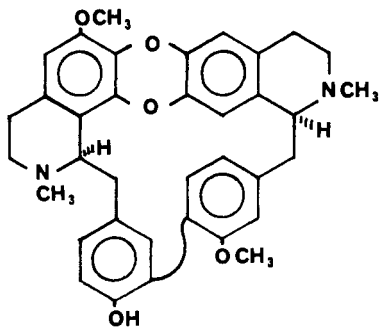
Prior to the initiation of this study, oblongine (**17**) had been isolated only once from a natural source, *Berberis oblonga* (Berberidaceae) (6). In addition to its occurrence in *T. dinklagei*, it has subsequently been found in *T. funifera* (7) and *B. baluchistanica* (8).

Because authentic oblongine (**17**) was not available to us for direct comparison and because its structure had not been proven previously by synthesis, we set out to prepare it by an unequivocal route. The synthetic product obtained was found to be identical to the isolated material.

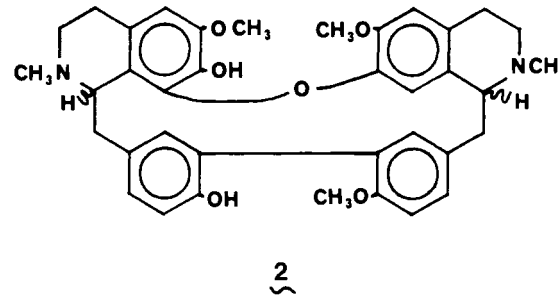
In the course of this work, we obtained several compounds (**11-13, 15, 16, 18,** and **19**) not previously prepared or isolated from natural sources. In anticipation of their isolation, we wish to present here their physical properties for future reference. Selected properties of certain other related compounds (**6-10, 14**) obtained in the course of the

[1]Previous paper: *Phytochemistry*, **19**, 1882 (1980).

[2]Present address: Department of Pharmacognosy, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt.



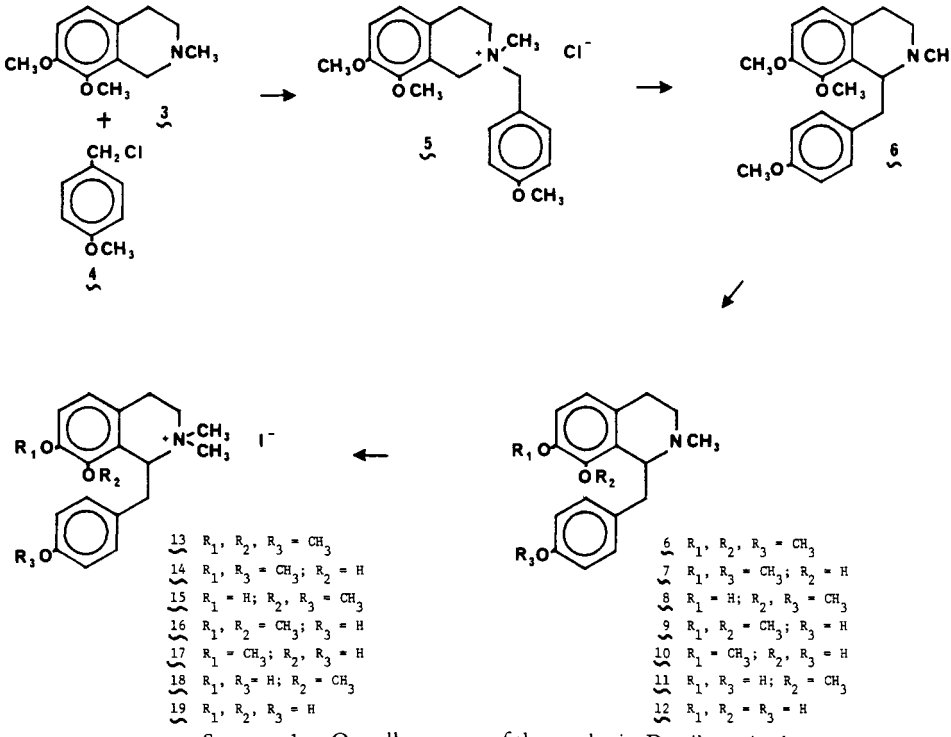
1



2

synthesis but not new, are also reported for the purpose of completeness and comparison.

The synthetic route to oblongine (**17**) and related compounds followed that described by Grethe *et al.* for the synthesis of petaline (**14**) (9). Modifications were made of various steps to increase yields or to favor the production of certain products. The overall synthesis is presented in scheme 1.



