Synthesis of Isoquinoline Alkaloids. IV. Steric Effects in the Electrolytic and Catalytic Oxidative Coupling of Phenolic Tetrahydroisoquinolines[1]

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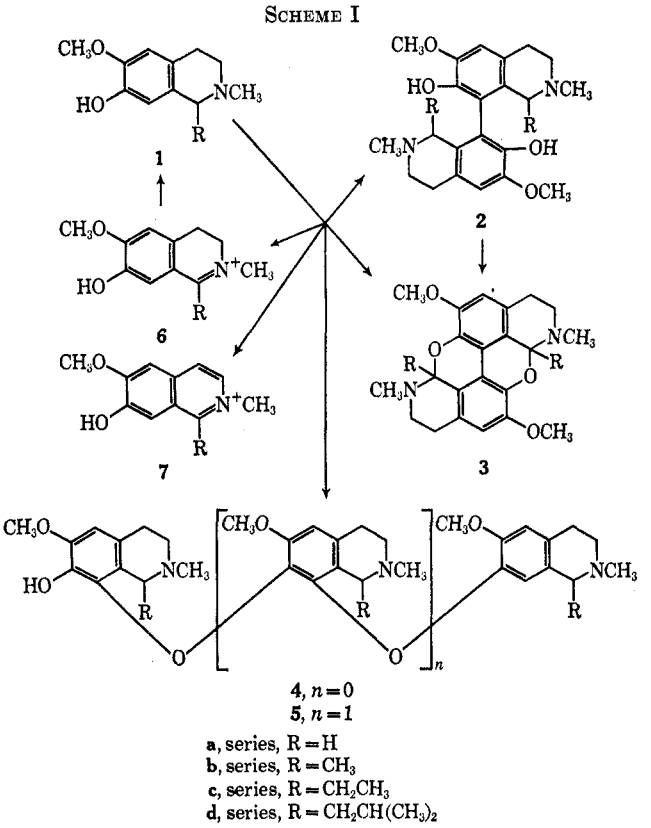
A series of 7-hydroxy-6-methoxy-N-methyl-1,2,3,4-tetrahydroisoquinolines with various substituents at the 1 position has been oxidized electrolytically on a platinum anode and catalytically with oxygen over platinum. In both methods, the increased size of the 1 substituent causes an increase in the proportion of carbon–oxygen dimers over the carbon–carbon dimers. Electrolytic oxidation appeared to be more sensitive to steric factors and to produce less oxidation in the nitrogen ring.

The oxidative coupling of phenols is one of the more important reactions used in nature for the elaboration of complex substances from simple precursors[3] and is especially important in the production of isoquinoline alkaloids.[4] These reactions may be intramolecular or intermolecular and generally lead, at least as a first step, to C–C linkages (such as in **2**) or C–O–C linkages (such as in **4**; the formation of both **2** and **4** being intermolecular). Many oxidizing systems have been explored over the last 50 years for carrying out these reactions in the laboratory.[5] The trimeric cactus alkaloid, pilocereine (**5d**), and its dimeric analog, **4d**, have been prepared by the $FeCl_3$ and $K_3Fe(CN)_6$ oxidation of the monomeric alkaloid lophocerine (**1d**).[1,6]

Of the various oxidation methods, two have been relatively unexplored. These are electrolytic oxidation, which has lain essentially dormant since the pioneering work of Fichter and his group prior to 1925,[3,7] and catalytic oxygenation over a platinum catalyst.[8] Of these two methods, electrolytic oxidation offers the greater promise as far as specificity and control are concerned.[3b] In recent years, the electrochemical reaction has been studied mechanistically[9] and preparatively (for nonalkaloidal materials).[10] We have published two brief communications on the preparative oxidation of the alkaloid corypalline (**1a**).[11] In this paper, we would like to describe the details of the corypalline work and to present a study of the oxidation of the series, **1a–c**, by catalytic and electrolytic oxidation. During the course of this work, papers have appeared on the $K_3Fe(CN)_6$ oxidation of **1a** and its metho salt,[12] on the $K_3Fe(CN)_6$ oxidation of **1b**,[13] and on the enzymatic oxidation of **1b** and **1d**.[14]

Oxidation of **1** can lead to two general types of products: compounds arising from oxidative coupling reactions, such as **2**, **4**, and **5**, and compounds arising from oxidation within the nitrogen ring, such as **3**, **6**, and **7** (Scheme I). **3** falls in both classes. The coupled

SCHEME I



products fall in two general groups, the C–C products, such as **2**, and the C–O–C products, such as **4** and **5**. One of the basic goals of this work was to show, within an homologous series, that the amount of C–O–C prod-

(1) Paper III: J. M. Bobbitt, R. Ebermann, and M. Schubert, *Tetrahedron Lett.*, 575 (1963). This work was sponsored, in part, by Training Grant GM-1139 from the National Institutes of Health, U. S. Public Health Service and Research Grant GP-7601 from the National Science Foundation. It was described partially at the IUPAC Congress on Natural Product Chemistry in London, 1968.

