ALKALOIDS OF THALICTRUM XXX.[1] ELEVEN MINOR ALKALOIDS FROM *THALICTRUM RUGOSUM*

WU-NAN WU,[2] JACK L. BEAL and RAYMOND W. DOSKOTCH

Division of Pharmacognosy and Natural Products Chemistry, College of Pharmacy, The Ohio State University, Columbus, Ohio 43210

ABSTRACT.—Additional alkaloids were obtained from *T. rugosum* and characterized by spectral methods. These minor constituents were obtained from the tertiary alkaloid fractions by extensive chromatography. The ether-soluble nonphenolic fraction gave oxyberberine (**1**), thalrugosinone (**2**), thalicthuberine (**3**), obaberine (**4**), protopine (**5**) and neothalibrine (**6**). The ether-soluble phenolic fraction afforded aromoline (**8**) and coryalline (**9**); while the chloroform-soluble fraction yielded rugosinone (**10**), noroxyhydrastinine (**12**) and 1,2-dihydro-6,7-methylenedioxy-1-oxoisoquinoline (**13**). All are new alkaloids for the source, with thalrugosinone (**2**), rugosinone (**10**) and 1,2-dihydro-6,7-methylenedioxy-1-oxoisoquinoline (**13**) also new natural products. Antimicrobial activity is reported for nine alkaloids and one derivative.

As part of a detailed study of the alkaloids from the genus *Thalictrum*, *T. rugosum* Ait. (*T. glaucum* Desf.) investigated in our laboratory has yielded over 20 alkaloids (see reference 1 and others therein) to which we wish to add, in this report, eleven others present in minor amounts. They were isolated from fractions which previously gave the major constituents for which details of isolation and structure elucidation are published (1).[3]

The ether-soluble tertiary nonphenolic alkaloid fraction afforded in the order of elution from the silica gel column the following six compounds: oxyberberine (**1**), thalrugosinone (**2**), thalicthuberine (**3**), obaberine (**4**), protopine (**5**) and neothalibrine (**6**). Of these, all but thalicthuberine (**3**) and neothalibrine are well-characterized known compounds. None have been reported, previously, from *T. rugosum*, and all were identified from their physical and spectral properties on direct comparison with authentic samples or from values reported in the literature. Neothalibrine (**6**), a recently characterized new alkaloid from the fruit of *T. revolutum* was identified by direct comparison with the known compound (2).

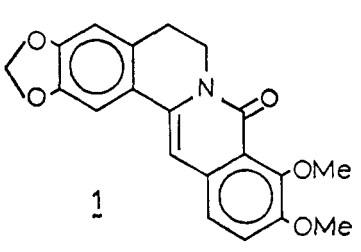
Thalrugosinone (**2**) is a new bisbenzylisoquinoline alkaloid, representing a first example of a variation not previously encountered, in which both the benzylic carbons are oxidized to the level of a ketone while the hetero ring of the isoquinoline system remains fully reduced. The limited quantities of material prevented a chemical characterization, but the spectral data is consistent with a unique structure. The high resolution mass spectrum showed an intense molecular ion that on accurate mass measurement is in excellent agreement with the formula $C_{38}H_{38}N_2O_9$. Its intensity supports the presence of two diphenyl ether groups (3), and the nmr spectrum clearly revealed peaks for one *N*-methyl and five *O*-methyls. Of the four remaining oxygens, two as stated are diphenyl ethers, and the other two must be carbonyls, since the molecular formula requires twenty-one double-bond equivalents and the simple bisbenzyltetrahydroisoquinoline system accounts for only nineteen. The ir spectrum contains a very intense peak

[1]For paper XXIX see J. Wu, J. L. Beal and R. W. Doskotch, *J. Org. Chem.*, **45**, 213(1980).

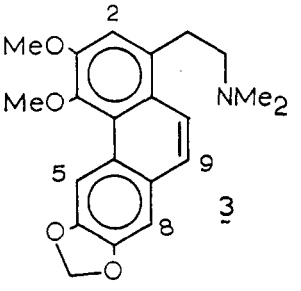
[2]Present address: McNeil Laboratories, Fort Washington, PA 19034.

[3]It has come to our attention that the alkaloid thaligosine of reference 2 has the identical structure as thalisopine [Kh. G. Pulatova, S. Kh. Maekh, Z. F. Ismailov and S. Yu. Yunusov. *Khim. Prir. Soedin.*, **4**, 394 (1968); CA **70**, 88033s (1969)]. Since the physical properties are comparable, there is little doubt that they are the same, and our independent structure proof confirms the assignment made. The name thalisopine should be the name used, henceforth.

