internal standard method.[2a] Hydrogen peroxide appears in the ^1H NMR as a broad singlet (7 Hz at half-height) at δ 2.3. This absorption exchanges with D_2O, increases in intensity on addition of 30% H_2O_2 (H_2O absorption is observed at δ 5.1), and gives 40-45% peroxide on iodometric titration.[15,18]

The fact that the same product distribution is obtained for both the FVP of **2a** and oxidation of **3a** argues convincingly for a common intermediate, 2-pyridinesulfenic acid (**4a**). Furthermore, when the oxidation of **3a** is carried out between -50 and -20 °C, the solution remains yellow in color with no H_2O_2 formation until it is warmed to room temperature. A similar yellow color is observed in the FVP synthesis of **4a** (**5**). Attempts to trap **4a** (**5**) at -20 °C with methyl propiolate, diazomethane, or methyl iodide have been unsuccessful. However, addition of methanolic $FeCl_3$ at this temperature generates a green solution which becomes colorless when warmed.[21] Iron complexes of thioamide *S*-oxides, i.e., **5**, have been reported to be this color.[12]

Similarly, oxidation of pentafluorobenzenethiol (**3b**) with **10** is very slow, with less than half of **3b** and **10** being consumed after 144 h. The disulfide **6b** is the principal product (entry 8). 4-Nitrobenzenethiol (**3c**) is completely oxidized by **10** to give a quantitative yield of disulfide **6c** after 4.5 h without consuming all of the oxidizing reagent (entry 11).

The slow rate of oxidation of thiols **3b,c** by **10** results in formation of sulfenic acids **4b,c** in the presence of a large excess of thiol. The exclusive formation of disulfide in the oxidation of these thiols (entries 8 and 11) is consistent with a mechanism whereby **3b,c** attacks the corresponding sulfenic acids to give water and disulfide (eq 4). As predicted by this mechanism **6a** and water

$$\text{R-SOH} + \text{R-SH} \rightarrow \text{R-S-S-R} + H_2O \qquad (4)$$

were formed quantitatively on oxidation of **3a** with 0.5 equiv of **10** (entry 5).

Biologically the most important reaction of thiols is their oxidation to disulfides and higher sulfur oxides.[4,7,19,20] Our experiments provide the first definitive evidence for the involvement of sulfenic acids in both of these important transformations (eq 4). Significantly, the oxidation of protein sulfhydryl groups to protein sulfenic acids has been considered necessary for the activity of certain enzyme systems as well as for the deactivation of other enzymes.[4,20,22] The formation of protein disulfides observed in the oxidation of protein thiols could well involve a reaction similar to that depicted in eq 4.[4,20,23]

Although the metal-catalyzed autoxidation of thiols to disulfides and hydrogen peroxide is well documented,[19,20,24] the coupling of two seemingly neutral units to disulfide and hydrogen peroxide (eq 3) is apparently unprecedented.[25] The possibility that hydrogen peroxide and disulfide could be formed in a manner other than that depicted in eq 3, such as from the thioamide *S*-oxide or from a thiosulfinate intermediate, is unlikely. 2-Pyridinethione *S*-oxide (**5**) reacts as the sulfenic acid **4a** (vida supra), and sulfenic acid **4b** cannot for a related structure. Although the reaction of water with an intermediate thiolsulfinate to afford H_2O_2 and disulfide cannot be eliminated absolutely, this possibility is unlikely. Thiolsulfinates have not been observed to undergo such reactions,[5d,28] and pyridine arylthiosulfinates (PySS(O)Ar) are reported to disproportionate according to eq 2.[30]

The reaction most characteristic of simple sulfenic acids when present in relatively high concentration is thiolsulfinate formation (eq 1).[31] The reason why sulfenic acids **4a-b** afford H_2O_2 and disulfide (eq 3) is unclear, but may be related to the strong electron-attracting pyridyl and pentafluorophenyl groups attached to the SOH group. We are currently exploring the scope of this unusual transformation.

