and R. C. Cookson, J. Henstock, and J. Hudec, *J. Amer. Chem. Soc.*, **88**, 1060 (1966).

(22) In conformations **19, 20,** and **22, 23,** the methylene bridge at the B/C ring junction interferes with the interaction between the lone pair of the nitrogen at the C/D ring junction and the amide chromophore.

(23) We applied the lactone sector rule [J. P. Jennings, W. Klyne, and P. M. Scopes, *J. Chem. Soc.*, 7211 (1965)] to the amide n $\rightarrow \pi^*$ Cotton effect [see H. Wolf, *Tetrahedron Lett.*, 1075 (1965), and A. F. Beecham, *Tetrahedron Lett.*, 4897 (1969)]. It is interesting to note that, upon addition of hydrochloric acid, the amide n $\rightarrow \pi^*$ absorption band at 220 nm in the CD spectra of **7** and **1** changes in sign from positive to negative (see Figures 3 and 4). This phenomenon has not yet been reported on the amide chromophore, and we are studying it in more detail by measuring the CD spectra of related amide compounds. We are indebted to Dr. K. Kuriyama, Shionogi Research Laboratory, Shionogi & Co., Ltd., Osaka, Japan, for the determination of the CD spectra and valuable comments.

(24) This conformation is in agreement with that suggested for aphylline from its ir studies by Bratek-Wiewiorowski, *et al.* (see reference 19). In the ir spectra of **1** and **7,** a Bohlmann trans band with a low intensity appears at 2820 cm^{-1}. Note that in conformations **18** and **19** there is only one hydrogen on carbons attached to N-16 and in a trans-diaxial relation to its lone pair of electrons, and in conformation **20** there are three such hydrogens. According to the criterion made originally by Bohlmann [F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958)], the occurrence of trans bands requires the presence of at least two such hydrogens.

Phlebicine, a New Biphenylbisbenzylisoquinoline Alkaloid from *Cremastosperma polyphlebum*

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Phlebicine, a new bisbenzylisoquinoline alkaloid from *Cremastosperma polyphlebum*, has been assigned structure 1 on the basis of spectroscopic evidence, oxidative degradation, and conversion to the known alkaloid rodiasine (3).

Although alkaloids have been isolated from many genera of the family Annonaceae,[1] the genus *Cremastosperma* has not previously been investigated phytochemically. We now report the isolation of the new alkaloid phlebicine from the bark of the Amazonian species *Cremastosperma polyphlebum* (Diels) Fries, and evidence in support of the assignment of structure **1** to phlebicine.

Countercurrent fractionation of the phenolic bases from *C. polyphlebum,* followed by crystallization from chloroform–methanol, gave white needles of phlebicine, mp 195°; the composition $C_{37}H_{40}N_2O_6$ was determined by mass spectrometry.

The infrared spectrum (KBr) of phlebicine showed the absence of a carbonyl band, but a band at 3400 cm^{-1}, attributable to a nonchelated hydroxyl, was observed.

The nmr spectrum of phlebicine showed the presence of three aromatic methoxyls at δ 3.80, 3.70, and 3.38, as well as two methylimino groups at δ 2.57 and 2.27. In the aromatic region, three one-proton singlets were observed at δ 6.69, 6.28, and 6.20, in addition to a total of six protons of higher multiplicity.

Treatment of phlebicine with excess diazomethane afforded *O,O*-dimethylphlebicine (**2**), mp 163–165°. The nmr spectrum of the latter now showed the presence of five methoxyls in the δ 3.3–3.9 region. Phlebicine is therefore a diphenolic base.

The optical rotatory dispersion curve of phlebicine (Figure 1) shows peaks at 297 and 252 nm, and troughs at 272 and 231 nm. It strongly resembles the reported ORD curve of rodiasine (**3**),[2] and therefore suggests that phlebicine is also a bisbenzylisoquinoline alkaloid which contains the structural feature of a biphenyl linkage.