13 R_1, R_2, R_3 = CH_3
14 R_1, R_3 = CH_3; R_2 = H
15 R_1 = H; R_2, R_3 = CH_3
16 R_1, R_2 = CH_3; R_3 = H
17 R_1 = CH_3; R_2, R_3 = H
18 R_1, R_3 = H; R_2 = CH_3
19 R_1, R_2, R_3 = H

6 R_1, R_2, R_3 = CH_3
7 R_1, R_3 = CH_3; R_2 = H
8 R_1 = H; R_2, R_3 = CH_3
9 R_1, R_2 = CH_3; R_3 = H
10 R_1 = CH_3; R_2, R_3 = H
11 R_1, R_3 = H; R_2 = CH_3
12 R_1, R_2 = R_3 = H

SCHEME 1. Overall sequence of the synthesis. Details are in the text.

A crucial step in the synthesis is the Stevens rearrangement of the *N*-benzylisoquinoline (**5**) to afford **6**. By carefully controlling the reaction conditions, especially by maintaining anhydrous conditions, it was possible to carry out the rearrangement in 97% yield. Demethylation of **6** was accomplished by heating with 48% hydrobromic acid. Grethe *et al.* used 36% hydrobromic acid (160 min) to affect the demethylation of **6** predominantly at the methoxyl on C-8 (9). In the present work, it was found that, by heating at 120° for 160 minutes, the tri-*O*-demethylated compound (**12**) was formed quantitatively. This compound has not been reported previously. It was quite

unstable as the free base, decomposing rapidly to a blood-red product. However, the hydrobromide salt and methiodide derivative (**19**) proved to be quite stable.

Lower temperature and shorter reaction time (116°, 15 minutes) afforded a mixture of demethylated products **7-11**, of which the desired compound **10** predominated. Finally, treatment of the *O*-demethylated bases with methyliodide was used to produce the quaternary analogs **13-19**.

Identification of the synthesized bases was readily made on the basis of mass spectral fragmentation and pmr spectral correlations. Most helpful was the observation that, in all cases, the signals due to the protons on C-5 and C-6 of the isoquinoline moiety appear as two doublets when C-8 bears a hydroxyl group and, as a two-proton singlet when this group is a methoxyl (9) (table 1).

Identification of the quaternary compounds **13-19** was facilitated by the observation that, like petaline (**14**), those compounds with an hydroxyl group at C-8 exhibited mass spectra characterized by strong M^+-1 peaks (>30%). This peak is presumed to be due to a fragment arising from a Hofmann elimination aided by participation of the hydroxyl group on C-8 (10,11). When this carbon carries a methoxyl group, the elimination is no longer facilitated, and the intensity of the M^+-1 fragment decreases dramatically (<10%).

In this study, the isolated oblongine (**17**) was found to be optically inactive. This was also the case in two of the previously reported isolations (7,8) although the original report (6) indicated a positive optical rotation ([α]D+8.5°). It is interesting to note that this value differs in sign, but not significantly in magnitude, from that of the other naturally occurring compound of this group, petaline (**14**), shown to have the R configuration (12). Whether the lack of optical activity found in the isolations of oblongine (**17**) subsequent to the original report is due to the isolation procedures or is an example of naturally occurring racemates remains unresolved.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined on a Fisher-Johns apparatus and are not corrected. A Hitachi-Perkin-Elmer Model R24 spectrometer (60 Mhz) was used to determine pmr spectra and results were recorded in δ (ppm) units. A Perkin-Elmer model 257 recording spectrometer established ir spectra in KBr; uv spectra were taken in methanol on a Perkin-Elmer model 202 recording spectrometer. Optical rotations were measured on a Perkin-Elmer model 241 automatic polarimeter. Column chromatography was performed on either acid alumina (Spence) or silica gel G (Camag), while tlc was performed on silica gel G (Camag). Solvents were evaporated *in vacuo* on a Buchler rotary evaporator at a temperature not exceeding 40°.

ISOLATION AND CHROMATOGRAPHY.—The extraction procedure and initial fractionation of the extract has been reported previously (2). The aqueous alkaline fraction (10 liters) remaining after the removal of the chloroform-soluble alkaloids was acidified (pH 2-3) with concentrated HCl and treated with an excess of Mayer's reagent (5) to precipitate the water-soluble bases as an insoluble complex. The precipitate was washed with water and dried to yield 12.5 g of alkaloid complex. The complex was dissolved in methanol-water (9:1; 8 liters) and the solution passed slowly through a column of Amberlite-IRA-401S anion exchange resin (I^- form). The column eluate yielded on evaporation 6.5 g of crude alkaloidal iodides.

The total alkaloidal iodides were dissolved in methanol and adsorbed onto 15 g of acid alumina by evaporation of the solvent. The resulting powder was then added to the top of a column of acid alumina (72 g) packed in chloroform. The column was then eluted with chloroform followed by chloroform-ethanol mixtures. Fractions of 100 ml were collected and combined using tlc (MeOH-NH_4OH-H_2O; 4:1:1) as a guide. Elution with chloroform-ethanol (95:5) afforded a combined fraction (850 mg) containing oblongine (**17**) (Rf 0.26).