Acknowledgment. We Thank Professor John Kice, Texas Tech University, for valuable discussions. We acknowledge financial support from the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation (CHE 7819890).

(18) The discrepancies in the yields of H_2O_2 determined by iodometric titration and determined by integration of NMR signals probably result from water and H_2O_2 absorbing at the same signal, thereby giving a high value. Water could be formed as illustrated in eq 4. A separate absorption for water does not appear until the concentration reaches approximately 10^{-4} M in the NMR.

(19) (a) For a general review on the oxidation of thiols, see G. Capossi and G. Modena, *Chem. Thiol. Group*, **2**, 367 (1974); (b) P. C. Jocelyn, "Biochemistry of the SH Group", Academic Press, New York, Chapter 4, 1972; (c) N. Kharasch and A. S. Arora, *Phosphorus Sulfur*, **2**, 1 (1976).

(20) Oxidation of protein thiols: (a) W. S. Lin, G. M. Gaucher, D. A. Armstrong, and M. Lal, *Can J. Chem.*, **54**, 242, (1976); (b) K. S. You, L. V. Benitez, W. A. McConachie, and W. S. Allison, *Biochim. Biophys. Acta*, **384**, 317 (1975); (c) M. Costa, L. Pecci, B. Pensa, and C. Cannella, *Biochem. Biophys. Res. Commun.*, **78**, 596 (1977).

(21) Methanolic $FeCl_3$ gave no color with **6a**, **10**, or **11**. A brown color was observed on addition of **3a** and H_2O_2 to methanolic $FeCl_3$ in $CHCl_3$.

(22) W. S. Allison and L. V. Benitez, *Proc. Natl. Acad. Sci.* U.S.A., **69**, 3004 (1972).

(23) W. S. Lin, D. A. Armstrong, and C. M. Gaucher, *Can. J. Biochem.*, **53**, 298 (1975).

(24) P. P. Trotto, L. M. Pinkus, and A. Meister, *J. Biochem.*, **249**, 1915 (1974).

(25) Certain sulfenyl halides (RSX; X = Br, I) decompose on standing to give X_2 and disulfide,[26] and thionitrosobenzene (PhN=S) disproportoinates to azobenzene (PhN=NPh) and sulfur.[27]

(26) See P. S. Magee, *Sulfur Org. Inorg. Chem.* **1**, 261 (1971); J. P. Danehy, *ibid.* **1**, 327 (1971).

(27) F. A. Davis and E. W. Skibo, *J. Org. Chem.*, **41**, 1333 (1976).

(28) Phenyl benzenethiosulfinate and 2,4,6-triisopropylbenzenethiosulfinate when treated under the reaction conditions with water proved to be unreactive. Attempts to synthesize independently the thiosulfinates corresponding to **4a,b** by oxidation of disulfides **6a,b** were unsuccessful. 4-Nitrophenyl 4-nitrobenzenethiosulfinate which is undoubtedly involved in the reactions of sulfenic acid **4c**, generated by FVP of **2c** (Table I, entry 9,10), could not be detected. Significantly aryl arenethiosulfinates with strong electron-attracting groups have never been prepared or even detected.[5d,29]

(29) S. Oae and S. Kawamura, *Bull. Chem. Soc. Jpn.*, **35**, 1156 (1962).

(30) W. Walter and P. M. Hell, *Liebigs Ann. Chem.*, **727**, 35 (1969).

(31) Hydrogen peroxide could not be detected in the reactions of benzenesulfenic acid generated by FVP of *tert*-butyl phenyl sulfoxide. See also ref 6.

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Reactions of Metal Complexes with Carbohydrates. 1. Synthesis and Characterization of Novel Blue Paramagnetic Nickel(II) Complexes Containing *N*-Glycosides

Sir:

We report the synthesis and characterization of new blue paramagnetic Ni(II) complexes containing *N*-glycosides which were derived from the reaction of tris(ethylenediamine)nickel(II) dichloride dihydrate with D-(+)-glucose (D-gl), D-(+)-mannose (D-man), or D-(-)-fructose (D-fru).