In accord with the presence of a biphenyl system in the molecule, attempted sodium–ammonia cleavage of *O,O*-dimethylphlebicine gave no characterizable products. However, *O,O*-dimethylphlebicine was successfully cleaved by photochemical air oxidation,[3] followed by borohydride reduction. Two crystalline products were isolated. The first product, derived from the two tetrahydroisoquinoline units of the alkaloid ether **2,** was the known isocarbostyril **4.**[3] The second product was the biphenyl diol **5,** which was identical with the borohydride reduction product of the known dialdehyde **6.**[4] Consequently, *O,O*-dimethylphlebicine must be assigned structure **2,** which is identical with that of *O*-methylrodiasine,[2,5] ignoring the stereochemistry at the two asymmetric carbons. Finally, incomplete methylation of phlebicine was found to afford a mono-*O*-methylphlebicine, which was identical in all respects, including optical properties, with authentic rodiasine (**3**).[2,5,6] Phlebicine is, therefore, one of the four possible isomeric *O*-demethylrodiasines.

The position of the second phenolic hydroxyl group in phlebicine was determined by a comparative nmr and mass spectrometric study of phlebicine and its products of deuteration, deuteriomethylation, O-acetylation, and O-ethylation.

The mass spectrum of rodiasine (**3**) shows an intense peak at *m/e* 198, attributable to the doubly charged ion **7.**[2,6] In phlebicine, the corresponding ion (**8**) appears at *m/e* 191, whereas in *O,O*-diethylphlebicine (**9**) and in *O,O*-bis(dideuteriomethyl)phlebicine (**10**) similar ions (**11** and **12**) appear at *m/e* 205 and 199, respectively. The second hydroxyl of phlebicine must, therefore, be present in one of the tetrahydroisoquinoline units of the molecule.

When phlebicine was subjected to base-catalyzed deuteration,[7,8] it was converted into a dideuteriophlebicine (**13**). Since the oxygenation pattern of phlebicine is identical with that of rodiasine, the two deuteriums of dideuteriophlebicine must have been introduced ortho to each of the two phenolic hydroxyls of phlebicine. The deuteration of phlebicine brings about a change in its nmr spectrum, in which both a one-proton singlet at δ 6.20 and a one-proton doublet at δ 6.78 (J = 8 Hz) vanish. The latter doublet must arise from H-13′ of the biphenyl unit of phlebicine. The replaceable singlet must represent a proton at either C-5 or C-5′ of the bisisoquinoline unit of the molecule.

The mass spectrum of dideuteriophlebicine (**13**) shows peaks due to the undegraded bisisoquinoline unit at *m/e*

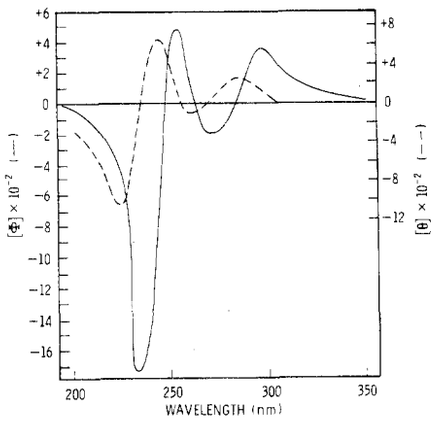
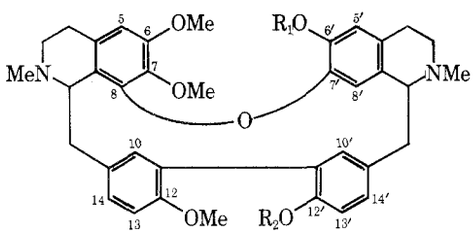
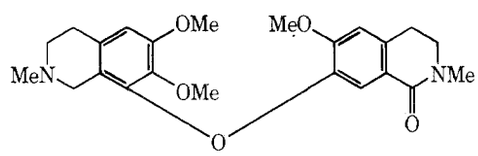


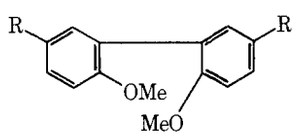
Figure 1. Optical rotatory dispersion (—) and circular dichroism (- - -) curves of phlebicine.



1, $R_1 = R_2 = H$
2, $R_1 = R_2 = Me$
3, $R_1 = Me; R_2 = H$
9, $R_1 = R_2 = Et$
10, $R_1 = R_2 = CHD_2$
13, = 1 (D at C-5′ and C-13′)
18, $R_1 = R_2 = Ac$