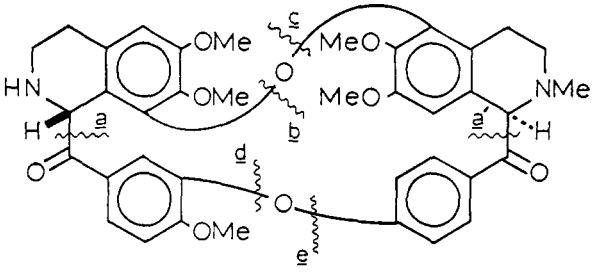
at 1660 cm^{-1} supportive of the aryl ketones (4). That the carbonyls are present at the α-benzylic positions rather than at C-4 of the tetrahydroisoquinoline rings was shown by the presence in the mass spectrum of a fragment ion peak at *m/e* 412 corresponding to the head-to-head linked isoquinoline portions. This fragment requires four methoxy groups, thereby placing thalrugosinone into one of three groups of bisbenzyltetrahydroisoquinolines (5), i.e., related to thalidasine, thalrugosaminine or hernandezine. Thalidasine and thalrugosaminine have been



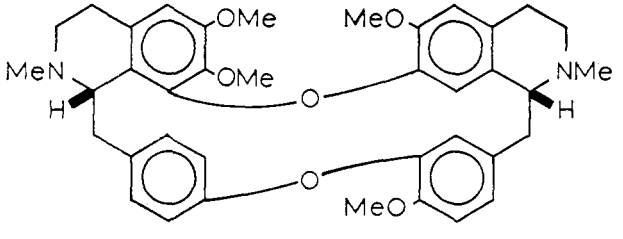
1



3



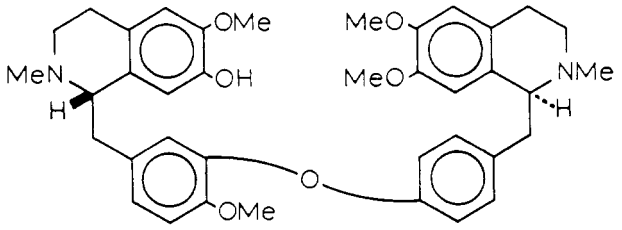
2



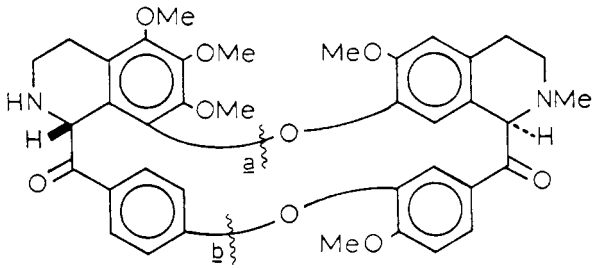
4

reported from *T. rugosum*, with thalidasine as the major base (6, 7, 8). The ions *m/e* 325 (base peak) and 341 from cleavage of **2** at *b* and *d* result in left- and right-side fragments, respectively. However, the mass spectral peaks do not permit exclusion of the thalrugosaminine-related structure **7**, as cleavage at *a* and *b* would give the same *m/e* 325 and 341 ions. Examination of other significant peaks failed to provide a clear choice between the two possibilities. The mass spectrum, however, did exclude the hernandezine-related structure.

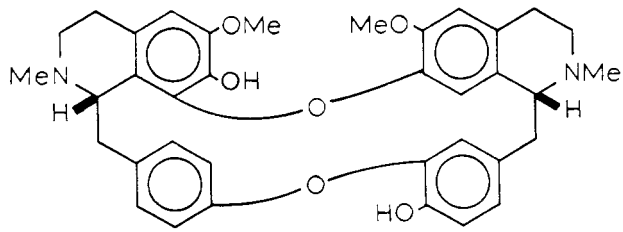
Comparison of the chemical shifts for the *N*-methyl and *O*-methyl groups of thalrugosinone (**2**) with those of thalidasine (6) and thalrugosaminine (7) showed only a very small difference from the thalidasine positions (largest difference of 3.6 Hz and average of 1.5 Hz), while with thalrugosaminine, the difference was greater (largest 15 Hz and average 5.3 Hz). Furthermore, the multiplicity pattern of the aromatic protons of thalrugosinone was similar to that of thalidasine, but clearly different from thalrugosaminine. The final comparison was the circular dichroism spectra; thalrugosinone and thalidasine curves were of similar shape, while thalrugosaminine (7) and hernandezine are markedly different.