ISOLATION OF OBLONGINE IODIDE (**17**).—Chromatography of the oblongine-containing fraction (850 mg) over a column of silica gel G (100 g) packed in and eluted with a mixture of ethyl acetate-1-butanol-acetic acid-water (60:10:10:15) afforded 240 mg of purified oblongine (**17**) as an amorphous material. Crystallization from methanol-acetone (1:1) gave needles of oblongine iodide (**17**) (137 mg), mp 153-55° $[\alpha]^{20}D$ 0° (c 1.44, MeOH); uv, λ max (MeOH) 213 nm (log ε 4.17), 227(4.09) and 283(3.50); λ max (0.01N KOH in MeOH) 218 nm (log ε 4.25) 250(3.57) and 300(3.63); ir, ν max (KBr) 3600-3100 (br),

2910, 1600, 1510, 1470, and 1450 cm^{-1}; ms, M^+ *m/z* 314 (10%) consistent with $C_{19}H_{24}NO_3$, with other fragment ions at *m/z* 313 (M^+-1) (44), 192(100), 177(10), 142(13), 128(46), 127(38) and 58(32); pmr (see table 1). These data were in good agreement with those published for oblongine (**17**) (6,8).

TABLE 1. Pmr data for compounds **6** to **19**.[a]

Compound	N-CH_3	4′-OCH_3	7-OCH_3	8-OCH_3	H-5, H-6	H-2′, H-3′; H-5′, H-6[b]
6	2.31	3.75	3.82	3.87	6.75	6.80
						7.20
7	2.32	3.75	3.82	—	6.55[c]	6.75
					6.72	7.18
8	2.40	3.78	—	3.80	6.70	6.72
						7.12
9	2.40	—	3.86	3.91	6.87	6.60
						7.07
10	2.45	—	3.84	—	6.70[c]	6.54
					6.82	7.07
11	2.48	—	—	3.81	6.76	6.69
						7.05
12[d]	3.00	—	—	—	6.91[c]	6.71
					7.05	7.25
13	3.38	3.75	3.89	3.94	6.84	6.78
	3.50					7.07
14	3.32	3.75	3.89	—	6.74[c]	6.78
	3.48				6.92	7.17
15[e]	3.35	3.78	—	3.89	6.96	6.72
	3.40					7.15
16[e]	3.42	—	3.89	3.89	6.90	6.82
	3.51					7.18
17[f]	3.02	—	3.80	—	6.73[c]	6.70
	3.10				7.05	7.10
18[f]	3.05	—	—	3.86	6.81	6.60
	3.20					7.00
19[f]	3.00	—	—	—	6.60[c]	6.50
	3.05				6.78	7.06

[a]Determined in $CDCl_3$ solution with TMS as internal standard.
[b]Each signal 2H, d, J=8 Hz.
[c]Each signal 1H, d, J=8 Hz.
[d]Determined in trifluoroacetic acid with TMS as internal standard.
[e]Determined in acetone-d_6 with TMS as internal standard.
[f]Determined in DMSO-d_6 with TMS as internal standard.

SYNTHESIS OF 7,8-DIMETHOXY-2-METHYL-1,2,3,4-TETRAHYDROISOQUINOLINE (**3**).—This compound was synthesized using the general method described by Bobbitt *et al.* (13,14). A mixture of 2,3-dimethoxybenzaldehyde[3] (3.32 g; 0.02 mole) and aminoacetaldehyde-diethylaceral[3] (2.66 g; 0.02 mole) in absolute ethanol was added to 0.2 g of platinum oxide that had previously been reduced with hydrogen in 20 ml of the same solvent. The mixture was then reduced at room temperature and atmospheric pressure until the consumption of hydrogen ceased (6 h). The mixture was filtered, and the filtrate was evaporated to give a residue, which was dissolved in 100 ml of 6 N HCl, washed with 50 ml of ether, and allowed to stand at room temperature for 15 h. Palladium (2 g) on carbon was added and the mixture reduced at room temperature and atmospheric pressure until the consumption of hydrogen ceased (9 h). The mixture was filtered and the filtrate evaporated to yield a residue of the 7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (3.3 g), mp 189-90°. The procedure was repeated until a large quantity (13 g) of the hydrochloride was obtained. This hydrochloride was dissolved in water (400 ml), the solution rendered alkaline (pH 9) with NH_4OH, and then extracted with chloroform (4 x 400 ml). The chloroform solutions were combined, dried over Na_2SO_4, and evaporated to yield 12.3 g of 7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline as a residue. This was dissolved in 160 ml ethanol, 16 ml of 37% formaldehyde solution added dropwise with stirring and the mixture stirred for 18 h. To this mixture was slowly added 12 g of

[3]Aldrich Chemical Co. Inc.

$NaBH_4$ and the mixture stirred for 9 h. The mixture was filtered and the filtrate evaporated. The resulting residue was dissolved in 10% aqueous HCl (200 ml), filtered, the filtrate basified (pH 9) with NH_4OH and extracted with chloroform (4 x 400 ml). The chloroform solutions were combined, dried over Na_2SO_4, and evaporated to yield a residue of 7,8-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**3**) (11.3 g). The spectral properties of this compound were in excellent agreement with those reported previously (9).