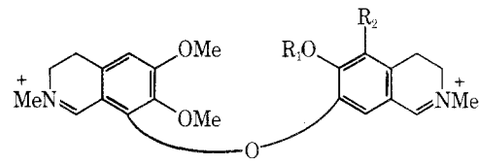
4



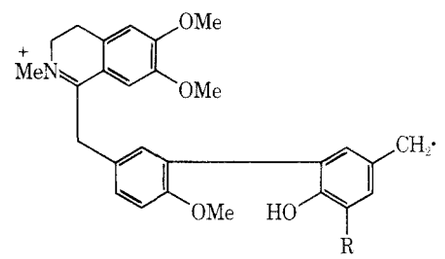
5, $R = CH_2OH$
6, R = CHO

383 and 191.5 (383/2, **14**), confirming the introduction of one deuterium in this portion of the molecule.[9] Other mass spectral evidence allows the placement of the isoquinoline phenolic group at C-6′ rather than at C-6. By analogy with other bisbenzylisoquinoline alkaloids having a C-7′ to C-8 ether bridge,[9,10] phlebicine should show a fragment due to loss of the upper right isoquinoline unit, but not show one due to the loss of the upper left isoquinoline unit. Indeed, fragments at *m/e* 431 (**15**) and 432 (**16**) appear in the mass spectrum of phlebicine and dideuteriophlebicine, respectively. Also, the same doubly charged dioxane fragment at *m/e* 175 (**17**)[2] appears prominently in the mass spectra of *O,O*-dimethylphlebicine (**2**), *O,O*-bis(dideuteriomethyl)-phlebicine (**10**), *O,O*-diethylphlebicine, (**9**), and *O,O*-diacethylphlebicine (**18**). Formation of this same ion from all of these derivatives is consistent with the presence of a phenolic function at C-6′ in phlebicine, but not at C-6.

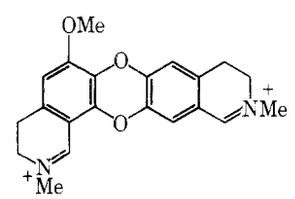
Phlebicine is thus a new member of the small group of



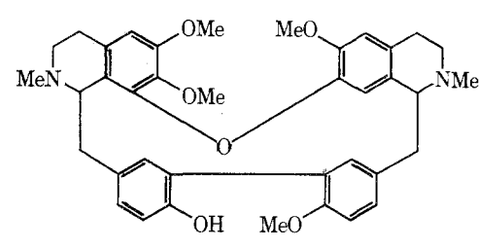
7, $R_1 = Me; R_2 = H$
8, $R_1 = R_2 = H$
11, $R_1 = Et; R_2 = H$
12, $R_1 = CHD_2; R_2 = H$
14, $R_1 = H; R_2 = D$



15, R = H
16, R = D



17



19

bisbenzylisoquinoline alkaloids which contain a biphenyl unit. Phlebicine (**1**), rodiasine (**3**), and funiferine (**19**)[10] belong to the same stereochemical series, since all three afford the same O-methylation product (**2**); however, the absolute configuration at the asymmetric centers of these bases remains unknown.

Phlebicine appears to be unique among bisbenzylisoquinoline alkaloids in that one of the benzylisoquinoline units from which it is derived has retained its phenolic functions in an entirely unalkylated state.

Experimental Section

Melting points are uncorrected. Nmr spectra were determined with Varian A-60 and Varian A-100 spectrometers in $CDCl_3$ using tetramethylsilane as internal standard unless otherwise noted. Infrared, ultraviolet, mass, and CD–ORD spectra were determined using Perkin-Elmer Models 137, 202, and 270, and Cary Model 60 instruments, respectively. The CD–ORD curves were run in methanol (*c* 0.05). Plant material was collected near Manaus, Brazil, in 1965 and was botanically verified at the Jardim Botanico, Rio de Janeiro; a voucher sample has been deposited with the INPA herbarium, Manaus.

Isolation of Phlebicine (1) from *Cremastosperma polyphlebum.* The ground tree bark (*ca.* 20 kg) was extracted thoroughly with boiling ethanol. Evaporation of the solvent gave a dark gum which was extracted several times with hot ammoniacal ethyl acetate. The ethyl acetate solution was extracted a number of times

with 5% H_2SO_4 (7 l. total), basified (pH 10) with ammonia, and extracted with $CHCl_3$. Evaporation of the dried $CHCl_3$ solution gave 69 g of bases. The insoluble tar obtained from the above ethyl acetate extraction was dissolved in glacial acetic acid and diluted with water. After filtration through super-cel, the acidic solution was basified with ammonia and extracted with $CHCl_3$ to give an additional 110 g of bases.