(2) Abstracted, in part, from the Ph.D. theses of K. H. W., University of Connecticut, 1969, and A. S. S., University of Connecticut, 1968.

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(5) H. Musso, in ref 3a, p 1.

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(7) F. Fichter and P. Müller, *Helv. Chim. Acta*, **8**, 290 (1925), and preceding papers of the series.

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(9) (a) J. F. Hedenburg and H. Freiser, *Anal. Chem.*, **25**, 1355 (1953). (b) J. C. Suatoni, R. E. Snyder, and R. O. Clark, *ibid.*, **33**, 1894 (1961). (c) Y. V. Vodzinskii and G. S. Semchikova, *Tr. Khim. Khim. Tekhnol.*, 272 (1963); *Chem. Abstr.*, **61**, 6640 (1964). (d) H. N. Simpson, C. K. Hancock, and E. A. Meyers, *J. Org. Chem.*, **30**, 2678 (1965).

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(11) (a) J. M. Bobbitt, J. T. Stock, A. Marchand, and K. H. Weisgraber, *Chem. Ind. (London)*, 2127 (1966); (b) G. F. Kirkbright, J. T. Stock, R. D. Pugliese, and J. M. Bobbitt, *J. Electrochem. Soc.*, **116**, 219 (1969).

(12) (a) M. Tomita, K. Fujitani, Y. Masaki, and K.-H. Lee, *Chem. Pharm. Bull.*, **16**, 251 (1968); (b) B. Umezawa, O. Hoshino, H. Hara, and J. Sakakibara, *ibid.*, **16**, 381 (1968).

(13) M. Tomita, Y. Masaki, and K. Fujitani, *ibid.*, **16**, 257 (1968).

(14) Y. Inubushi, Y. Aoyagi, and M. Matsuo, *Tetrahedron Lett.*, 2363 (1969).

TABLE I

OXIDATION OF 1-SUBSTITUTED N-METHYL-7-HYDROXY-6-METHOXY-1,2,3,4-TETRAHYDROISOQUINOLINES

Method	Yield of products, %[a] Type 2	Type 3	Type 4	Type 5	Type 6	Type 7
			1a			
Electrolytic	34 (31)		3 (2.7)			
Catalytic	51	2	2		2	4
Chemical	28[b]					
	55 (40)[c]					
			1b			
Electrolytic	0.7 (0.6)		22 (20.4)	5 (4.4)		
Catalytic	25.5 (23.7)		18.2 (17)	0.8 (0.74)	3.1 (2.9)	3.4 (3.2)
Chemical[d]	(*ca.* 6)		(*Ca.* 1.2)			
Enzymatic[e]	(5.5)		(8)			
			1c			
Electrolytic[f]			30.5 (29.4)			
Catalytic			24.8 (14.9)		6.8 (4.1)	7.8 (4.5)
			1d			
Chemical[g]			32	3		
Enzymatic[e]			3			

[a] The yields are actually conversions since they have been corrected for recovered starting materials. True yields are given in parentheses. In the case of the catalytic oxygenation of **1a** and electrolytic oxidation of **1a**, greater than 96% of the starting material was consumed. [b] See ref 12a. [c] See ref 12b. [d] See ref 13. [e] See ref 14. [f] This oxidation was carried out in a H_2O–CH_3CN system. [g] See ref 1.

ucts formed is a function of the steric hindrance around the incipient diphenyl ether. This has been postulated,[5,6c,12] but only fragmentary evidence has been presented to support the hypothesis. Nitrogen ring oxidation is undesirable for our general purpose of preparing coupled products. Since the material balance was not complete in any of the experiments, other types of oxidation or decomposition leading to polymeric products[15] seem to have taken place.

The three compounds, **1a–c**, were prepared as previously described[16,17] and oxidized as described in the Experimental Section. The crude reaction mixtures were examined by tlc, and all of the major components were isolated using chromatography (column and preparative tlc). The products were identified as described below, and the results are shown in Table I along with the results of chemical oxidations. The data for **1d** is taken from our previous work[1] and the enzymatic work mentioned previously.[14]