6



7

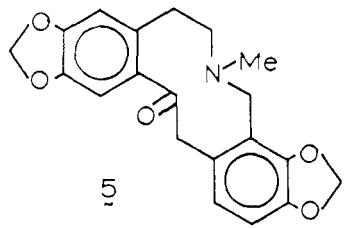


8

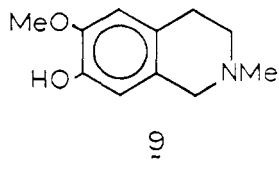
In making the spectral comparisons, the assumption was made that changing the benzylic sp^3 carbons (methylene) of the normal bisbenzylisoquinoline alkaloids to sp^2 carbons (carbonyl) of thalrugosinone would not appreciably change the conformation of the molecule and, in particular, that chemical shifts in the nmr would be little affected. This appears to be the case, but more surprisingly, there was also no significant change in the cd spectrum. To our knowledge, thalrugosinone (**2**) is the first reported natural dioxobisbenzyltetrahydroisoquinoline alkaloid (5).

The ether-soluble tertiary phenolic alkaloid fraction yielded two additional alkaloids, aromoline (**8**) and corypalline (**9**), which are known compounds but not previously reported from *T. rugosum*. Identification was by direct comparison of physical properties with those of authentic samples.

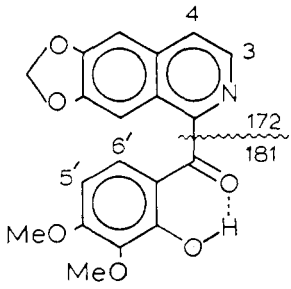
The chloroform-soluble tertiary alkaloid fraction gave a new oxobenzylisoquinoline alkaloid, rugosinone (**10**) whose structural features were established by spectral methods. Firstly, the nmr spectrum showed peaks for two methoxy, one methylenedioxy, six aromatic protons, and one D_2O exchangeable proton at very low field (δ 12.40). There were no methylene or methine absorptions. Of the six aromatic protons, two were singlets and the remainder were doublets;



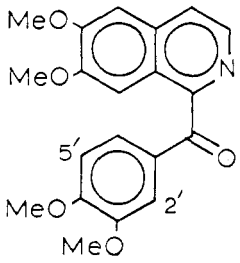
5



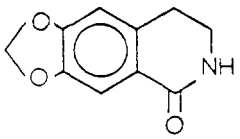
9



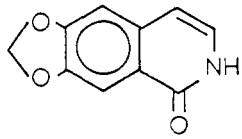
10



11



12



13

one pair had a coupling constant of 5 Hz and the other 9 Hz. Double irradiation experiments confirmed the relationship. Secondly, the uv spectrum showed absorption more complex than for a simple benzenoid system (e.g., λ max 329, 298 and 237 nm) and consistent with the presence of an isoquinoline ring. (The pair of doublets with $J=5$ Hz is characteristic of H-3 and H-4 of such a system.) The bathochromic shift to 380 nm under alkaline conditions established that the D_2O exchangeable peak in the nmr spectrum was a phenolic hydroxyl. Thirdly, the mass spectrum (both from electron impact and chemical ionization) fixed the molecular weight at 353 daltons, which corresponds to the formula $C_{19}H_{15}NO_6$. This formula accounts for all of the protons observed in the nmr spectrum and

for one more oxygen than suggested by the functional groups inferred from that spectrum. The ir spectrum with strong absorption at 1627 cm^{-1} required the presence of a carbonyl group. Rugosinone (**10**) was considered, therefore, to be related to papaveraldine (**11**, 9). Comparison of the spectral properties showed many similarities; the difference of -30 cm^{-1} in the carbonyl absorption (1657 cm^{-1} for papaveraldine) for rugosinone was taken as indication of intramolecular H-bonding between the phenolic hydroxyl and the ketone (4). The phenolic proton position at δ 12.40 in the nmr is in accord, although the ir spectrum did not clearly show hydroxyl absorption.

Location of the methylenedioxy, two methoxy and phenolic groups on the oxobenzylisoquinoline skeleton was assisted by the ms peaks *m/e* 172 and 181; thereby assigning the methylenedioxy to the isoquinoline part and the two methoxys and the phenol to the phenyl ring. For intramolecular H-bonding to occur, the phenolic group must be placed at C-2'. A total of five structures can be drawn to take care of the other substituents that would agree with the nmr data. Three would have the methylenedioxy group at C-6 and C-7 and the methoxys at C-3' and C-4' (as in **10**), C-3' and C-6', or C-5' and C-6', and the other two would bear the methoxys at C-4' and C-5' and the methylenedioxy group between C-5 and C-6, or C-7 and C-8. The physical data did not allow for differentiation between these structures, and lack of material prevented degradative studies, but on biogenetic grounds, structure **10** appeared the most likely. The synthesis of compound **10**, to be reported later, was undertaken and the product proved to be identical with natural rugosinone (10).