A portion of the above base mixture (5.0 g) was extracted with 50 ml of benzene–$CHCl_3$ (1:1). The filtered solution was extracted with 5% NaOH (4 × 40 ml) and the extract was acidified with 4 *N* HCl, followed by basification to pH 11 with ammonia. Extraction with $CHCl_3$ and evaporation of the dried extract gave the phenolic bases (1.266 g).

Countercurrent separation of the phenolic bases (100 transfers) was carried out using $CHCl_3$ and pH 4.5 citrate–phosphate buffer. The combined tubes 77–88 gave material (0.675 g) which was subjected to ptlc separation (silica; benzene–$CHCl_3$–MeOH, 1:1:1) to give phlebicine (**1**, 0.051 g). Recrystallization from $CHCl_3$–MeOH afforded colorless crystals: mp 195° (sint 180°); ir ν (KBr) 3400 cm^{-1} (OH); uv λ_{max} (EtOH) (log ϵ) 292 nm (3.93); $[\alpha]D$ +182.5° (*c* 1.0, $CHCl_3$); ORD ($[\theta]$) 297 (+ 3.52 × 10^4), 272 (− 2.06 × 10^4), 252 (+ 4.95 × 10^4), 231 nm (− 16.9 × 10^4); CD ($[\theta]$) 285 (+ 2.57 × 10^4), 260 (− 1.10 × 10^4), 246 (+ 6.95 × 10^4), 225 nm (− 6.60 × 10^4); nmr ($CDCl_3$) δ 7.28 (1 H, d, J = 2.0 Hz, H-10), 7.25–7.08 (2 H, m, H-14 and H-14′), 6.78 (1 H, d, J = 8.0 Hz, H-13), 6.73 (1 H, d, J = 8.0 Hz, H-13′), 6.69 (1 H, s, H-5), 6.50 (1 H, d, J = 2.0 Hz, H-10′), 6.28 (1 H, s, H-8′), 6.20 (1 H, s, H-5′), 3.80, 3.70, 3.38 (each 3 H, s, 3 × OMe), 2.57, 2.27 (each 3 H, s, 2 × NMe); mass spectrum (*m/e*) 608 (M^+), 607 (M − 1), 487, 431, 430, 382, 381, 367, 206, 191 (base peak).

Anal. Calcd for $C_{37}H_{40}N_2O_6 \cdot 1.5H_2O$: C, 69.89; H, 6.82; N, 4.40; O, 18.87. Found: C, 69.94; H, 6.94; N, 4.48; O, 18.44.

The hydrochloride formed colorless needles, mp 290° dec.

***O*-Monomethylphlebicine.** Phlebicine (100 mg) was dissolved in CH_2Cl_2 (5 ml) and ethereal diazomethane was added. The mixture was allowed to stand at 0–5° for 2 days. The usual work-up, followed by purification by ptlc (silica; $CHCl_3$–benzene–MeOH, 1:1:1), gave a colorless solid (40 mg). Crystallization from MeOH–ether gave *O*-monomethylphlebicine (**3**) as colorless needles: mp 201–203°; ir ν (KBr) 3300 cm^{-1} (OH); uv λ_{max} (EtOH) (log ϵ) 231 (sh, 4.68), 288 (4.13), 295 nm (sh, 4.11); nmr ($CDCl_3$) δ 3.84, 3.78, 3.49, 3.35, (each 3 H, s, 4 × OMe), 2.69, 2.40 (each 3 H, s, 2 × NMe); $[\alpha]_D$ +147° (*c* 0.32, $CHCl_3$); mass spectrum (*m/e*) 622 (M^+), 621, 607, 592, 430, 396, 395 (base peak), 381, 198, 175, 174.

The ir spectrum (KBr) of **3** was superimposable upon that of (+)-rodiasine (provided by Professor M. Shamma) and the mixture melting point (mp 201–203°) with (+)-rodiasine showed no depression.

***O,O*-Dimethylphlebicine (2).** Phlebicine (650 mg) was dissolved in CH_2Cl_2 (20 ml) and MeOH (10 ml) and ethereal diazomethane (80 ml containing 80 mg of CH_2N_2) was added. The mixture was allowed to stand at room temperature for 5 days, then evaporated and worked up in the usual manner to give *O,O*-dimethylphlebicine (**2**) as a pale yellow powder (645 mg), which was purified by ptlc (silica; $CHCl_3$–MeOH, 100:112) to give, after crystallization from ether–hexane, pure **2**: mp 163–165°; mass spectrum (*m/e*) 636 (M^+), 635 (M − 1), 623, 622, 621, 607, 515, 462, 445, 430, 396, 395 (base peak), 382, 381, 198, 175, 174; nmr ($CDCl_3$) δ 3.83, 3.46, 3.36 (each 3 H, 3 × OMe), 3.76 (6 H, br s, 2 × OMe), 2.63, 2.33 (each 3 H, s, 2 × NMe).