We isolated three Ni(II) complexes containing *N*-glycosides by the following procedure.

To a stirred solution of $[Ni(en)_3]Cl_2 \cdot 2H_2O$ (2.90 g, 8.38 mmol) in 50 mL of methanol was added 4.53 g (25.14 mmol) of a monosaccharide (D-gl, D-man, or D-fru). The solution was warmed to about 70 °C with stirring and became blue after about 1 h. The reaction solution was evaporated to 30 mL and loaded on a LH-20 gel permeation column and eluted with methanol. The colored materials separated into a major blue band and minor purple, yellow, and green ones. The blue band fractions were collected and concentrated to dryness under reduced pressure. Each blue compound thus obtained was recrystallized from a minimum amount of hot methanol. The crystals were collected and washed with ethanol followed by ether and dried in vacuo.[1] Elemental analyses[2] indicated that the D-gl and D-man complexes,

(1) The yields were 4.16, 1.13, and 4.53 g for the D-gl, D-man, and D-fru compounds, respectively.

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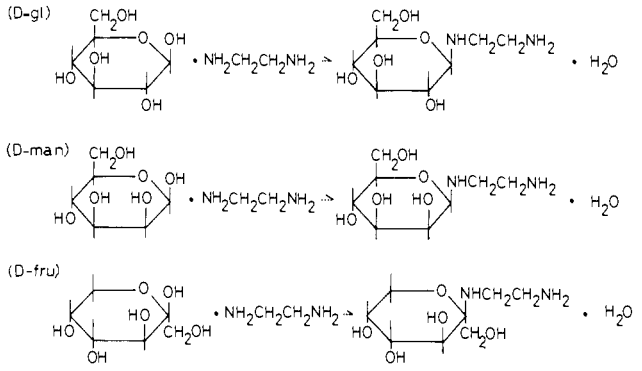

Figure 1. Reaction scheme.

$[NiC_{16}H_{36}N_4O_{10}]Cl_2 \cdot H_2O$ (**1**) and $[NiC_{16}H_{36}N_4O_{10}]Cl_2$ (**2**), respectively, contain two monosaccharide residues and two ethylenediamine moieties and the D-fru complex, $[NiC_{10}H_{26}N_4O_5]Cl_2 \cdot CH_3OH$ (**3**), has a sugar residue and two ethylenediamine moieties. The near-infrared and visible absorption spectra of the three complexes closely resemble each other, and they show three main bands with comparatively low intensities,[3-5] which are characteristic of octahedral nickel(II) complexes. The magnetic moments of the three complexes fall within range 2.9–3.4 μ_B reported for octahedral complexes of nickel(II).[6] The infrared spectra of these complexes show bands assigned to the C–O–C antisymmetrical stretching vibration in pyranose ring forms.[7]

It is well-known that sugars react with amines to produce *N*-glycosides under mild conditions. This is generally accepted as being the first step in the "Maillard reaction" or nonenzymic browing.[8] Consequently it can be predicted that D-gl, D-man, or D-fru will react with one of the amine centers of $[Ni(en)_3]^{2+}$ to form the corresponding *N*-glycoside (Figure 1).