The chloroform-soluble tertiary alkaloid fraction also afforded two isoquinoline alkaloids, noroxyhydrastinine (**12**) and its 3,4-dehydro-derivative **13** for which no trivial name was assigned and can be named systematically, 1,2-dihydro-6,7-methylenedioxy-1-oxoisoquinoline or 6,7-methylenedioxyisocarbostyril. Noroxyhydrastinine (**12**) has been reported previously from *Thalictrum* (11) and its dehydro-derivative **13**, although not previously known as a natural product, was prepared synthetically (12). Its structure was assigned from spectroscopic data.

Some of the alkaloids isolated from *T. rugosum* were tested for antimicrobial activity according to the procedure routinely employed in our laboratory (13), with the results given in table 1. Thalicthuberine (**3**) has the broadest activity,

TABLE 1. Antimicrobial activity for the alkaloids from *T. rugosum* roots.

Organism / Alkaloids	Staph. aureus 13709a[a]	E. Coli 9637	Salmonella gallinarum 9184	Klebsiella pneumoniae 10031	Mycobact. smegmatis 607	Candida albicans 10231
Streptomycin	3.1	12.5	25	1.56	0.78	i
Thaligosidine[c]	1000	i	i	i	100	1000
Thalirugine[c]	1000	i	i	i	1000	i
Thaligosinine[c]	1000	i	i	i	1000	i
Thaligosine[c]	100	i	i	1000	100	1000
Thalirugidine[c]	1000	i	i	i	1000	i
Thaligosine-ethyl ether[c]	100	i	i	1000	100	100
Noroxyhydrastinine	i[b]	i	i	i	i	i
Thalicthuberine	100	i	1000	1000	25	50
Protopine	i	i	i	i	1000	i
Neothalibrine	1000	i	i	i	1000	i

[a]ATCC culture numbers.
[b]i = inactive at 1000 ug/ml.
[c]Discussed in reference 1.

inhibiting all of the test organisms, but *E. coli*, and showing the greatest effect against *M. smegmatis* and *C. albicans*. The next most active alkaloid was thaligosine, active against four of the six test organisms. Its ethyl ether appears to have increased potency against *C. albicans*.

EXPERIMENTAL[4]

SOURCE OF ALKALOID FRACTIONS.—The minor alkaloids reported in this paper were obtained from the column fractions recorded in reference 1, including the fraction numbers. The original partition source is designated as one of the following: diethyl ether-soluble tertiary nonphenolic alkaloids, diethyl ether-soluble phenolic tertiary alkaloids, or chloroform-soluble tertiary alkaloids.

CHROMATOGRAPHY OF ETHER-SOLUBLE TERTIARY NONPHENOLIC ALKALOIDS.—The ether-soluble tertiary nonphenolic alkaloid fraction (40 g, ref 1) was chromatographed on 1 kg of silica gel with chloroform (2 liters) and the following mixtures of methanol in chloroform, 1.25% (2 liters), 2.5 (8), 5 (9), 7.5 (4), 10 (4), 20 (6), 50 (4), and methanol (4 liters) as eluents. A final column wash of 1% HCl in methanol followed. Effluent fractions of 500 ml were evaporated to dryness, the residues weighed and analyzed by tlc. The numbered fractions were used in the separations that follow.

OXYBERBERINE (**1**).—The residue (256 mg) of column fraction no. 16 of the ether-soluble tertiary nonphenolic alkaloids eluted with 2.5% methanol in chloroform was rechromatographed on 12 g of silica gel with the following eluents: benzene (50 ml), benzene-chloroform and 1% methanol in chloroform (150 ml each). The latter two eluates contained a pale yellow residue that formed colorless crystals from methanol, mp 199–200° [lit. (14) mp 198–200°], and showed identical tlc mobility, uv, ir and nmr spectra as authentic oxyberberine.

