1,4-Diaminoalkanes from Pyrroles. A New Synthetic Approach to Substituted Putrescines

Daniel O. Alonso Garrido, Graciela Buldain, and Benjamín Frydman*

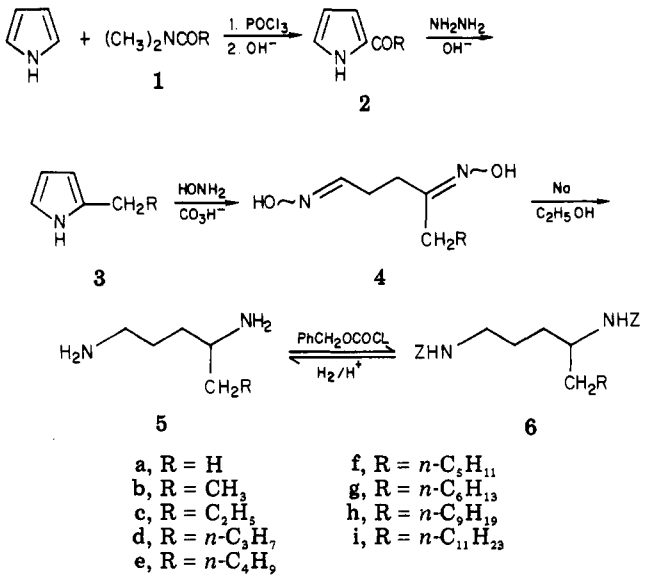
Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Junín 956, Buenos Aires, Argentina

Received December 20, 1983

One hundred years ago, Ciamician and Dennstedt reported that when pyrrole reacted with hydroxylamine a ring opening of the former took place with formation of succinaldehyde dioxime.[1] Reduction of succinaldehyde dioxime to putrescine (1,4-diaminobutane) therefore afforded a synthesis of the latter starting from pyrrole. The ring opening of pyrrole by hydroxylamine found little application in pyrrole chemistry, and it was occasionally used to prepare succinaldehyde and putrescine.[1,2] The mechanism of the reaction was briefly explored in 1956,[3] and it found some synthetic use.[4] Putrescine was recently recognized as an important natural polyamine and together with its derivatives spermidine and spermine became part of a group of substances that are known to be deeply involved in cell proliferation and "in vivo" protein synthesis.[5] Synthetic analogues and derivatives of the natural polyamines were prepared, and their effect on cell growth and as inhibitors of putrescine biosynthesis was explored.[6] α,ω-Diaminoalkanes with 3–12 carbon atoms were found to inhibit the enzymatic polyamine formation from its precursors.[7] Since pyrrole itself can be substituted in many ways,[8] substituted pyrroles can be considered as good synthons for the obtention of substituted putrescines that are not easily accesible by other routes. This will be exemplified in this paper, where the synthesis of 1,4-diaminoalkanes (hydrophobic putrescines) from 2-alkylpyrroles will be discussed (Scheme I).

Acylation of pyrrole with acyl chlorides under conditions of the Friedel–Craft reaction did not afford the expected 2-acylpyrroles in good yields, although it is a convenient

Scheme I



1 2 3 4 5 6

a, R = H
b, R = CH_3
c, R = C_2H_5
d, R = n-C_3H_7
e, R = n-C_4H_9
f, R = n-C_5H_{11}
g, R = n-C_6H_{13}
h, R = n-C_9H_{19}
i, R = n-$C_{11}H_{23}$

reaction for the acylation of substituted pyrroles.[9] The specific acylation of pyrrole at the C-2 position was achieved by the Vilsmeier–Haak reaction with use of *N,N*-dimethylacylamines (Scheme I). The *N,N*-dimethylacylamines **1b–i** (obtained in 80–90% yield by reaction of the acyl chlorides dissolved in benzene with dry dimethylamine at 5 °C) were condensed with pyrrole in the presence of phosphorus oxychloride in a benzene solution at 20 °C during 18 h. After hydrolysis of the imonium salt with a concentrated sodium hydroxide solution, the crude 2-acylpyrroles (75–80% yield) were used directly in the next step. Purification, if desired, was achieved by distillation followed by crystallization in several cases. That the acylations were specific for the C-2 position of pyrrole was clear from analysis of the ^{13}C NMR spectra of **2**.