Thus the analytical and spectroscopic data indicate that the D-gl and D-man complexes are coordinated with two tridentate *N*-glycoside ligands, viz., D-glucopyranosylethylenediamine (D-gl-en)[9] and D-mannopyranosylethylenediamine (D-man-en),[10] and the D-fru complex is surrounded with bidentate ethylenediamine and tetradentate D-fructopyranosylethylenediamine (D-fru-en) ligands,[11] as shown in Figure 2. Consequently, **1**, **2**, and **3** will be denoted $[Ni(D\text{-gl-en})_2]Cl_2 \cdot H_2O$ (**4**), $[Ni(D\text{-man-en})]Cl_2$ (**5**), and $[Ni(en)(D\text{-fru-en})]Cl_2 \cdot CH_3OH$ (**6**). We have confirmed these structural assignments by an X-ray crystallographic study of the D-fru complex.[12] It reveals that nickel is octahedrally coordinated with a bidentate ethylenediamine ligand and a tetradentate *N*-glycoside ligand of D-fru-en, as assigned above (Figure 3). One nitrogen atom of ethylenediamine expectedly binds to carbon 2 of D-fru. The pyranose ring of the sugar is in the usual $^2C_5$ chair form. These structural features will be dealt with in detail in a subsequent paper.[13] The first example of a crystal structure suggests that the coordination patterns of D-gl-en and D-man-en are predictable. We previously proposed that the hydroxyl group on carbon 2 of the sugar moieties in **4** or **5** coordinates to the nickel atom and involves five-membered chelate rings (Figure 2). The gauche conformations of the two five-membered chelate rings and the absolute configurations around carbon 1, carbon 2, and the secondary nitrogen atom have opposite sense for the two complexes. These structural features are evident in the circular dichroism curves of **4**[14] and **5**,[15] which are nearly mirror images of

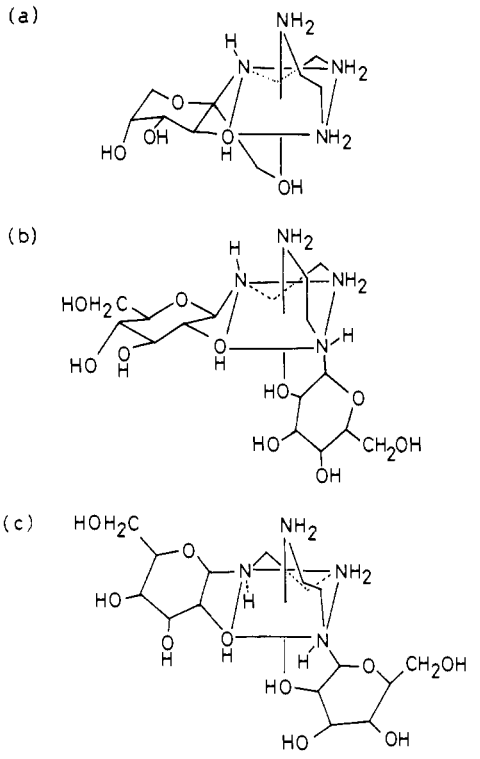

Figure 2. Structures of $[Ni(en)(D\text{-fru-en})]^{2+}$ (a), $[Ni(D\text{-gl-en})_2]^{2+}$ (b), and $[Ni(D\text{-man-en})_2]^{2+}$ (c).

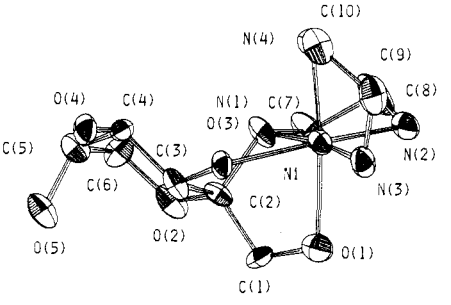

Figure 3. ORTEP drawing and atomic numbering scheme for the $[Ni(en)(D\text{-fru-en})]^{2+}$ ion. Selected bond length (Å): Ni–Ni(1) = 2.070 (8), Ni–O(1) = 2.205 (7), Ni–O(3) = 2.137 (6), N(1)–C(2) = 1.51 (1), O(1)–C(1) = 1.42 (2), C(1)–C(2) = 1.51 (2), C(2)–C(3) = 1.58 (1), O(3)–C(3) = 1.44 (1), C(3)–C(4) = 1.50 (2), O(4)–C(4) = 1.42 (2), C(4)–C(5) = 1.51 (2), O(5)–C(5) = 1.42 (2), C(5)–C(6) = 1.55 (2), C(6)–O(2) = 1.44 (2), O(2)–C(2) = 1.42 (2). Selected angles (deg): N(1)–Ni–O(1) = 79.5 (3), N(1)–Ni–O(3) = 79.5 (3), C(2)–O(2)–C(6) = 118.9 (9).