The mother liquor afforded, after ptlc and crystallization from MeOH–ether, colorless needles of rodiasine (**3**), mp 201–203°,[2] identical in all respects with the authentic sample described above.

O-Ethylation of Phlebicine. To a solution of phlebicine (120 mg) in CH_2Cl_2 (3 ml) and MeOH (2 ml) was added an ethereal solution of diazoethane prepared from nitrosoethylurea (5.0 g). After 12 days at room temperature, the usual work-up, followed by ptlc (silica; $CHCl_3$–MeOH, 100:115), afforded *O,O*-diethylphlebicine (**9**) as a pale yellow syrup: nmr ($CDCl_3$) δ 3.78, 3.73, 3.38 (each 3 H, s, 3 × OMe), 2.61, 2.32 (each 3 H, s, 2 × NMe); mass spectrum (*m/e*) 664 (M^+), 663 (M − 1), 637, 636, 635, 410, 409 (base peak), 395, 381, 379, 205, 191, 175, 174, 168.

***O,O*-Diacetylphlebicine (18).** A mixture of phlebicine (30 mg), acetic anhydride (0.6 ml), tetrahydrofuran (3 ml), and sodium carbonate (0.5 g) was stirred for 16 hr at room temperature. After filtration, solvent evaporation and purification by ptlc (silica; $CHCl_3$–MeOH, 10:1) gave *O,O*-diacetylphlebicine (**18**) as a syrup, converted by ether to a yellow powder (21 mg): mp 200–203° (sint 190°); nmr ($CDCl_3$) δ 3.77, 3.67, 3.34 (each 3 H, s, 3 × OMe), 2.61, 2.34 (each 3 H, s, 2 × NCH_3), 2.06, 1.97 (each 3 H, s, 2 × $OCOCH_3$); mass spectrum (*m/e*) 692 (M^+), 691, 650, 649, 424, 423, 382, 381, 364, 363, 212, 206, 191, 175, 174, 168.

Photooxidation of *O,O*-Dimethylphlebicine (2). (a) *O,O*-Dimethylphlebicine (215 mg) was dissolved in MeOH (250 ml) and then photolyzed (Hanovia lamp, O_2) for 3.5 hr. Evaporation of the solvent left a dark residue which was shaken with a mixture of CH_2Cl_2 (100 ml), water (50 ml), and 37% HCl (1 ml). Evaporation of the dried organic layer, followed by ptlc (silica; $CHCl_3$–MeOH, 100:104) afforded aldehyde **6** (18 mg), which crystallized from *n*-hexane as colorless crystals: mp 134–135° (lit.[4] mp 134–136°). ir ν (KBr) 1690 cm^{-1} (CHO); uv λ_{max} (EtOH) 277 nm; mass spectrum (*m/e*) 270 (M^+), 269, 255, 254, 134 [½(M − 2)]; nmr ($CDCl_3$) δ 10.02 (2 H, s, 2 × CHO), 8.00 (2 H, pair of doublets, J = 8.0, 2.0 Hz, 4- and 4′-H), 7.85 (2 H, d, J = 2.0 Hz, 6- and 6′-H), 7.14 (2 H, d, J = 8.0 Hz, 3- and 3′-H), 3.87 (6 H, s, 2 × OMe).

The above aqueous layer, MeOH (50 ml), and sodium borohydride (1.5 *g*) were heated (steam bath) for 20 min, concentrated *in vacuo*, and extracted with $CHCl_3$. Evaporation of the dried extract, followed by ptlc (silica; $CHCl_3$–MeOH, 10:1), gave 12 mg of isocarbostyril **4**, which crystallized from ether as colorless crystals: mp 125–127°; ir ν (KBr) 1650 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.25 (1 H, s, H-8), 6.68, 6.51 (1 H each, s, H-5 and H-5′), 3.95, 3.80, 3.64 (each 3 H, s, 3 × OMe), 3.58–3.37 (2 H, m, H-3), 3.45 (2 H, s, H-1′), 3.03 (3 H, s, 2-NMe), 3.05–2.50 (6 H, m, methylenes), 2.37 (3 H, s, 2′-NMe); mass spectrum (*m/e*) 412 (M^+), 411 (M − 1), 397, 222, 221, 206 (M^{2+}). The compound was identical with an authentic sample provided by Professor I. R. C. Bick on the basis of ir, nmr, and mixture melting point.