Two structures corresponding to type **2** were obtained, **2a** and **2b**. The nmr spectrum of **2a** corresponded exactly to the one reported by Tomita, Fujitani, Masaki, and Lee,[12a] although the melting point did not agree. However, the compound was identical with an authentic sample.[12b,25] Structure **2b** is much more complex since an asymmetric center at C-1 of each isoquinoline has been introduced. Furthermore, the strong probability of restricted rotation at the diphenyl linkage and the creation of atropisomers must be considered. A study of molecular models suggests that three pairs of enantiomers will be formed from the coupling of racemic **1b** to yield **2b**. The compounds which are *RS* and *SR* with respect to C-1 stereochemistry and which would normally produce a *meso* situation give rise instead to two rotamers, which are enantiomers. In the case of the *RR* and *SS* dimers which would normally constitute an enantiomeric pair, four rotamers can exist. However, the rotamers of one form (the *RR*), although diastereomers of one another, are *also enantiomers of the rotamers* of the other form (the *SS*). In summary, one would expect the formation of three separable enantiomeric pairs: *RS* rotamer A and *RS* rotamer B, *RR* rotamer A and *SS* rotamer A, and *RR* rotamer B and *SS* rotamer B. All three pairs were isolated. Two were crystalline and one was a glass. The nmr spectra of the three isomers were almost identical and essentially identical with the spectrum of **2b** as published by Tomita, Masaki, and Fujitani.[13,18] We were not able to establish, with certainty, the exact structures of the isomers.

One substance corresponding to type **3** was obtained, **3a**. The compound appears to have been formed by an intermolecular coupling, followed by oxidation within the nitrogen rings and ring closure. Compound **3a** is identical, by melting point and spectra, with a substance of the same structure isolated by Kametani and Yagi[19] from a coupling reaction of N-methylcoclaurine. Compound **3a** could also be formed in 71% yield from **2a** by allowing it to stand in chloroform under an inert atmosphere. The reaction occurred only in chlorinated solvents and may be traceable to the charge-transfer complex formation between amines and halomethanes. This complex formation leads to decomposition of the amines.[20] One structure of this type, **3b**, was observed[13] in the chemical oxidation of **1b**.

Three substances corresponding to type **4** were obtained, **4a**, **4b**, and **4c**. Of these, only **4b** is known.[13,14]

(15) H. Finkbeiner, A. S. Hay, H. S. Blanchard, and G. F. Endres, *J. Org. Chem.*, **31**, 549 (1966), and papers cited therein.

(16) J. M. Bobbitt, D. N. Roy, A. Marchand, and C. W. Allen, *ibid.*, **32**, 2225 (1967).

(17) J. M. Bobbitt, A. S. Steinfeld, K. H. Weisgraber, and S. Dutta, *ibid.*, **34**, 2478 (1969).

(18) The nmr spectrum reported[13] was said to be quite dependent upon the mode of isolation of the material. The presence of two isomers was suggested, but the mixture was not resolved.

(19) T. Kametani and H. Yagi, *J. Chem. Soc. C*, 2182 (1967).

(20) W. J. Lautenberger, E. N. Jones and J. G. Miller, *J. Amer. Chem. Soc.*, **90**, 1110 (1968).

The nmr spectrum of our **4b** corresponded exactly to the one published,[13] although both are almost surely mixtures of stereoisomers. We could not resolve the mixture nor could the other group. The mass spectra of compounds **4a**, **4b**, and **4c** showed each to be a dimer. The nmr spectrum in the region of δ 6–7 of **4b** is quite characteristic of this type of dimer, since is shows three sharp singlets attributable to the three aromatic protons. Compound **4a** has no stereochemical complications and was obtained as a noncrystalline material. It had an nmr spectrum identical with that of **4b**[13] except for the regions involved with the C–CH_3 groups of **4b**. Structure **4c** should consist of a mixture of two pairs of enantiomers. This was resolved, and both pairs were isolated as glasses. Each isomeric pair had an nmr spectrum identical with the published spectrum of **4b** except for the regions involved with the ethyl groups.

Only one substance corresponding to the trimeric type **5** was obtained, **5b**. The mass spectrum showed its trimeric nature. The nmr spectrum contained four aromatic singlets. Furthermore, the mass spectrum splitting pattern corresponded closely with that reported by Franck[6] for pilocereine, (**5d**). The substance is a glass and almost surely consists of a mixture of stereoisomers.

The dimers and the trimer are not very stable materials. Some are sensitive to heat and gave poor microanalysis owing to the difficulty involved in removing the last traces of solvent, mainly methanol. However, each was homogeneous in tlc and, except as noted for mixtures of isomers, each gave a clean nmr spectrum which could be completely interpreted. Precision mass spectra were measured for the molecular ions of several of the compounds and showed excellent agreement with the calculated values.

Three substances corresponding to type **6** were obtained, **6a**, **6b**, and **6c**. All were rather unstable glasses which showed, in their nmr and ir spectra, typical patterns for the grouping C=N^+–CH_3. Furthermore, the nmr spectrum of **6a** contained a singlet at δ 8.5 corresponding to the C-1 proton. If compounds **6** had had an alternate structure such as the 1,2-dihydroisoquinoline, such would not have been the case. Compounds **6a**, **6b**, and **6c** were reduced back to the known compounds **1a**, **1b**, and **1c** as further proof of structure.