SYNTHESIS OF p-METHOXYBENZYL CHLORIDE (**4**).—Thionyl chloride (0.15 mole) in dry chloroform (100 ml) was added dropwise with stirring to a previously cooled (0°) chloroform solution of 0.15 mole of *p*-methoxybenzyl alcohol. The mixture was stirred for 1.5 h at 0°, then for an additional 0.5 h at room temperature. The reaction mixture was evaporated to a residue and the residue redissolved in chloroform and re-evaporated several times to remove the remaining thionyl chloride. The residue was distilled at atmospheric pressure and the fraction, boiling at 190-210°, was collected to give the required *p*-methoxybenzyl chloride (**4**), whose properties were in excellent agreement with those reported previously (15).

SYNTHESIS OF 7,8-DIMETHOXY-2-(4-METHOXYBENZYL)-2-METHYL-1,2,3,4-TETRAHYDROISOQUINOLINE CHLORIDE (**5**).—To a solution of 8.69 g of 7,8-dimethoxyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (**3**) in 100 ml of dry benzene, 10 g of *p*-methoxybenzyl chloride (**4**) was added and the mixture allowed to stand at 35° for 15 h. The precipitate formed was recovered and washed with dry benzene to afford 9.6 g of 7,8-dimethoxy-2-(4-methoxybenzy)-2-methyl-1,2,3,4-tetrahydroisoquinoline (**5**), mp 204-5°, whose properties were in close agreement with those reported (9).

SYNTHESIS OF 7,8-DIMETHOXY-2-METHYL-1-(4-METHOXYBENZYL)-1,2,3,4-TETRAHYDROISOQUINOLINE (**6**).—This reaction was carried out in an apparatus that ensured very dry conditions. The reaction vessel consisted of a flask fitted with a bubbler for dry nitrogen, a magnetic stirring bar, and a rubber septum for the introduction of phenyllithium solution. The flask was vented through a reflux condenser whose outlet was connected to a bubbler immersed in heavy mineral oil. To 100 ml of dry ether in the flask was added 10.9 g of 7,8-dimethoxy-2-(4-methoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline chloride (5). Dry nitrogen was bubbled and the mixture stirred for 30 min. A solution of phenyllithium (Aldrich Chemical Co., Inc.;—1.9 M) in benzene-ether (7:3, 57 ml) was added dropwise via the rubber septum by means of a glass syringe. The reaction mixture was stirred for 4 h at room temperature with constant, slow bubbling of nitrogen. The reaction mixture was poured onto ice (approx. 200 ml), the flask washed twice with benzene-ether (7:3), and washings added to the ice. To this was added 400 ml of ether; the mixture was shaken and the ether layer removed. The process was repeated twice; the resulting ether solutions were combined, dried (Na_2SO_4), and evaporated to yield a brown residue of 7,8-dimethoxy-2-methyl-1-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (**6**) (9.5 g, 97%), which was purified by conversion to the hydrochloride salt. The residue was dissoved in a small amount of absolute ethanol and an equal volume of ethanolic HCl was added. The resulting hydrochloride salt, when recovered and dried, showed mp 178-9°. The free base regenerated from this hydrochloride showed: $[\alpha]^{26}D=0$ (C, 0.83, $CHCl_3$); ir: ν max (KBr) 2915, 2815, 2410, 1605, 1580, 1510, 1490, 1440, 1420, 1350, 1280, 1250, 1240, 1180, 1130, 1110, 1090, 1060, 1025, 985, 960, 835, 825, and 805, cm^{-1}; uv: λ max (MeOH) 235 nm (log ϵ 3.30), 280(305); ms: M+ (*m/z*) 327 (0.12%) consistent with $C_{20}H_{25}NO_3$ and other fragment ions at *m/z* 326 (M^+-1) (0.28), 206(100), 191(7), 190(13), 121(4), and 43(9). The pmr spectrum is presented in table 1. These data were in close agreement with those reported previously (9).