(b) A solution of *O,O*-dimethylphlebicine (150 mg) in MeOH (250 ml) was photolyzed for 4 hr, followed by work-up as above and separation into the organic and aqueous layers. After evaporation of the organic layer, the residue was dissolved in MeOH (20 ml) and then treated with $NaBH_4$ (300 mg) for 1 hr. The usual work-up, followed by ptlc (silica; $CHCl_3$–MeOH, 10:1), gave diol **5** (28 mg) as an oil, converted by $CHCl_3$–ether to colorless crystals: mp 149–150°; ir ν (KBr) 3450 cm^{-1} (OH); nmr ($CDCl_3$) δ 7.04–6.87 (6 H, m, ArH), 4.61 (4 H, s, 2 × CH_2OH), 3.75 (6 H, s, 2 × OMe), 2.50–2.10 (2 H, broad, 2 × OH); mass spectrum (*m/e*) 274 (M^+). The ir spectrum was superimposable upon that of an authentic sample prepared (see below) from synthetic aldehyde **6** and mixture melting point showed no depression.

Work-up of the above aqueous layer after borohydride treatment gave isocarbostyril **4**.

5,5′-Bis(hydroxymethyl)-2,2′-dimethoxybiphenyl (5). To a stirred solution of synthetic aldehyde **6**[4] (9.0 g) in MeOH (200 ml) and $CHCl_3$ (50 ml) was added in portions sodium borohydride (4 g). After stirring for 1 hr, the solvent was removed and the residue was worked up in the usual manner. The crude product (8.5 g) crystallized from MeOH to give diol **5** as colorless prisms, mp 149–150°.

Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 70.21; H, 6.88.

Base-Catalyzed Deuteration of Phlebicine (1). Phlebicine hydrochloride (35 mg) in 3% NaOD–D_2O (1.0 ml) and carbitol-d[11] (0.5 ml) was heated in a sealed tube, under nitrogen, at 110–118° for 30 hr. The usual work-up, followed by ptlc purification (silica; $CHCl_3$–MeOH, 8:2), afforded dideuteriophlebicine (**13**, 11 mg) as a colorless powder: mp 197° (180° sint) ($CHCl_3$–ether–hexane); nmr ($CDCl_3$) δ 7.31 (1 H, d, J = 2.0 Hz, H-10), 7.20–7.08 (2 H, m, H-14 and H-14′), 6.74 (1 H, d, J = 8.0 Hz, H-13), 6.71 (1 H, s, H-5), 6.53 (1 H, d, J = 2.0 Hz, H-10′), 6.31 (1 H, s, H-8), 3.82, 3.72, 3.40 (each 3 H, s, 3 × OMe), 2.58–2.28 (each 3 H, s, 2 × NMe); mass spectrum (*m/e*) 610 (M^+), 609, 489, 432, 431, 383, 382 (base peak), 368, 206, 191.5, 175.5.

O-Dideuteriomethylation of Phlebicine. To a solution of phlebicine (20 mg) in dry ether (20 ml) and dry dioxane (3 drops) was added an ethereal solution of diazomethane-d_2.[11] After standing at room temperature for 3 days, excess reagent was decomposed with acetic acid. Work-up for the nonphenolic product in the usual manner, followed by ptlc purification (silica; $CHCl_3$–MeOH, 8:2), gave *O,O*-bis(dideuteriomethyl)phlebicine (**10**, 4 mg) as a colorless powder: mp 161° ($CHCl_3$–hexane); mass spectrum (*m/e*) 640 (M^+), 639, 624, 609, 519, 447, 446, 409, 398 (base peak), 397, 381, 364, 205, 199.5, 199, 191, 175, 174, 168.

Acknowledgment. We thank the National Institutes of Health for a grant (CA 11445) in support of this work. We also thank Professor M. Shamma, Pennsylvania State Uni-

versity, and Professor I. R. C. Bick, University of Tasmania, for generous gifts of comparison samples.