Three substances corresponding to type **7** were obtained, **7a**, **7b**, and **7c**. After correction for the anion present, all were shown to be identical with crystalline compounds formed by known methods.

It is difficult to draw any conclusions from the comparison of our work with the chemical oxidations reported in Table I. As far as the relative amounts of C–C and C–O–C dimers formed, we are in essential agreement, but our yields are generally higher. One does not know whether such compounds, as types **6** and **7**, were looked for in the chemical oxidations. In our work they were definitely shown to be absent in the electrolytic oxidations. It should be noted also that the metho salts of **1a** and **1b** were oxidized chemically[12] and that the metho salts of dimers of type **2** were obtained from **1a** in yields of 33[12a] and 10%.[12b]

A few conclusions can be drawn from our work, subject, of course, to the lack of a complete materials balance. First, C–O–C dimers can be formed by both electrolytic oxidation (agreeing with the older literature[7]) and catalytic oxygenation. These methods now become attractive for the synthesis of complex natural products. Second, electrolytic oxidation leads to less oxidation of the nitrogen ring system (no **6** or **7** formed) than many of the better known phenol coupling reagents. Third, the proportion of C–O–C dimer formed, in the isoquinoline series at least, is definitely a matter of steric hindrance since the amount of C–O–C dimer increases markedly (3 to 22 to 30.5% by electrolysis and 2 to 18 to 24% by oxygenation), and the amount of C–C dimer decreases markedly (34 to 0.7 to 0% by electrolysis and 51 to 25.5 to 0% by oxygenation) as a substituent is built up on the 1 position. Finally, electrolytic oxidation seems to be somewhat more sensitive to steric effects, since the transition from C–C to C–O–C dimers is much sharper than that seen in catalytic oxygenation. We are presently applying electrolytic oxidation to a number of precursors of natural products.

Experimental Section[21]

Isoquinoline Methiodides (**7**).—6-Methoxy-7-hydroxyisoquinoline[22] (0.2 g) was warmed with 2 ml of CH_3I in 15 ml of benzene for 1 hr. The quaternary salt, **7a** (0.28 g, 78%), precipitated from the cooled solution. The analytical sample, mp 217–218°, was crystallized from ethanol.

Anal. Calcd for $C_{11}H_{12}NO_2I$: C, 41.68; H, 3.79; N, 4.42. Found: C, 41.62; H, 3.83; N, 4.41.

6-Methoxy-7-hydroxy-1-methylisoquinoline[23] was prepared from its 1,2,3,4-tetrahydro derivative[17] by dehydrogenation over Pd on carbon[22] and was converted to **7b** as described above. The yield of **7b** for the quaternization step was 80%. The analytical sample, mp 224–227°, was crystallized from ethanol.

Anal. Calcd for $C_{12}H_{14}NO_2I$: C, 43.54; H, 4.23; N, 4.23; I, 38.34. Found: C, 43.02; H, 4.27; N, 4.18; I, 38.66.

1-Ethyl-7-hydroxy-6-methoxyisoquinoline was prepared by dehydrogenation[22] of its 1,2,3,4-tetrahydro derivative.[17] It was obtained in 59% yield and melted at 166–170°.

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.77; H, 6.47; H, 6.95.

N-Methyl-1-ethyl-7-hydroxy-6-methoxyisoquinolinium iodide, **7c**, was prepared from the isoquinoline by quaternization (83% yield) as described above. The analytical sample, mp 197.5–199°, was crystallized from ethanol.

Anal. Calcd for $C_{13}H_{16}NO_2I$: C, 45.26; H, 4.64; N, 4.09. Found: C, 44.80; H, 4.53; N, 4.05.

Catalytic Oxygenation of Corypalline (**1a**).—Platinum oxide (1.7 g) was catalytically hydrogenated at room temperature in ethanol. The platinum black, so obtained, was separated from the ethanol by decantation, washed with water, and added to 750 ml of 0.3 *M* aqueous $NaHCO_3$. The solution was stirred and oxygen was passed into it through a sintered-glass disk for 15 min. Corypalline hydrochloride (11 g) was dissolved in water and added to the solution. The reaction was monitored by tlc (5% NH_4OH in methanol) and was stopped when the starting material was essentially gone. The catalyst was removed by filtration and the solution was basified (NH_4OH) and extracted several times with $CHCl_3$.