PREPARATION OF 7,8-DIHYDROXY-2-METHYL-1-(4-HYDROXYBENZYL)-1,2,3,4-TETRAHYDROISOQUINOLINE (**12**).—The hydrochloride salt of **6** (1 g) and 48% HBr (50 ml) was heated at 120° under nitrogen for 160 min. The reaction mixture was cooled, diluted with 100 ml of water and evaporated *in vacuo* to yield a crystalline deposit (1.12 g). Recrystallization from hot methanol afforded very hygroscopic crystalline needles of 7,8-dihydroxy-2-methyl-1-(4-hydroxybenzyl)-1,2,3,4-tetrahydroisoquinoline (**12**) as the hydrobromide salt (mp 217-219°). The compound showed: ir ν max (KBr) 3450-2950 (broad), 2820, 2720, 2640, 1610, 1585, 1495, 1470, 1435, 1360, 1295, 1310(sh), 1285, 1255, 1235, 1200, 1125, 1075, 1030, 985, 965, 920, 900, 860, 845, 820, and 805 cm^{-1}; uv λ max (MeOH) 218 nm (log ϵ 3.80), 239(3.90) and 284(3.54); ms (free base) M^+ (*m/z*) 285 (1%) indicative of $C_{17}H_{19}NO_3$ and other fragment ions at *m/z* 284(2), 179(87), 178(100), 163(10), 153(9), 148(8), 147(10), 132(11), 108(20), 107(43), 97(15), 91(16), 83(19), 77(28), 71(28), 69(28), 60(24), 57(40), 56(53), 55(40), 51(15), and 43(69). The pmr spectrum is presented in table 1.

PREPARATION OF 7,8-DIHYDROXY-2,2-DIMETHYL-1-(4-HYDROXYBENZYL)-1,2,3,4-TETRAHYDROISOQUINOLINE IODIDE (**19**).—A solution of 100 mg of the hydrobromide salt of **12** in 100 ml of water was alkalinized with NH_4OH and quickly extracted with ethyl acetate (3 x 80 ml). The combined extract was dried (Na_2SO_4) and rapidly added to a dry solution of methyl iodide (5%) in ethyl acetate. The solution was kept under nitrogen, in dark for 2 h and evaporated. The residue obtained was dissolved in hot petroleum ether-ethyl acetate-methanol (40:10:15), filtered, and left in the dark overnight. The crystals ob-

tained were washed once with cold ethyl acetate-methanol and dried to yield 7,8-dihydroxy-2,2-dimethyl-1-(4-hydroxybenzyl)-1,2,3,4-tetrahydroisoquinoline (**19**), mp 206-8°, ir ν max (KBr) 3440, 3220 (broad), 2990, 1610, 1595, 1505, 1490(sh), 1480, 1465, 1445, 1380, 1365, 1350, 1330, 1310, 1300, 1280, 1260, 1240, 1200, 1160, 1155, 1120, 1100, 1070, 1060, 1035, 1015, 990(sh), 980, 930, 910, 890, 860, 840, 820, 810, 800 cm^{-1}; uv λ max (MeOH) 232 nm (log ε 4.08), 283(3.5; ms M^+ *m/z* 300 (7%) consistant with $C_{18}H_{22}NO_3$, with other fragment ions at *m/z* 299(38), 178(43), 163(2), 147(9), 142(5), 133(11), 128(100), 127(53), 107(22), 91(8), 65(8), 77(14), 65(68), and 58(86). The pmr spectrum is presented in figure 1.

PREPARATION OF COMPOUNDS **7-11**.—7,8-Dimethoxy-2 methyl-1-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (**6**) (1 g) was heated with 50 ml of 48% HBr at 116°, under nitrogen, for 15 min. The reaction mixture was diluted with water (50 ml), basified with concentrated NH_4OH and extracted with chloroform (5 x 50 ml). The chloroform extracts were combined, dried (Na_2SO_4), and evaporated to yield a residue (598 mg). The residue was chromatographed over a column (37 x 3 cm) of silica gel G (75 g) and acid-washed Celite (25 g) packed in and eluted with benzene-methanol (95:5). Fractions of 20 ml were collected and combined using tlc (benzene-acetone-NH_4OH; 16:16:3) as a guide.

ISOLATION OF COMPOUND **7** (GORTSCHAKOINE).—Column fractions 7-11 yielded an oily residue (55 mg; Rf 0.78) which, on treatment with ethereal HCl, gave the hydrochloride of **7**, mp 106-10°; ir ν max (KBr) 3400(broad), 2910, 2820, 2545(broad), 2345(broad), 1610, 1580, 1510, 1500, 1450, 1400, 1360, 1320, 1280, 1245, 1180, 1125, 1090, 1070, 1020, 980, 920(broad), and 880(broad) cm^{-1}; uv λ max (MeOH) 232 nm (log ε 4.19) and 282(3.65). The ms of the free base showed M^+, *m/z* 313 (0.14%) indicative of $C_{19}H_{23}NO_3$ and other fragment ions at *m/z* 312(07), 193(59), 192(100), 140(12), 177(76), 176(12), 175(5), 162(6), 121(32), 78(16), 77(15), and 43(14). The pmr spectrum of the free base is presented in table 1. These data were in good agreement with those published for gortschakoine (**7**) (16).