THALRUGOSINONE (**2**).—The 1% methanol in chloroform effluent from the column that gave oxyberberine (**1**) also afforded 50 mg of an amorphous base that was further purified on a column of neutral alumina (5 g). Eluting solvents were 25 ml each of benzene, benzene-chloroform (4:1), benzene-chloroform (3:1), benzene-chloroform (1:1) and chloroform. The benzene-chloroform (3:1) eluates gave 20 mg of a white amorphous substance which darkend on exposure to air, and had the following properties: tlc R_f 0.86 on silica gel G with benzene-acetone-ammonium hydroxide solution (20:20:0.5); $[\alpha]^{22}D$ −46.4° (*c* 0.125, MeOH); cd (C 1.88 x 10^{-3}M, MeOH) $[\theta]_{300}$ 0, $[\theta]_{286}$ −25,000, $[\theta]_{274}$ 0, $[\theta]_{268}$ +7,500, $[\theta]_{260}$ 0, $[\theta]_{242}$ +67,000, $[\theta]_{230}$ 0 and $[\theta]_{220}$ (end abs) −48,000; uv[5] λ max 283 nm (shld) (log ε 3.86) and 274 (3.89) with no significant change in 0.01N NaOH or HCl; ir ($CHCl_3$) ν max 1660 cm^{-1} (ArCO); nmr (90 MHz, $CDCl_3$) δ 2.64 (s, NMe), 3.33, 3.48, 3.78, 3.88 and 3.90 (5s, 5 OMe), 4.4–4.75 (brm, 2 methine protons) and 6.1–7.7 (m, 9 ArH); and ms *m/e* 666.2591 (56%, $C_{38}H_{38}N_2O_9$ requires 666.2577), 412 (16, fragment $C_{23}H_{28}N_2O_5$ from cleavage at *a* and a'), 341 [12, $C_{19}H_{19}NO_5$ cleavage at *b* + *d* (right), *b* + *e* and *c* + *d* (left)], 325 [100, $C_{19}H_{19}NO_4$ cleavage at *b* + *d* (left), *b* + *e* and *c* + *d* (right)], 221 (11, $C_{12}H_{15}NO_3$ cleavage at *a*' and *b*), 207 (8, $C_{11}H_{13}NO_3$ cleavage at *a* and *c*), 206 (10 ,doubly charged 412 fragment), 205 (6, $C_{12}H_{15}NO_2$ cleavage at *a*' and *c*) and 191 (6, $C_{11}H_{33}NO_2$ cleavage at *a* and *b*).

Thalidasine cd values: (C 3.68 x 10^{-3}M, MeOH) $[\theta]_{307}$ 0, $[\theta]_{286}$ −27,000, $[\theta]_{273}$ 0, $[\theta]_{270}$ +3,300, $[\theta]_{258}$ 0, $[\theta]_{244}$ +45,000, $[\theta]_{234}$ 0 and $[\theta]_{224}$ −60,000.

Hernandezine cd values: (C 3.83 x 10^{-3}M, MeOH) $[\theta]_{310}$ 0, $[\theta]_{286}$ +28,000, $[\theta]_{265}$ (shld) +6,700, $[\theta]_{258}$ 0, $[\theta]_{246}$ −52,000, $[\theta]_{241}$ 0, and $[\theta]_{222}$ +300,000.

THALICTHUBERINE (**3**) AND OBABERINE (**4**).—The residue (1.18 g) of column fraction no. 33 of the ether -soluble tertiary nonphenolic alkaloids eluted with 5% methanol in chloroform was rechromatographed on a column of neutral alumina (60 g, activity 1) with benzene (50 ml), benzene-chloroform (1:1, 250 ml), chloroform (250 ml) and 1% methanol in chloroform (100 ml) as eluents. The benzene-chloroform (1:1) effluent gave 100 mg of a residue that formed thalicthuberine (**3**) as colorless needles from ether: mp 126° [lit. (15) mp 126–7°]; R_f 0.41 on tlc with silica gel G and benzene-acetone-ammonium hydroxide solution (10:10:0.3); and nmr (60 MHz, $CDCl_3$) δ 2.36 (s, 2NMe), 3.88 and 3.99 (2s, 2 OMe), 6.03 (s, OCH_2O), 7.13 (s, 2H, H-2 and H-8), 7.45 and 7.71 (AB q, *J* 9, H-9 and H-10), 9.10 (H-5) and an ABCD multiplet between 2.4–3.4 ppm for the methylene groups. Direct comparison (tlc, uv, ir, nmr and mmp) with an authentic sample of thalicthuberine showed the two to be identical.

The chloroform and 1% methanol chloroform effluents gave a 600 mg residue that was further separated on a silica gel (30 g) column with chloroform (50 ml) and the following mixtures of methanol in chloroform: 1% (150 ml), 2 (200), 4 (200) and 8 (200). The 2% methanol in chloroform eluent residue (260 mg) was again separated by preparative tlc (0.5 mm) and ben-

[4]The instruments and reagents used, plant supply, extraction procedure, partition method and chromatographic conditions are given in reference 1.

[5]The uv spectrum shows a gradual but important increase in absorption from higher wavelengths [400 nm (log ε 2.52), 350 (2.94) and 300 (3.46)] but no discernible shoulder was evident, indicating additional absorption than observed for the usual bisbenzylisoquinoline alkaloids.

zene-acetone-ammonium hydroxide solution (10:10:0.1) afforded 70 mg of crystalline thalichuberine (**3**), as well as thalrugosidine (84 mg) and thalrugosaminine (58 mg) previously reported (7, 16). The 4% methanol in chloroform effluent left a pale yellow amorphous base (70 mg) that was again chromatographed on neutral alumina (4 g) with benzene (50 ml), benzene-chloroform (1:1, 120 ml) and $CHCl_3$ (200 ml). The last two solvents gave 35 mg of a homogeneous alkaloid that was identified (tlc, uv, ir, nmr and cd) as obaberine by direct comparison with an authentic sample.