The aqueous phase was evaporated under vacuum. As the volume was reduced, inorganic salts precipitated and were

(21) The melting points were taken on a Kofler hot-stage apparatus and are corrected. The nmr spectra were measured on a Varian A-60 instrument, mass spectra were measured on an AEI MS-12 instrument and on a Hitachi Perkin-Elmer RMU-7 instrument, and the microanalyses were carried out by Baron Consulting Co., Orange, Conn. The tlc was carried out on silica gel GF layers and the column chromatography was carried out on silica gel M, obtained from Hermann Brothers in Cologne, Germany. The analytical samples of the noncrystalline dimers and the trimer were prepared by dissolving them in methanol, passing the solution over a short column of silica gel, evaporating to dryness, and drying under vacuum at room temperature. Nmr spectra of the analytical samples showed the presence of methanol.

(22) J. M. Bobbitt, J. M. Kiely, K. L. Khanna, and R. Ebermann, *J. Org. Chem.*, **30**, 2247 (1965).

(23) H. Brüderer and A. Brossi, *Helv. Chim. Acta*, **48**, 1945 (1965).

removed by filtration and discarded. The residue was taken up in methanol, filtered, and chromatographed over 100 g of silica gel using CH_3OH–NH_4OH (50:1) as developer. Two compounds were obtained and were converted to chlorides with HCl gas. The first compound, **7a** (0.2 g), was identical with the synthetic sample of **7a** by tlc comparison and ir spectra.[24] The second compound, **6a** (0.4 g), could not be crystallized or purified to any extent. When evaporated to a glass, it showed the following properties: nmr (D_2O) δ 8.50 (s, 1, $ArCH{=}N^+$), 6.89 (s, 1, aromatic), 6.74 (s, 1, aromatic), 3.78 (s, 3, $ArOCH_3$), 3.50 (s, 3, N^+CH_3); ir 1655 cm^{-1} ($ArC{=}N^+$). Catalytic hydrogenation of **6a** over platinum gave a 53% yield of starting material, **1a**.

The chloroform phase from the extraction was dried (Na_2SO_4), evaporated to dryness, dissolved in a few milliliters of ethanol and cooled. The C–C dimer, **2a**, precipitated, giving 3.5 g of product, mp 235–237° (lit.[12] 247–249°[25] and 229°). The spectral properties agree completely with the literature.[12]

The mother liquor from the crystallization of **2a** was chromatographed over 100 g of silica gel using benzene–methanol (3:1) as a developer. Three major fractions were obtained. The first contained 0.3 g of starting material, **1a**. The third fraction contained an additional 1.1 g of C–C dimer, **2a**. The second fraction, a mixture of two components by tlc, was rechromatographed on silica gel using the same developer. The first fraction eluted contained 0.2 g of the C–O–C dimer, **4a**, which was obtained as a glass: nmr ($CDCl_3$) δ 6.59 (s, 1, aromatic), 6.40 (s, 1, aromatic), 6.10 (s, 1, aromatic), 5.30 (s, 1, ArOH), 3.82 (s, 3, $ArOCH_3$), 3.71 (s, 3, $ArOCH_3$), 2.32 (s, 6, NCH_3); mass spectrum M^+ 384.2049 (calcd 384.2049).

Anal. Calcd for $C_{22}H_{28}N_2O_4 \cdot CH_3OH$: C, 66.32; H, 7.74; N, 6.73. Found: C, 66.71; H, 7.16; N, 6.81.

The second fraction contained 0.1 g of **3a**, mp 218–220° (lit.[17] 219–220°).

Catalytic Oxygenation of 1b.—Compound **1b** (6.0 g) was oxygenated as described above over the platinum from 0.9 g of PtO_2. The reaction mixture was separated in the same manner to yield residues from the $CHCl_3$ and the aqueous phases. The residue from the aqueous phase was chromatographed over 200 g of neutral alumina (Woelm) using $CHCl_3$–CH_3OH–NH_4OH (300:50:1) as the developer. Two compounds were obtained. Both were quaternary and were converted to the chlorides with HCl gas. The first fraction contained 0.19 g of **7b** chloride, mp 258° dec, which was identical with a synthetic sample.[22] The second compound, **6b** chloride (0.19 g), was obtained as an unstable glass: nmr (D_2O) δ 6.66 (s, 1, aromatic), 6.40 (s, 1, aromatic), 3.46 (s, 3, $ArOCH_3$), 3.30 (s, 3, NCH_3), 2.26 (s, 3, $N^+{=}CCH_3$); ir 1650 cm^{-1} ($ArC{=}N^+$). Compound **6b** was reduced to starting material, **1b**, in 43% yield.

The dried residue from the $CHCl_3$ phase was chromatographed over 275 g of silica gel using 0.3% NH_4OH in CH_3OH as developer. The first fraction contained 0.55 g of starting material, **1b**. The second fraction contained 0.83 g (18.5%) of the C–O–C dimer, **4b**, a noncrystalline glass: nmr ($CDCl_3$) δ 6.72 (s, 1, aromatic), 6.58 (s, 1, aromatic), 6.38 (s, 1, aromatic), 6.29 (s, 1, ArOH), 3.90 (s, 3, $ArOCH_3$), 3.88 (s, 3, $ArOCH_3$), 2.48 (s, 1, NCH_3), 1.37 (m, 6, $C\text{-}CH_3$); uv max (95% EtOH) 285 mμ (ϵ 5410), shifted to 292 mμ in base; mass spectrum M^+ 412.2365 (calcd 412.2361).