7-HYDROXY-8-METHOXY-2-METHYL-1-(4-METHOXYBENZYL)-1,2,3,4-TETRAHYDROISOQUINOLINE (**8**).—Column fractions 14-15 yielded a yellow oil (9 mg; Rf 0.66) which, on treatment with ethereal HCl, gave the hydrochloride of **8**, mp 115°; ir ν max (KBr) 3400(broad), 2945(sh), 2920, 2845, 1600, 1570, 1555, 1510, 1505(sh), 1465, 1455, 1450, 1400(broad), 1380, 1365, 1300, 1175, 1125, 1080, 1025, and 815 cm^{-1}; uv λ max (MeOH) 230 nm (log ε 4.20), and 280(3.7). The ms of the free base showed M^+, *m/z* 313 (0.12%) consistent with $C_{19}H_{20}NO_3$ and other fragment ions at *m/z* 312(0.36), 192(100), 177(27), 121(7), 72(10), 69(11), 57(11), and 43(15). The pmr spectrum is presented in table 1. These data were in good agreement with those published previously (9).

7,8-METHOXY-2-METHYL-1-(4-HYDROXYBENZYL)1,2,3,4-TETRAHYDROISOQUINOLINE (**9**).—Column fractions 18-20 yielded a residue (8 mg; Rf 0.59) which, on treatment with ethereal HCl, gave the hydrochloride of **9**; ir ν max (Kbr) 3400(broad), 3200(broad), 2920, 2840, 1610, 1510, 1495, 1450, 1440, 1280, 1230, 1170, 1085, and 820 cm^{-1}; uv λ max (MeOH) 232 nm (log ε 4.13) and 282(3.68). The ms of the free base showed M^+, *m/z* 313 (0.14%) consistent with $C_{19}H_{23}NO_3$ and other fragment ions at *m/z* 312(0.4), 207(27), 206(100), 192(23), 191(11), 190(26), 163(10), 148(10), 107(10), and 43(8). The pmr spectrum of the free base is presented in figure 1. These data were in close agreement with those published previously (9).

COMPOUND **10** (JUZIPHINE).—Column fractions 27-59 yielded a residue from which compound **10** (juziphine) (350 mg; Rf 0.50) was crystallized from ether as a colorless, granular material, mp 166-9°, ir ν max (KBr) 3500(broad), 3460(broad), 2920, 1610, 1585, 1510, 1490, 1460(sh), 1445, 1360, 1320, 1275, 1230, 1085, 1020, 890, 845, 825, 795, 765, and 740 cm^{-1}; uv λ max (MeOH) 232 nm (log ε 4.24) and 281 (3.66); ms M^+, *m/z* 299 (0.6%) consistent with $C_{18}H_{21}NO_3$ with other fragment ions at *m/z* 298(0.2), 192(100), 177(25), 107(9), 78(48), and 43(24). The pmr spectrum is presented in figure 1. These data were in good agreement with those reported earlier for juziphine (**10**) (9,17).

7-HYDROXY-8-METHOXY-2-METHYL-1-(4-HYDROXYBENZYL)-1,2,3,4-TETRAHYDROISOQUINOLINE (**11**).—Column fractions 73-113 afforded a residue (37 mg; Rf 0.42) which, on treatment with ethereal HCl, yielded 7-hydroxy-8-methoxy-2-methyl-1-(4-hydroxybenzyl)-1,2,3,4-tetrahydroisoquinoline (**11**) as a brownish, granular hydrochloride (6 mg), mp 130-135°, ir λ max (KBr) 3345(broad), 2920, 2845, 1610, 1595, 1510, 1450, 1380, 1300, 1020, and 820 cm^{-1}; uv λ max (0.01N methanolic NaOH) 232 nm (log ε 4.18), 302(3.53) and 336(3.40). The ms of the free base showed M^+ *m/z* 299 (0.5%) attributable to $C_{18}H_{21}NO_3$ and other fragment ions at *m/z* 298(0.6), 192(100), 190(10), 177(59), 148(8), 107(13), 83(10), 77(11), 69(17), 67(9), 57(23), 55(24), and 43(22). The pmr spectrum of the free base is presented in table 1.

PREPARATION OF 7,8-DIMETHOXY-2,2-DIMETHYL-1-(4-METHOXYBENZYL)-1,2,3,4-TETRAHYDROISOQUINOLINE IODIDE (**13**).—To 20 mg of 7,8-dimethoxy-2-methyl-1-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (**6**) in 5 ml of acetone was added five drops of methyl iodide and the mixture allowed

to stand at room temperature for 1 h. The reaction mixture was evaporated *in vacuo* and the residue crystallized from acetone-ether to yield 7,8-dimethoxy-2,2-dimethyl-1-(4-methoxy-benzyl)1,2,3,4-tetrahydroisoquinoline iodide (**13**) (10 mg); mp 99-100°; ir ν max (KBr) 2930, 2830, 1605, 1510(sh), 1495, 1450, 1280, 1245, 1020, and 810 cm^{-1}, uv λ max (MeOH) 235 nm (log ϵ 3.70) and 283(3.00); ms M^+ *m/z* 342 (0.3%) consistent with $C_{21}H_{28}NO_3$ and other fragment ions at *m/z* 341(0.63), 327(8), 208(15), 207(15), 206(86), 192(8), 191(6), 190(13), 177(4), 163(5), 148(4), 142(48), 127(13), 121(7), and 58(100). The pmr spectrum is presented in table 1.