The crude 2-acylpyrroles **2b–i** (as well as 2-formylpyrrole, **2a**) were reduced to the 2-alkylpyrroles in about 60% yield by heating with potassium hydroxide and 95% hydrazine in ethylene glycol at 200 °C during 1.5 h. Catalytic hydrogenation, which was efficient for the reduction of substituted 2-acylpyrroles to 2-alkylpyrroles,[9d] afforded only 2-(hydroxyalkyl)pyrroles in the aforementioned cases. The lower homologues **3a–g** were isolated by direct distillation from the reaction mixture, while the higher homologues **3h–i** were extracted with chloroform from the latter. All the 2-alkylpyrroles were purified by distillation in vacuo.

The 2-alkylpyrroles **3a–i** were heated with hydroxylamine hydrochloride in the presence of sodium bicarbonate in a 96% ethanol solution during 48 h. After filtration of the salts and evaporation of the solvent, the residue was dissolved in a 10% sodium hydroxide solution which was washed with ethyl ether (extraction of unreacted pyrrole), and the aqueous solution was adjusted to pH 6 and again extracted with ethyl ether. Evaporation of the latter extracts left behind the crude dioximes **4a–i** (45–50% yield).

(1) Ciamician, G.; Dennstedt, M. *Ber. Deutsch. Chem. Ges.* **1884**, *17*, 533. Ciamician, G.; Zanetti, C. U. *Ibid.* **1889**, *22*, 1968, 3176; **1890**, *23*, 1787. Willstatter, R.; Heubner, W. *Ibid.* **1907**, *40*, 3871. Mannich, C.; Budde, H. *Arch. Pharm. (Weinheim, Ger.)* **1932**, *270*, 283.
(2) Keagle, L. C.; Hartung, W. *J. Am. Chem. Soc.* **1946**, *68*, 1608.
(3) Findlay, S. P. *J. Org. Chem.* **1956**, *21*, 644.
(4) Buchta, E.; Huhn, Ch. *Justus Liebigs Ann. Chem.* **1966**, *695*, 42.
(5) Bachrach, U. "Function of Naturally Occurring Polyamines"; Academic Press: New York, 1973. Ganem, B. *Acc. Chem. Res.* **1982**, *15*, 292. Cohen, S. S. "Introduction to the Polyamines"; Prentice Hall: Englewood Cliffs, NJ, 1971. Tabor, H.; Tabor, C. W. *Ann. Rev. Biochem.* **1976**, *45*, 285. "Advances in Polyamine Research"; Campbell, R. A., Morris D. R., Bartos, D., Davies, G. D.; Bartos, F., Eds.; Raven: New York, 1978; Vol. 1, 2. Caldarera, C. M., Zappia, V., Bachrach, U. *Ibid.* 1981; Vol. 3. Bachrach, U.; Kaye, A.; Chayen, R. *Ibid.* Vol. 1983; Vol. 4.
(6) Geiger, L. E.; Morris, D. R. *Biochim. Biophys. Acta* **1980**, *609*, 264. Geiger, L. E.; Morris, D. R. *J. Bacteriol.* **1980**, *141*, 1192. Igarashi, K.; Kashiwagi, K.; Kakegawa, T.; Hirose, S.; Yatsumina, T.; Kimura, E. *Biochim. Biophys. Acta* **1980**, *633*, 457. Jorstad, C. M.; Harada, J. J.; Morris, D. R. *J. Bacteriol.* **1980**, *141*, 456. Karpetsky, T. P.; Shriver, K. K.; Levy, C. C. *Biochem. J.* **1981**, *193*, 325. Relyea, N.; Rando, R. R. *Biochem. Biophys. Res. Commun.* **1975**, *67*, 392. Kameji, T.; Murakami, Y.; Hayaishi, S. *J. Biochem. (Tokyo)* **1979**, *86*, 191. Israel, M.; Rosenfeld, J. M.; Modest, E. J. *J. Med. Chem.* **1964**, *7*, 710. Israel, M.; Modest, E. J. *J. Med. Chem.* **1971**, *14*, 1042. Mamont, P. S.; Danzin, C. In "Advances in Polyamine Research"; Raven: New York, 1981; Vol. 3, p 123; Goldemberg, S. H.; Algranati, I. D.; Miret, J. J.; Alonso Garrido, D. O.; Frydman, B. *Ibid.* 1983; Vol. 4, p 233.
(7) Heller, J. S.; Chen, K. Y.; Kyriakidis, D. A.; Fong, W. F.; Canellakis, E. S. *J. Cell. Physiol.* **1978**, *96*, 225. Holtta, E.; Korpela, H.; Hovi, T. *Biochim. Biophys. Acta* **1981**, *677*, 90. Bethell, D. R.; Pegg, A. H. *Biochem. J.* **1979**, *180*, 87. Pegg, A. E.; Conover, Ch.; Wrona, A. *Biochem. J.* **1978**, *170*, 651.
(8) Fischer, H.; Orth, H. "Die Chemie des Pyrrols"; Akad. Verlagsgesellschaft; Leipzig, 1934; Band I. Gossauer, A. "Die Chemie der Pyrrole"; Springer-Verlag; Berlin, 1974. Jones, R. A.; Bean, G. P. "The Chemistry of Pyrroles"; Academic Press: London, 1977.
(9) (a) Ripas, R. N.; Buu-Hoi, N. P. *J. Org. Chem.* **1959**, *24*, 372, 551. (b) Loader, C. E.; Anderson, H. J. *Tetrahedron* **1969**, *25*, 3879. (c) Heine, H. W.; Peavy, R.; Durbetaki, A. J. *J. Org. Chem.* **1966**, *31*, 3924. (d) Berger, J. G.; Teller, S. R.; Pachter, I. J. *Ibid.* **1970**, *35*, 3122. (e) Anderson, H. J.; Huang, C. W. *Can. J. Chem.* **1967**, *45*, 897. (f) Linda, P.; Marino, G. *Ric. Sci.* **1967**, *37*, 424. (g) Badger, G. M.; Ward, A. D. *Aust. J. Chem.* **1964**, *17*, 649. (h) Anderson, H. J. *Can. J. Chem.* **1957**, *35*, 21. (i) For the early literature on the subject, see: Fischer, H.; Orth, H. "Die Chemie des Pyrrols"; Akad. Verlagsgess.: Leipzig, 1934; Vol. 1, pp 181–204.