Anal. Calcd for $C_{24}H_{32}N_2O_4 \cdot CH_3OH$: C, 67.54; H, 8.16; N, 6.30. Found: C, 67.86; H, 7.74; N, 6.69.

The third fraction contained 0.4 g of one of the crystalline isomers of **2b**: mp 222–224°; nmr ($CDCl_3$) δ 6.69 (s, 2, aromatic), 5.35 (s–broad, 2, ArOH), 3.89 (s, 6, $ArOCH_3$), 2.42 (2, 6, NCH_3), 0.95 (d, J = 7.5 cps, 6, $CHCH_3$); uv max (absolute EtOH) 290 mμ (ϵ 7190) shifted to 306 mμ in base; mass spectrum M^+ 412.2361 (calcd 412.2361).

Anal. Calcd for $C_{24}H_{32}N_2O_4$: C, 69.88; H, 7.82; N, 6.79. Found: C, 69.50; H, 7.98; N, 7.16.

The fourth fraction contained a mixture of the crystalline isomer of **2b**, mp 222–224°, and the noncrystalline isomer of **2b**. The crystalline isomer was removed by crystallization from acetone. The mother liquor appeared to contain only the noncrystalline isomer (tlc), a glass (0.34 g): nmr ($CDCl_3$) δ 6.63 (s, 2, aromatic), 4.94 (s, 2, ArOH), 3.83 (s, 6, $ArOCH_3$), 2.31 (s, 6, NCH_3), 1.08 (d, J = 7.5 cps, 6, $CHCH_3$); uv max (absolute EtOH) 289 mμ (ϵ 6320) shifted to 303 mμ in base; mass spectrum M^+ 412.2365 (calcd 412.2361).

Anal. Calcd for $C_{24}H_{32}N_2O_4$: C, 69.88; H, 7.82; N, 6.79. Found: C, 62.77; H, 6.97; N, 5.89.[26]

The fifth fraction was a mixture of the second crystalline isomer of **2b** and the C–O–C trimer, **5b**. The fraction was evaporated to dryness and taken up in acetone. The isomer of **2b**, mp 132–134° (0.16 g), precipitated: uv max (absolute EtOH) 292.5 mμ (ϵ 6590) shifted in base to 310 mμ; mass spectrum M^+ 412.2365 (calcd 412.2361).

Anal. Calcd for $C_{24}H_{32}N_2O_4 \cdot CH_3OH$: C, 67.54; H, 8.16; N, 6.30. Found: C, 66.76; H, 8.09; N, 6.56.

The mother liquor was separated by preparative tlc on silica gel using 5% NH_4OH in CH_3OH as a developer to yield an additional 0.05 g of the crystalline isomer of **2b**, mp 132–134°, and 0.04 g of the trimer, **5b**. Compound **5b** was a glass: nmr ($CDCl_3$) δ 6.48 (s, 1, aromatic), 6.46 (s, 1, aromatic), 6.37 (s–broad, 1, aromatic), 6.20 (s, 1, aromatic), 3.70 (s, 3, $ArOCH_3$), 3.68 (s, 3, $ArOCH_3$), 3.59 (s, 3, $ArOCH_3$), 2.37 (s, 9, NCH_3), 1.19 (m, 9, $CHCH_3$); uv max (95% EtOH) 285 mμ (ϵ 5555) shifted in base to 287 mμ; mass spectrum M^+ 617.3464 (calcd 617.3463).

Anal. Calcd for $C_{36}H_{47}N_3O_6 \cdot CH_3OH$: C, 68.39; H, 7.91; N, 6.47. Found: C, 68.75; H, 7.65; N, 6.84.

Catalytic Oxygenation of 1c.—The oxygenation of **1c** was carried out as described above except that small amounts of methanol were added to prevent foaming. The mixture was treated as described to yield an aqueous phase and a $CHCl_3$ phase.

The aqueous phase was treated as described for **1b** and chromatographed over 100 g of neutral alumina using $CHCl_3$–MeOH–NH_4OH (300:25:1) as developer, resulting in the isolation of 0.113 g of **7c** and 0.132 g of **6c**, which were converted to their chloride salts as described before. Compound **7c** was identical with the synthetic sample after its conversion to a chloride.[22] Compound **6c** chloride existed as a glass: nmr (D_2O) δ 6.88 (s, 1, aromatic), 6.71 (s, 1, aromatic), 3.76 (s, 3, $ArOCH_3$), 3.68 (s, 3, NCH_3), 1.20 (t, J = 7.5 cps, 3, CH_2CH_3); ir 1642 cm^{-1} ($ArC{=}N^+{-}$). It was reduced over a platinum catalyst to yield starting material in 59% yield.