PREPARATION OF COMPOUND **14** (PETALINE IODIDE).—A solution of 33 mg of compound **7**(gortschakoine) in 10 ml of ether-acetone was treated with six drops of methyl iodide as before. The residue obtained on evaporation of the reaction mixture was crystallized from petroleum ether-acetone to give crystals of **14** (racemic petaline iodide) (34 mg); mp 136°; ir ν max (KBr) 3400(broad), 3000, 2920, 2830, 1610, 1585, 1520(sh), 1500, 1440, 1280, 1245, 1175, 1080, 1050, 1040, 920, and 810 cm^{-1}; uv λ max (MeOH) 230nm (log ϵ 3.98) and 283(3.24); ms M^+ *m/z* 328 (16%) consistent with $C_{20}H_{26}NO_3$ and other fragment ions at *m/z* 327(69), 206(15), 193(43), 192(100), 177(60), 142(63), 128(41), 127(32), 121(36), 59(19), and 58(66). The pmr spectrum is presented in table 1. These data were in good agreement with those reported previously for petaline (10,11,18,19).

PREPARATION OF 7-HYDROXY-8-METHOXY-2,2-DIMETHYL-1-(4-METHOXYBENZYL)-1,2,3,4-TETRAHYDROISOQUINOLINE IODIDE (**15**).—Treatment of 6 mg of 7-hydroxy-8-methoxy-2-methyl-1-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (**8**) in 2 ml acetone with six drops of methyl iodide, as before, gave, after evaporation 7-hydroxy-8-methoxy-2,2-dimethyl-1-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline iodide (**15**) as a residue 6 mg; mp 86-90°; ir ν max (KBr) 3400(broad), 3200(broad), 2945(sh), 2920, 2850, 1610, 1510, 1465, 1455, 1300, 1250, 1180, 1025, and 825 cm^{-1}; uv λ max (MeOH) 229 (log ϵ 4.0) and 282 (3.36); ms M^+, *m/z* 328 (2%) indicative of $C_{20}H_{26}NO_3$ and other fragment ions at *m/z* 327(7), 313(12), 282(7), 286(16), 242(7), 192(8), 142(73), 141(10), 128(12), 127(43), 122(9), 121(70), 107(18), 91(8), 77(12), 59(36), 58(100), and 43(15). The pmr spectrum is presented in table 1.

PREPARATION OF 7,8-DIMETHOXY-2,2-DIMETHYL-1-(4-HYDROXYBENZYL)-1,2,3,4-TETRAHYDROISOQUINOLINE IODIDE (**16**).—A solution of 4 mg of 7,8-dimethoxy-2-methyl-(4-hydroxybenzyl)1,2,3,4-tetrahydroisoquinoline (**9**) in 10 ml of acetone was treated with six drops of methyliodide as before. The residue obtained on evaporation of the reaction mixture was treated with methanol ether to afford 7,8-dimethoxy-2,2-dimethyl-1-(4-hydroxybenzyl)-1,2,3,4-tetrahydroisoquinoline iodide as granules)3 mg); mp 116°; ir ν max (KBr) 3200(broad), 3000, 2920, 2880, 1610, 1510, 1495, 1450, 1280, 1090, 1010, and 815 cm^{-1}; uv λ max (MeOH) 230 nm (log ϵ 3.07) and 282 (2.56); ms M^+, *m/z* 328 (0.13%) indicative of $C_{20}H_{26}NO_3$ and other fragment ions at *m/z* 327(0.5), 313(6), 207(3), 206(100), 192(13), 191(14), 190(31), 177(5), 163(14), 148(14), 142(53), 128(8), 127(36), 107(15), 77(13), 59(6), and 58(38). The pmr spectrum is presented in table 1.

PREPARATION OF COMPOUND **17** (OBLONGINE IODIDE).—Treatment of a solution of 55 mg of 7-methoxy-8-hydroxy-2-methyl-1-(4-hydroxybenzyl)-1,2,3,4-tetrahydroisoquinoline (**10**) (juziphine) in 10 ml acetone with 1 ml methyl iodide, as before, gave, after evaporation, a residue that was crystallized from acetone-petroleum ether to yield oblongine iodide (**17**) (59 mg); mp 161°. The spectral data for this compound all were in complete agreement with those of the isolated oblongine iodide.