0022-3263/84/1949-2619$01.50/0

The ^{13}C NMR spectra showed that they were mixtures of the syn and anti isomers and they were used as such for the next reduction step. The dioximes could be purified by column chromatography on TLC silica gel, using 15% absolute ethanol in benzene as eluant, after which they could be crystallized either from benzene–hexane (**4a–f**) or from hexane (**4g–i**).

The crude dioximes **4a–i** were reduced with a fivefold weight of sodium in a 50-fold volume of ethanol at reflux during 4 h. Dilution with water, extraction with chloroform, and evaporation of the latter afforded the diamines **5a–i**. The crude diamines were transformed into their bis(benzyloxycarbonyl) derivatives **6a–i** by dissolution of the crude residues in a 10% NaOH–chloroform mixture to which benzyl chloroformate was slowly added. The obtained carbamates were filtered through a TLC silica gel column (using 3% methanol in benzene as packing and elution solvent) and were crystallized from benzene–*n*-hexane. The pure biscarbamates **6** were thus obtained in 40–50% yield from the crude dioximes **4**. When a large amount of crude dioxime was reduced, the 1,4-diamine could also be purified by direct distillation of the crude reduction product.

The carbamates **6** were convenient derivatives for the storage of the 1,4-diaminoalkanes. By hydrogenolysis over PtO_2 in ethanol–hydrochloric acid they afforded the dihydrochlorides of the diamines **5a–i**. Most of them could be crystallized from dry ethanol–ether but were unstable when stored at 20 °C. The purity of the dihydrochlorides could be easily checked by TLC on cellulose plates (Merck) using either 2-propanol, concentrated hydrochloric acid, water (8:3:2) for the dihydrochlorides of **5a–e** or methanol, concentrated hydrochloric acid (9:1) for the dihydrochlorides of **5f–i**. Their solubility in aqueous media was suitable for biological assays.

The general procedure outlined above allowed the synthesis of many substituted putrescines from their pyrrole precursors.