PROTOPINE (**5**).—The residue (408 mg) of column fraction no. 35 of the ether-soluble tertiary nonphenolic alkaloids that was eluted with 5% methanol in chloroform was rechromatographed on silica gel (20 g) with chloroform (50 ml), 1% methanol in chloroform (250 ml) and 2% methanol in chloroform (500 ml) as eluents. The last solvent eluted 53 mg of protopine (**5**) that crystallized from methanol as colorless prisms: mp 203–4° [lit. (17) mp 207°]; R_f 0.85 on tlc with silica gel G and benzene-acetone-ammonium hydroxide solution (20:20:0.6); ir ($CHCl_3$) ν max 1655 cm^{-1} (C=O); nmr (18) (90 MHz, $CDCl_3$) δ 1.91 (s, NMe), 2.52 and 2.84 (2 brm, 2H each, CH_2CH_2), 3.57 and 3.77 (2s, 2H each, 2 CH_2), 5.90 and 5.93 (2s, 2H each, OCH_2O), 6.66 (s, 2H, *o*-ArH), 6.63 and 6.89 (2s, 1H each, 2 ArH). Identification was made by comparison of physical properties to those reported in the literature.

NEOTHALIBRINE (**6**).—The residue (1.99 g) from column fraction no. 51–67 of the ether-soluble tertiary nonphenolic alkaloids, that was eluted with 10% methanol in chloroform, was chromatographed on 80 g of silica gel with chloroform (50 ml) and the following mixtures of methanol in chloroform, 2% (600 ml), 5 (500) and 10 (500). The 5% and 10% methanol in chloroform effluents gave 95 mg of a base fraction that was purified successively by preparative tlc on silica gel HF (0.5 mm) and benzene-acetone-ammonium hydroxide solution (20:20:0.8), and by column chromatography on neutral alumina (10 g) with chloroform as eluent. The homogeneous alkaloid (80 mg) obtained was identified as neothalibrine (**6**) by direct comparison (tlc, ir, nmr and cd) with an authentic sample (2).

AROMOLINE (**8**).—The column fraction no. 73–79 residue (0.5 g, ref 1) from the ether-soluble tertiary phenolic alkaloids eluted with 10% methanol in chloroform was rechromatographed on 25 g of silica gel with chloroform (50 ml) and the following mixtures of methanol in chloroform: 2% (250 ml), 3 (250), 4 (500), 5 (250) and 10 (100 ml). The 4% and 5% methanol in chloroform effluents gave a base fraction that was chromatographed on neutral alumina (4 g) with 2% methanol in chloroform (50 ml) to give 25 mg of a white residue that crystallized from ether, mp 180–2°. It was identified as aromoline (**8**) by direct comparison (mp, mmp, tlc, uv, ir, nmr, ms and cd) with an authentic sample previously isolated from *T. lucidum* (19).

CORYPALLINE (**9**).—The residue (792 mg) from column fraction no. 80–100 (2) of the ether-soluble tertiary phenolic alkaloids was rechromatographed on silica gel (32 g) with chloroform (50 ml) and the following mixtures of methanol in chloroform: 2.5% (125 ml), 5 (250) and 7.5 (250) as eluents. The 5% methanol in chloroform effluent gave 5 mg of colorless needles that were recrystallized from chloroform: mp 166–7° [lit. (20) mp 167–8°] and R_f 0.3 on tlc with silica gel G and benzene-acetone-ammonium hydroxide solution (20:20:1). The compound was identified as corypalline (**9**) by direct comparison (mp, mmp, tlc, ir, nmr and ms) with a known sample (20).

CHROMATOGRAPHY OF CHLOROFORM-SOLUBLE TERTIARY ALKALOIDS.—The chloroform-soluble tertiary alkaloid fraction (11 g, ref 1) was chromatographed on 330 g of silica gel with chloroform (2 liters) and the following mixtures of methanol in chloroform, 2.5% (2.5 liters), 5 (2), 10 (3), 20 (2), 40 (1) and 50 (1) as eluents. Effluent fractions of 100 ml were evaporated, the residues weighed and analyzed by tlc. The fractions yielded the compounds reported below.