PREPARATION OF 7-HYDROXY-8-METHOXY-2,2-DIMETHYL-1-(4-HYDROXYBENZYL)-1,2,3,4-TETRAHYDROISOQUINOLINE IODIDE (**18**).—Treatment of a solution of 6 mg of 7-hydroxy-8-methoxy-2-methyl-1-(4-hydroxybenzyl)-1,2,3,4-tetrahydroisoquinoline (**11**) in 1 ml of acetone with five drops of methyl iodide gave, after evaporation, a residue which, on treatment with acetone-ether, afforded 7-hydroxy-8-methoxy-2,2-dimethyl-1-(4-hydroxybenzyl)-1,2,3,4-tetrahydroisoquinoline iodide as an amorphous powder (5 mg); ir ν max (KBr) 3300(broad), 2920, 1590, 1515, 1500, 1450, 1380, 1300, 1250, 1020, and 820 cm^{-1}; uv λ max (MeOH) 236 nm (log ϵ 4.02) and 282(3.73); ms M^+, *m/z* 314 (0.25%) consistent with $C_{19}H_{24}NO_3$ and other fragment ions at *m/z* 313(1), 193(13), 192(100), 178(9), 177(40), 148(7), 142(64), 128(10), 127(28), 107(28), 177(10), 59(13), and 58(60). The pmr spectrum is presented in table 1.

ACKNOWLEDGMENTS

The authors are grateful to Mr. John Naworal, Graduate School of Public Health, University of Pittsburgh, for determining the mass spectra and to Dr. A. Brossi, Hoffman-LaRoche, Inc., for supplying an authentic sample of petaline. The mass spectrometry facility was supported by Research Grant RR-00273 to the University of Pittsburgh from the National Insitutes of Health.

Received 9 July 1982

LITERATURE CITED

1. A. N. Tackie, D. Dwuma-Badu, T. T. Dabra, J. E. Knapp, D. J. Slatkin, and P. L. Schiff, Jr., *Experientia*, **30**, 847 (1974).
2. A. N. Tackie, D. Dwuma-Badu, J. S. K. Ayim, T. T. Dabra, J. E. Knapp, D. J. Slatkin, and P. L. Schiff, Jr., *Lloydia*, **38**, 210 (1975).
3. D. Dwuma-Badu, J. S. K. Ayim, N. Y. Fiagbe, A. N. Tackie, J. E. Knapp, D. J. Slatkin, and P. L. Schiff, Jr., *Lloydia*, **39**, 213 (1976).
4. D. Dwuma-Badu, S. F. Withers, S. A. Ampofo, M. M. El-Azizi, D. J. Slatkin, P. L. Schiff, Jr., and J. E. Knapp, *J. Nat. Prod.* **42**, 116 (1979).
5. United States Pharmacopeial Convention, Inc., "The Pharmacopeia of the United States, 16th rev." Mack Publishing Co., Easton, PA., 1960, p. 1097.
6. A. Karimov, N. D. Abdullaev, M. V. Telezhenetskaya, K. Lutfullin, and S. Yu. Yunusov, *Chem. Nat. Comp.*, **12**, 111 (1976).
7. A. N. Tackie, J. B. Reighard, M. M. El-Azizi, D. J. Slatkin, P. L. Schiff, Jr., and J. E. Knapp, *Phytochemistry*, **19**, 1882 (1980).
8. M. H. Abu Zarga, G. A. Miana, and M. Shamma, *Tetrahedron Lett.*, 541 (1981).
9. G. Grethe, H. L. Lee, M. R. Uskokovic, and A. Brossi, *Helv. Chim Acta*. **53**, 875 (1970).
10. G. Grethe, M. Uskokovic, and A. Brossi, *J. Org. Chem.*, **33**, 2500 (1968).
11. G. Grethe, M. Uskokovic, and A. Brossi, *Tetrahedron Lett.*, 1599 (1966).
12. J. C. Craig, M. Martin-Smith, S. K. Roy, and J. B. Stenlake, *Tetrahedron*, **22**, 1335 (1966).
13. J. N. Bobbit, J. M. Kiely, K. L. Khanna, and R. Ebermann, *J. Org. Chem.* **30**, 2247 (1965).
14. J. M. Bobbit, D. N. Roy, A. Marchand, and C. W. Allen, *J. Org. Chem.*, **32**, 2225 (1976).
15. J. G. Grasse, "Atlas of Spectral Data and Physical Constants for Organic Compounds," Chemical Rubber Co., 1960, p. 239.
16. T. Irgashev, I. A. Israilov, N. D. Abdullev, M. S. Yunusov, and S. Yu. Yunusov, *Chem. Nat. Comp.*, **13**, 118 (1977).
17. R. Ziyaev, T. Irgashev, I. A. Israilov, N. D. Abdullaev, M. S. Yunusov, and S. Yu. Yunusov, *Chem. Nat. Comp.*, **13**, 204 (1977).
18. N. J. McCorkindale, A. W. McCulloch, D. S. Magrill, B. Caddy, M. Martin-Smith, S. J. Smith, and J. B. Stenlake, *Tetrahedron*, **25**, 5475 (1969).
19. N. J. McCorkindale, D. S. Magrill, M. Martin-Smith, S. J. Smith, and J. B. Stenlake, *Tetrahedron Lett.*, 3841 (1964).