(2) Elemental analyses of both the D-gl ($C_{16}H_{38}N_4O_{11}Cl_2Ni$) and D-man ($C_{16}H_{36}N_4O_{10}Cl_2Ni$) complexes for C, H, N, Cl, and Ni agreed with calculated values within ±0.4%. Satisfactory analysis was obtained for the D-fru complex. Anal. Calcd for $[Ni(en)(D\text{-fru-en})]Cl_2 \cdot CH_3OH$ ($C_{11}H_{30}N_4O_6Cl_2Ni$): C, 29.75; H, 6.81; N, 12.62; Cl, 15.97; Ni, 13.22. Found: C, 29.25; H, 6.38; N, 12.64; Cl, 15.94; Ni, 13.05.

(3) Near-infrared and visible spectral data for **1** in methanol: ν_{max} 10 720 (ϵ 15.2), 12 640 (6.0) (sh), 17 120 (12.5), 27 320 (19.1) cm^{-1}.

(4) Near-infrared and visible spectral data for **2** in methanol: ν_{max} 10 290 (ϵ 8.9), 12 840 (4.9) (sh), 17 450 (11.5), 27 780 (26.3) cm^{-1}.

(5) Near-infrared and visible spectral data for **3** in methanol: ν_{max} 10 580 (ϵ 6.8), 12 740 (3.4) (sh), 17 120 (8.1), 28 010 (12.2) cm^{-1}.

(6) Cotton, F.; Wilkinson, G. "Advanced Inorganic Chemistry", 2d ed.; Interscience: New York, 1966; p 882.

(7) Barker, A. S.; Bourne, J. E.; Whiffen, D. H. *Methods Biochem. Anal.* **1956**, *3*, 213–45.

(8) Maillard, L. C. *C. R. Hebd. Seances Acad. Sci.* **1912**, *154*, 66–8.

(9) The fully systematic name is 1-[(2-aminoethyl)amino]-1-deoxy-D-glucose.

(10) The fully systematic name is 1-[(2-aminoethyl)amino]-1-deoxy-D-mannose.

(11) The fully systematic name is 2-[(2-aminoethyl)amino]-2-deoxy-D-fructose.

(12) The compound forms in the orthorhombic space group $P2_12_12_1$, with a = 12.348 (5) Å, b = 18.478 (8) Å, c = 8.464 (4) Å, and Z = 4. The structure was solved by heavy-atom methods and refined by full-matrix least-squares procedures with anisotropic temperature factors; $R = \sum||F_o| - |F_c||/\sum|F_o| = 0.068$; $R' = [\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2} = 0.053$, where $w = 1/[\sigma^2(F_o)]$. A table of the final positional and thermal parameters is available as supplementary material.

(13) Yano, S.; Takizawa, S.; Yoshikawa, S., to be submitted for publication.

(14) CD (methanol): ν_{max} 11 470 ($\Delta\epsilon$ +11.76), 16 780 (−3.99), 25 380 (−5.08), 28 250 (+5.59) cm^{-1}.

(15) CD (methanol); ν_{max} 12 350 ($\Delta\epsilon$ −12.10), 13 180 (−10.43), 16 030 (−2.84), 18 620 (+14.75), 26 880 (+10.62), 29 940 (−2.18) cm^{-1}.

the corresponding CD curves in the first absorption region due to the vicinal and conformational effects of each *N*-glycoside ligand of opposite sense.

Supplementary Material Available: Final positional and thermal parameters and their estimated standard deviations (2 pages). Ordering information is given on any current masthead page.