The dried $CHCl_3$ residue was chromatographed over 150 g of silica gel as described above. The first fraction contained starting material which was isolated as its hydrochloride (1.175 g).[12] The second fraction contained one isomer of **4c** (0.137 g) and the third fraction contained the second isomer (0.250 g). Both were noncrystalline, and they had virtually identical spectra. They had different R_f values on tlc, however. The spectral properties were nmr ($CDCl_3$) δ 6.56 (s, 1, aromatic), 6.42 (s, 1, aromatic), 6.17 (s, 1, aromatic), 5.09 (s, broad, 1, ArOH), 3.83 (s, 3, $ArOCH_3$), 3.79 (s, 3, $ArOCH_3$), 2.31 (s, 3, $N\text{-}CH_3$), 2.29 (s, 3, NCH_3); uv max (absolute EtOH) 286 mμ (ϵ 6240) shifted in base to 294 mμ; mass spectrum M^+ 440 (calcd 440).

Anal. Calcd for $C_{26}H_{36}N_2O_4 \cdot CH_3OH$: C, 68.62; H, 8.53; N, 5.93. Found for first isomer: C, 68.72; H, 8.24; N, 5.73. Found for second isomer: C, 69.83; H, 7.98; N, 6.11.

Anodic Oxidation of 1a.—Sodium bicarbonate solution (140 ml of 0.1 M) was placed in an electrolytic cell[11b] containing a platinum gauze anode (5 × 7.5 cm). The cathode was separated by a porous disk and was also platinum. The cell was connected to a saturated calomel electrode through a salt bridge. The anode potential was controlled at +0.3 V[27] (Wenking potentiostat, Model 61TR).[28] The circuit was opened and compound **1a** (0.6 g) dissolved in 50 ml of ethanol was added in 1-ml portions fast enough to maintain a current of 50 mA. After 15 min, the current fell below 40 mA and did not respond to additional **1a**. The remainder of **1a** was added over 10 min. The reaction was monitored by tlc (CH_3OH–NH_4OH 97:3). After 5 hr, the current was down to about 3 mA and little starting material was detectable (although present). The reaction mixture was removed from the cell, basified with NH_4OH, and extracted with $CHCl_3$. The $CHCl_3$ extracts were concentrated almost to dryness and cooled. Starting material (0.057 g) crystallized. The mother liquor was evaporated to dryness and taken up in ethanol whereupon the C–C dimer, **2a**, crystallized (0.18 g). The mother

(24) The synthetic methiodides were passed over a short column of silica gel (CH_3OH–NH_4OH, 10:1) and converted to chlorides with HCl gas.

(25) Through the courtesy of Dr. O. Hoshino of the Science University of Tokyo, we have obtained an authentic sample of **2a**. He now believes the melting point to be the same as ours, 235–237°. The compounds were identical in all respects.

(26) This analysis did not check and could not be repeated for lack of material. However, the structure is almost surely correct on spectral grounds.

(27) The voltage for the reaction was chosen after a valtammetric study.

(28) U. S. Distributor, Brinkmann Instruments, Inc., Westbury, N. Y.

liquor was evaporated to dryness and chromatographed by preparative tlc (CH_3OH–NH_4OH 97:3) to yield 0.016 g of **4a**. Compounds **1a**, **2a**, and **4a** were all identical with the compounds described above.

Examination of the aqueous phase by tlc showed the absence of any of the monomeric compounds, **6a** or **7a**. No other compounds could be isolated from this fraction.

Anodic Oxidation of 1b.—Compound **1b** was oxidized in the same manner as described above. After 12 hr, the reaction mixture was processed to yield a $CHCl_3$ extract.[29] The extract derived from the oxidation of 2.4 g of **1b** (four runs) was chromatographed over 200 g of silica gel using methanol–NH_4OH (99.75:0.25) as developer. Three fractions were obtained. The first fraction contained 0.23 g of starting material, **1b**. The second fraction contained 0.47 g of **4b**. The third fraction consisted of two compounds and was rechromatographed over neutral alumina using benzene–methanol (99:1) as a developer. The first fraction contained 0.104 g of the C–O–C trimer, **5b**. The developer was changed to benzene–methanol (49:1) and **2b** came off contaminated with **5b**. Preparative tlc yielded 0.016 g of the C–C dimer, **2b**. Compounds **1b**, **2b**, **4b**, and **5b** were identical with the compounds described above. No products could be isolated from the aqueous phase.