RUGOSINONE (**10**).—The residue (530 mg) from column fraction no. 10–17 of the chloroform-soluble tertiary alkaloids was rechromatographed on a column of silica gel (20 g) with benzene-chloroform (1:1, 100 ml), chloroform (175 ml) and 1% methanol in chloroform (150 ml) as eluents. The chloroform effluent gave a total of 15 mg of a white crystalline residue of rugosinone (**10**): mp 223–4° (*from ethyl acetate*); CD (MeOH) no absorption; ir ($CHCl_3$) ν max 1627 cm^{-1} (C=O); uv (MeOH) λ max 329 nm (log ϵ 3.95), 298 (4.13) and 237 (4.57), with NaOMe, 380 (3.65), 327 (3.79), 296 (4.05) and 236 (4.60); nmr (90 MHz, $CDCl_3$) δ 3.91 and 3.95 (2s, 2 OMe), 6.11 (s, OCH_2O), 6.41 and 7.20 (AB q, *J* 9, H-5′ and H-6′), 7.15 and 7.38 (2s, H-5 and H-8), 7.61 and 8.43 (AB q, *J* 5, H-3 and H-4), and 12.40 (s, OH, lost in D_2O); and ms(ei) *m/e* 353 (93%, M^+, $C_{19}H_{15}NO_6$ requires 353), 338 (6, M-Me), 336 (14, M-OH), 294 (100), 279 (15), 181 (13), 174 (33), 173 (24), 172 (75) and 134 (24), ms(ci, i-butane) *m/e* 354 (100%, M+1).

Rugosinone (**10**) gives only a very weak color test with Dragendorff's reagent, but intense ones with phosphomolybdic acid (for phenols) and chromatropic acid (for methylenedioxy group).

PAPAVERALDINE (**11**).—Papaverine (100 mg) was oxidized with 300 mg of sodium dichromate in 10 ml acetic acid for 19 hrs at room temperature, as a modification of the procedure by Kabachnik and Zitser (21) to give papaveraldine (11): mp 206–7° (from ethanol), ir ($CHCl_3$) ν max 1657 cm^{-1} (C=O); nmr (90 MHz, $CDCl_3$) δ 3.94 and 4.05 (2s, 2 OMe), 3.96 (s, 2 OMe),

6.87 (d, *J* 8.3, H-5'), 7.14 (s, H-8), 7.43 (dd, *J* 1.9, 8.3, H-6'), 7.55 (s, H-5), 7.63 (d, *J* 5.4, H-4), 7.72 (d, *J* 1.9, H-2') and 8.46 (d, *J* 5.4 ,H-3); and ms *m/e* 353 (100%, M^+), 338 (31, M-Me), 324 (25), 322 (50, M-OMe), 294 (21), 279 (15), 266 (3), 188 (2) and 165 (9).

NOROXYDRASTININE (**12**).—The residue (175 mg) of fraction no. 18–20 of the chloroform soluble tertiary alkaloids eluted with chloroform was rechromatographed on 8 g of silica gel with chloroform (50 ml), 1% (120 ml) and 2% (100 ml) methanol in chloroform as eluents. The 1% methanol in chloroform effluent gave 20 mg of a colorless residue that crystallized from methanol to give noroxyhydrastinine (**12**), mp 183–4° [lit. (11) mp 182–3°]. Identification was made by direct comparison of physical data (tlc, mp, ms, ir and nmr) with those from an authentic sample prepared from tetrahydroberberine (see below). The mmp was undepressed, and the tlc R_f on silica gel G with benzene-acetone (1:1) was 0.4.

1,2-DIHYDRO-6,7-METHYLENEDIOXY-1-OXOISOQUINOLINE (6,7-METHYLENEDIOXY-ISO-CARBOSTYRIL OR 3,4-DEHYDRONOROXHYDRASTININE) (**13**).—The residue (760 mg) from fraction no. 21–27 of the chloroform-soluble tertiary alkaloids eluted with 2.5% methanol in chloroform was rechromatographed on 30 g of silica gel with chloroform, 1% and 2% methanol in chloroform (200 ml for each) as eluents. The 2% methanol in chloroform effluent residue on crystallization from chloroform gave 3.5 mg of the carbostyril **13**: mp 268–270° (dec.) [lit. (12) mp 278°]; R_f 0.55 on tlc with silica gel G and benzene-acetone (1:1); ir ($CHCl_3$) ν max 3400 (NH) and 1660 cm^{-1} (C=O); uv (MeOH) λ max 340 nm (log ϵ 3.36), 326 (3.47), 312 shld (3.37), 293 (3.59), 282 (3.58) and 268 shld (3.60) with no shift in 0.01N NaOH or HCl; nmr (90 MHz, $CDCl_3$) δ 6.08 (s, OCH_2O), 6.42 (d, *J* 7, H-4), 6.89 (s, H-5), 7.01 (brd, *J* 7, H-3) and 7.76 (s, H-8); and ms *m/e* 189 (100%, M^+, $C_{10}H_7NO_3$ requires 189), 162 (3), 131 (4), 103 (2) and 76 (2), ms(ci, i-butane) *m/e* 190 (100%, M+1).