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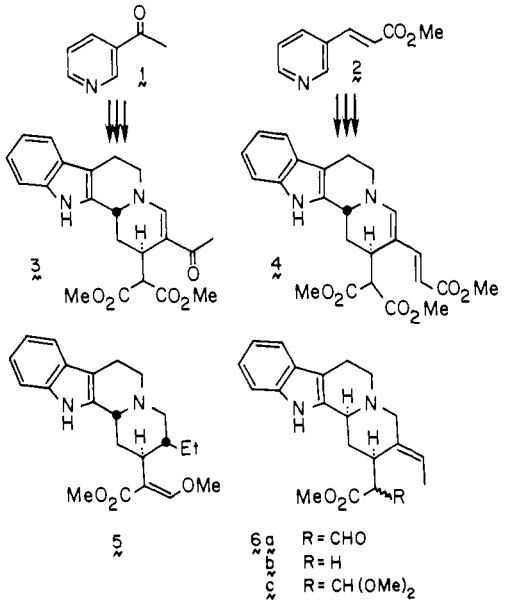
Short Syntheses of Hirsutine and Geissoschizine

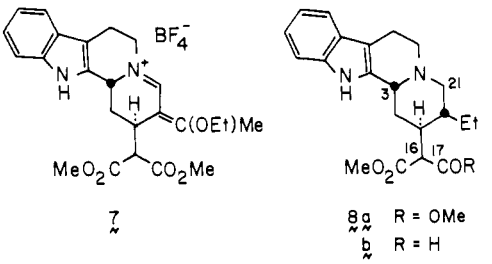
Sir:

The recent introduction of a short, new scheme of construction of the indoloquinolizidine skeleton characteristic of the indole alkaloids of the heteroyohimboid, yohimboid, and corynantheioid types[1] has led the way to total syntheses of a variety of heteroyohimboid[2] and yohimboid[3] bases. Thus N-alkylation of β-acetylpyridine (**1**) and methyl β-(β-pyridyl)acrylate (**2**) with tryptophyl bromide, treatment of the salts with dimethyl sodiomalonate, and acid-induced cyclization of the resultant 1,4-dihydropyridines have afforded indoloquinolizidines **3** and **4** en route to the heteroyohimboid and yohimboid alkaloids, respectively. The following syntheses of hirsutine (**5**) and geissoschizine (**6a**) from the tetracyclic intermediates also illustrate the power of the new method of synthesis in the construction of members of the corynantheioid alkaloid family.



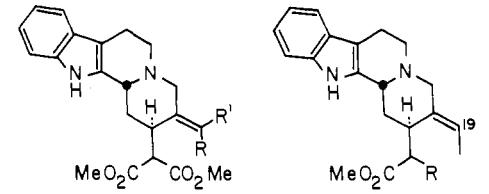
6a R = CHO; **b** R = H; **c** R = CH(OMe)$_2$

Exposure of tetracycle **3** to triethyloxonium tetrafluoroborate in methylene chloride solution gave salt **7**, whose immediate hydrogenation (20% Pd–C, MeOH, atmospheric pressure) yielded (74%) ester **8a** [mp 175–176 °C; IR (KBr) 3408, 1748, 1717 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.82 (t, 3, J = 6 Hz, Me), 3.73 [s, 6, $(OMe)_2$], 3.97 (m, 1, H-3), 6.6–7.2 (m, 4, aromatic Hs)]. Reduction of the latter [$(i\text{-Bu})_2AlH$, CH_2Cl_2, −78 °C] afforded (61%) amorphous aldehydo ester **8b** [IR ($CHCl_3$) 3467, 1716, 1658 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.80 (m, 3, Me), 3.80 (s, 3, OMe), 4.53 (m, 1, H-3), 6.9–7.6 (m, 4, aromatic Hs), 8.00 (s, 1, H-17)], whose treatment with methanolic acid (1:1 aldehyde–MeOH, CH_2Cl_2 saturated with HCl gas, −20 °C, 3 days) yielded (56%) (±)-hirsutine (**5**) (mp 152–153 °C; IR and ^{1}H NMR spectra are identical with those of an authentic sample).