Anodic Oxidation of 1c.—Compound **1c** was oxidized as described above except that the medium consisted of 0.1 *M* $Na_2B_4O_7$–CH_3CN (7:3) rather than aqueous bicarbonate. The oxidation was carried out at +0.4 V. Periodically, the anode was removed and washed with acetone to remove the product coating it. After 24 hr, the reaction was stopped and the buffer mixture was extracted with $CHCl_3$. The $CHCl_3$ extract and the acetone washings from the electrode were combined and the solvent was evaporated. The residue was chromatographed over 150 g of silica gel using CH_3OH–NH_4OH (99.9:0.1) as developer. The first fraction contained 0.023 g of starting material, **1c**. The second fraction contained a mixture of the isomers of **4c** as described previously (0.176 g). The mixture was not separated. Compounds **1c** and **4c** were identical with the compounds described above.

(29) It was necessary to clean the electrode in HNO_3 frequently to keep the current at a reasonable level (30–40 mA).

Registry No.—**2b**, 25383-49-7; **4a**, 25383-50-0; **4b**, 19626-08-5; **4c**, 25383-52-2; **5b**, 25383-53-3; **7a**, 25383-54-4; **7b**, 25442-32-4; **7c**, 25383-55-5; 1-ethyl-7-hydroxy-6-methoxyisoquinoline, 25383-56-6.

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Tetraneurin-E and -F. New C-15 Oxygenated Pseudoguaianolides from *Parthenium* (*Compositae*)

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Three sesquiterpene lactones were isolated from *Parthenium confertum* var. *lyratum* (Gray) Rollins collected in Nuevo Laredo, Mexico. Two of the compounds, tetraneurin-E (**1**) and -F (**2**), are new C-15 oxygenated pseudoguaianolides, and their structure determinations are reported here; the third compound, tetraneurin-A, was previously isolated from *Parthenium alpinum* var. *tetraneuris* (Barneby) Rollins. *Parthenium integrifolium* L. yielded tetraneurin-E and tetraneurin-C (**3**), a compound previously isolated from a number of *Parthenium* species.

In a continuation of our chemosystematic investigation[1-3] of the genus *Parthenium*, a May 1969 collection of *Parthenium confertum* var. *lyratum* from Nuevo Laredo, Mexico, yielded two new sesquiterpene lactones, tetraneurin-E (**1**), $C_{17}H_{24}O_6$, mp 200–201°, $[\alpha]^{25}D$ −70.3°, and tetraneurin-F (**2**), $C_{19}H_{26}O_7$, mp 135–136°, $[\alpha]^{25}D$ −47.4°, and tetraneurin-A (**4**),[1] which was previously isolated from *Parthenium alpinum* var. *tetraneuris*. A 1969 collection of *Parthenium integrifolium* from near Cisco, Ill., also yielded tetraneurin-E (**1**) and the previously described tetraneurin-C (**3**).[2]

Tetraneurin-E (1) and -F (2).—The uv, ir, and nmr data for tetraneurin-E (**1**) and -F (**2**) indicated that both were pseudoguaianolides with structural features similar to the C-15 oxygenated compounds which had been previously isolated from other *Parthenium* species [hysterin (**5**)[4] tetraneurin-A (**4**)[1] and conchosin-A and -B[3]]. The presence of an α,β'-unsaturated γ-lactone ring, an acetate function, and a tertiary hydroxyl group in tetraneurin-E (**1**) was evident from the following data: λ_{max} 212 nm (ϵ 10,000); ir bands at 1730, 1750, and 3500 cm^{-1} (the latter was still observed after acetylation); the nmr spectrum in deuterated acetone exhibited signals typical for protons associated with a lactone function (see Table I). Although the nmr spectrum of tetraneurin-E displayed a three-proton singlet at 0.83,[5] typical for a C-5 tertiary methyl group, a doublet for a C-10 secondary methyl group was missing. Instead the spectrum displayed a two-proton multiplet at 3.75, which could be attributed to the presence of a C-10 CH_2OH group. An acetate three-proton singlet occurred at 1.99.

Treatment of the monoacetate tetraneurin-E (**1**) with acetic anhydride and pyridine yielded a diacetate which was identical in all respects with tetraneurin-F (**2**) and thus established that tetraneurin-E is the deacetyl analog of tetraneurin-F.

Treatment of tetraneurin-E with *p*-toluenesulfonyl chloride afforded a monotosylate, $C_{24}H_{30}O_8S$, mp 170–171°, whose structure appeared from nmr data to correspond to **6**. When compound **6** was refluxed with 2,6-lutidine it was converted into $\Delta^{10(15)}$-anhydrotetraneurin-E (**7**), $C_{17}H_{22}O_5$, mp 177–179°, whose 10,15-exocyclic double bond was evidenced on nmr by two

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(5) All chemical shift values are reported in parts per million, δ scale.