Registry No.—**1**, 52674-06-3; **1** HCl, 52759-92-9; **2**, 52674-07-4; **3**, 6391-64-6; **4**, 35611-57-5; **5**, 52674-08-5; **6**, 52674-09-6; **9**, 52674-10-9; **10**, 52729-64-3; **13**, 52729-65-4; **18**, 52674-11-0.

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Notes

Synthesis and Properties of *N*-Acetimidoyl Derivatives of Glycine and Sarcosine[1a]

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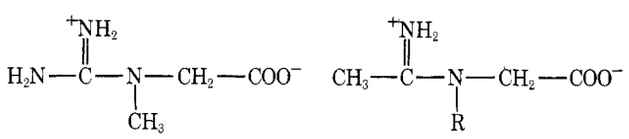
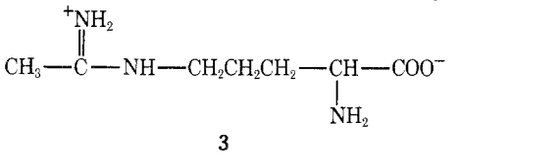
Analogs of creatine **1** which have been prepared and tested for their properties have been restricted to *N*-amidino derivatives (*i.e.*, guanidino compounds) of appropriate amino acids.[2,3] No attempts have been made, however, to test other derivatives, such as *N*-acetimidoylamino acids (*i.e.*, amidines) that are structurally related to creatine and may provide interesting information concerning their biological properties. In fact, acetimidoyl compounds of biological interest in relation to their amidino counterparts have been noted; for example, N^5-acetimidoyl-L-ornithine (**3**), an L-arginine **4** antagonist, has recently been isolated by Scannell, *et al.*[4]

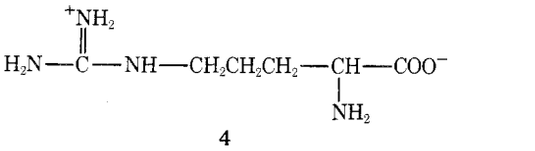


1

2a, R = H
b, R = CH_3



3

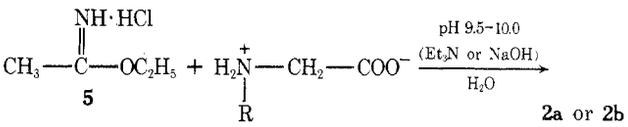


4

We, therefore, synthesized acetimidoyl derivatives of glycine **2a** and sarcosine **2b** in an attempt to understand their properties including those of biological interest.

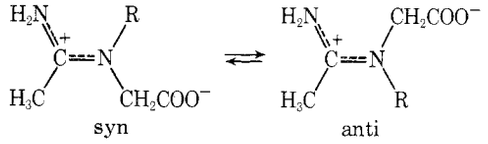
Results and Discussion

The well-known imido ester–amine reaction[5] is useful in the synthesis of amidines **2** derived from amino acids. Most products have been obtained in high yields by carrying out reactions in alcoholic solvents at elevated temperature (60–160°).[6] We have synthesized two new amidines, *N*-acetimidoylglycine (**2a**) and *N*-acetimidoylsarcosine (**2b**), in aqueous media at pH 9.5–10.0 and room temperature, utilizing the pH–rate relationship of the reactions of imidoester with amines,[7] amino acids,[8] and proteins.[8]



5 **2a** or **2b**

Both compounds have characteristic ir absorption bands for the carboxylate and C=N groups. Their nmr spectra reveal that, like other aminidium ions,[9] the rotation about the C–N bond is restricted, and both compounds can exist in syn and anti forms, which result in two sets of proton signals for each compound (Table I).



syn anti

The chemical shifts are assigned to the syn and anti forms by analogy with *N*,*N*-dimethylformamide.[10] The acetimidoyl methyl protons in the syn form absorb at higher field presumably because of an electric field effect arising from the carboxylate group that lies on the same side. The low syn/anti ratio for **2a** is in accord with the preference of the anti form of *N*-methylacetamidium ion in D_2O (syn/anti, 0.04).[11] It is of interest to note that the syn preference in the internal salt **2b** is opposite to that of the neutral *N*-acetylsarcosine methyl ester in DMSO-d_6 (syn/anti, 0.4).[12] Downfield shifts of α protons in **2a** and **2b** in acidic medium are of the same magnitude observed for amino acids and peptides.[13] In trifluoroacetic acid, the spin–spin coupling of N–H and N–CH_2 in **2a** indicates that no protonation occurs on the substituted α-amino nitrogen.