7 **8a** R = OMe; **b** R = H

By the utilization of both intermediates **3** and **4**, there emerged three routes of geissoschizine synthesis of which the first two to be described constitute formal total syntheses of the alkaloid by virtue of a connection with an earlier synthesis. Reduction ($NaBH_4$, MeOH, 0 °C) of salt **7** yielded (65%) a ca. 5:4:1 mixture of enol ether **9a** [mp 178–180 °C; IR ($CHCl_3$) 3480, 3400, 1752, 1730, 1673 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.18 (t, 3, J = 7 Hz, OEt Me), 1.87 (s, 3, Me), 3.3–4.3 (m, 6, H-3, H-16, H_2-21, OCH_2), 3.61, 3.80 [s, 3 each, $(OMe)_2$], 6.8–7.4 (m, 4, aromatic Hs)], diester **9b** [mp 99–101 °C; IR ($CHCl_3$) 3478, 1751, 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.60 (d, 3, J = 6 Hz, Me), 3.18 (s, 2, H_2-21), 3.64, 3.80 [s, 3 each, $(OMe)_2$], 5.52 (q, 1, J = 6 Hz, H-19), 6.9–7.5 (m, 4, aromatic Hs)], and diester **9c**,[4] respectively. Sequential alkaline hydrolysis, acid-catalyzed thermal decarboxylation, and esterification in methanolic acid converted (87%) malonic ester **9b** into monoester **10a** [mp 134–136 °C (lit.[5] mp 134–136 °C); IR ($CHCl_3$) 3495, 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.58 (d, 3, J = 6 Hz, Me), 3.13 (s, 2, H_2-21), 3.3–3.6 (m, 1, H-3), 3.67 (s, 3, OMe), 5.42 (q, 1, J = 6 Hz, H-19), 6.9–7.5 (m, 4, aromatic Hs)].



9a R = Me (or OEt), R′ = OEt (or Me); **b** R = Me, R′ = H; **c** R = H, R′ = Me

10a R = H; **b** R = CHO; **c** R = CH(OMe)$_2$

Ester **10a** also was the product (69%) of hydrolysis and didecarboxylation of tetracycle **4** (4 N HCl, 100 °C, 5 h), esterification (HCl, MeOH, ambient temperature, 18 h), and reduction ($NaBH_4$, MeOH, 0 °C, 1 h) of the resultant immonium salt 21-dehydro-**10a**.[6] Racemic deformyl-3-isogeissoschizine (**10a**) has been transformed previously into (±)-geissoschizine (**6a**)[5] by sequential mercuric acetate oxidation, zinc–acetic acid reduction,

(1) E. Wenkert, *Recent Chem. Nat. Prod., Incl. Tob., Proc Phillip Morris Sci. Symp., 2nd*, 15–28 (1975).
(2) E. Wenkert, C.-J. Chang, H. P. S. Chawla, D. W. Cochran, E. W. Hagaman, J. C. King, and K. Orito, *J. Am. Chem. Soc.*, **98**, 3645 (1976).
(3) E. Wenkert, T. D. J. Halls, G. Kunesch, K. Orito, R. L. Stephens, W. A. Temple, and J. S. Yadav, *ibid.*, **101**, 5370 (1979).

(4) In view of the difficulty of isolation of **9c** from a mixture of the isomers **9b** and **9c**, diester **9c** was not obtained in a pure state. It could be identified, however, by ^{1}H and ^{13}C NMR analyses of the mixture and by the characterization of the acetic ester equivalent of malonate **9c** after decarbomethoxylation of the **9b–9c** mixture and separation of the resultant acetic esters.
(5) K. Yamada, K. Aoki, T. Kato, D. Uemura, and E. E. van Tamelen, *J. Chem. Soc., Chem. Commun.* 908 (1974).
(6) The hydrolysis and decarboxylation of the 5-amino-2,4-pentadienoic ester moiety of the doubly vinylogous urethane **4** are based on earlier experience: E. Wenkert, K. G. Dave, and F. Haglid, *J. Am. Chem. Soc.*, **87**, 5461 (1965). For a recent example see R. Besselièvre, B.-P. Cosson, B. C. Das, and H.-P. Husson, *Tetrahedron Lett.*, 63 (1980).

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