OXIDATION OF TETRAHYDROBERBERINE.—Tetrahydroberberine (900 mg), prepared from berberine by reduction with $NaBH_4$, was dissolved in 120 ml of acetone and $KMnO_4$ (2 g) was added during 1 hr. The mixture was stirred an additional 6 hr. Excess methanol was added and the reaction mixture was heated on the steam bath to destroy excess reagent. The precipitate of MnO_2 was removed by filtration and the clear pale yellow filtrate was concentrated to 25 ml by evaporation, and 50 ml water was added. The mixture was extracted with 250 ml chloroform, and the extract washed with water and dried with Na_2SO_4. Removal of solvent left 469 mg of a yellow-brown solid, that was separated on a column of 16 g of silica gel with benzene, benzene-chloroform (1:1) (100 ml for each), chloroform and 1% methanol in chloroform (120 ml for each) as eluents. The early 1% methanol in chloroform effluent gave a residue that crystallized from methanol to give 45 mg of oxyberberine (**1**), mp 199–200–, identical to the material isolated from the plant. The later 1% methanol in chloroform effluent gave 50 mg of noroxyhydrastinine (**12**), mp 182–3–, identical to the material isolated from the plant.

ACKNOWLEDGMENTS

We thank the National Institutes of Health, U.S. Public Health Service, for the grant (HL-07502) supporting this study, and Mr. R. Weisenberger of the Chemistry Department for some of the mass spectra.

LITERATURE CITED

1. Wu-Nan Wu, J. L. Beal, E. H. Fairchild and R. W. Doskotch, *J. Org. Chem.*, **43**, 580 (1978).
2. J. Wu, J. L. Beal, W.-N. Wu and R. W. Doskotch, *J. Nat. Prod.*, in press.
3. D. C. DeJongh, S. R. Shrader and M. P. Cava, *J. Am. Chem. Soc.*, **88**, 1052 (1966).
4. K. Kakanishi, "Infrared Absorption Spectroscopy," Holden-Day Inc., San Francisco, 1962, p. 42.
5. K. P. Guha, B. Mukherjee and R. Mukherjee, *J. Nat. Prod.*, **42**, 1 (1979).
6. T. Tomimatsu, M. Hashimoto and J. L. Beal, *Chem. Pharm. Bull.* (Tokyo) **16**, 2070 (1968).
7. W.-N. Wu, J. L. Beal, G. W. Clark and L. A. Mitscher, *Lloydia* **39**, 65 (1976).
8. W.-N. Wu, J. L. Beal and R. W. Doskotch, *Lloydia* **40**, 508 (1977).
9. A. Burger in R. H. F. Manske and H. L. Holmes (ed.) "The Alkaloids," Academic Press, New York **4**, 32 (1954).
10. H.-Y. Cheng, M.S. Thesis, Ohio State University, Columbus, Ohio, 1979.
11. R. W. Doskotch, P. L. Schiff, Jr. and J. L. Beal, *Tetrahedron* **25**, 469 (1969).
12. F. Eloy and A. Deryckere, *Helv. Chim. Acta.*, **52**, 1755 (1969).
13. L. A. Mitscher, R.-p. Leu, M. S. Bathala, W.-N. Wu and J. L. Beal, *Lloydia* **35**, 157 (1972).
14. W. H. Perkins, Jr., *J. Chem. Soc.*, **57**, 992 (1890).
15. E. Fujita and T. Tomimatsu, *J. Pharm. Soc.*, (Japan) **79**, 1252 (1957).
16. L. A. Mitscher, Wu-Nan Wu, R. W. Doskotch and J. L. Beal, *Chem. Commun.*, 589 (1971).
17. W. H. Perkin, Jr., *J. Chem. Soc.*, **109**, 815 (1916).
18. "Varian NMR Spectra Catalog," Vol. I, Spectrum No. 339, Varian Assoc., Palo Alto, California, 1962.
19. W.N. Wu, J. L. Beal and R. W. Doskotch, *Lloydia*, **39**, 378 (1976).
20. C. R. Chen, J. L. Beal, R. W. Doskotch, L. A. Mitscher and G. H. Svoboda, *Lloydia*, **37**, 493 (1974).
21. M. I. Kabachnik and A. I. Zitser, *J. Gen. Chem. (USSR)*, **7**, 162 (1937).