Experimental Section

Melting points were determined on a Kofler melting point apparatus and are uncorrected. ^{13}C NMR spectra were recorded on a FT-80A spectrometer. Mass spectra were obtained with a Varian CH-7 spectrometer. TLC was performed either on silica gel F-254 plaques (Merck, 0.25 mm layer thickness) or on precoated cellulose plaques (Merck, 0.1 mm layer thickness). Pyrroles were spotted by spraying with Ehrlich's reagent (2% (dimethylamino)benzaldehyde in 6 N hydrochloric acid) followed by heat (100 °C) when necessary, dioximes were spotted with a 5% ferric aqueous solution, and diamines were spotted by spraying with a ninhydrin solution (0.5% ninhydrin, 0.4% acetic acid, 5% 2,6-lutidine in acetone) followed by heat (100 °C).

Preparation of *N,N*-Dimethylacylamines 1c–i. General Procedure. Dry dimethylamine carried by a nitrogen stream was bubbled through an acid chloride (0.5 mol) solution in 1 L of dry benzene, while the mixture was vigorously stirred and kept at 5 °C. The gas stream was interrupted when the precipitation of dimethylamine hydrochloride ceased; the stirred mixture was then kept overnight at 20 °C. It was then extracted with water (500 mL), and the aqueous solution was reextracted with chloroform (3 × 100 mL). The pooled chloroform and benzene solutions were dried (Na_2SO_4) and evaporated to dryness. The crude dimethylamino residue was distilled in vacuo.

***N,N*-Dimethylpropionamide (1c)** was obtained (80%) from propionyl chloride; bp 176 °C (lit.[10] bp 175 °C (765 mm)).

***N,N*-Dimethylbutanamide (1d)** was obtained (84%) from butyryl chloride: bp 120 °C (110 mm) (lit.[10] bp 124 °C (110 mm)).

***N,N*-Dimethylpentanamide (1e)** was obtained (79%) from pentanoyl chloride: bp 142 °C (100 mm) (lit.[10] bp 141 °C (100 mm)); ^{13}C NMR ($CDCl_3$) δ (Me_4Si = 0) 171.1 (CO), 35.4, 35.3 ($N(CH_3)_2$), 31.1 (CH_2CO), 25.5 ($CH_2CH_2CH_3$), 20.1 (CH_2CH_3), 12.1 (CH_3).

***N,N*-Dimethylhexanamide (1f)** was obtained (90%) from hexanoyl chloride: bp 135 °C (2.5 mm) (lit.[10] bp 158 °C (100 mm)); ^{13}C NMR ($CDCl_3$) δ 172.1 (CO), 36.3, 34.3 ($N(CH_3)_2$), 32.3 (CH_2CO), 30.1 (CH_2CH_2CO), 23.9 ($CH_2CH_2CH_3$), 21.6 (CH_2CH_3), 12.9 (CH_3).

***N,N*-Dimethylheptanamide (1g)** was obtained (78%) from heptanoyl chloride: bp 68 °C (0.1 mm) (lit.[10] 172 °C (100 mm)); ^{13}C NMR ($CDCl_3$) δ 171.0 (CO), 35.1, 33.1 ($N(CH_3)_2$), 31.2 (CH_2CO), 11.9 (CH_3).

***N,N*-Dimethyldecanamide (1h)** was obtained (93%) from decanoyl chloride: bp 110 °C (0.5 mm) (lit.[11] bp 80–81 °C (0.01 mm)); ^{13}C NMR ($CDCl_3$) δ 170.8 (CO), 35.4, 33.4 ($N(CH_3)_2$), 31.6 (CH_2CO), 12.4 (CH_3).

***N,N*-Dimethyllauramide (1i)** was obtained (92%) from lauroyl chloride: bp 124 °C (0.3 mm) (lit.[12] bp 180 °C (15 mm)); ^{13}C NMR ($CDCl_3$) δ 37.1, 35.12 ($N(CH_3)_2$), 33.2 (CH_2CO), 13.9 (CH_3).

Preparation of 2-Acylpyrroles 2b–i. General Procedure. A solution of 85.3 g (556 nmol) of phosphorus oxychloride in 90 mL of dry benzene was slowly added during 30 min to a stirred solution of 610 mmol of *N,N*-dimethylacylamine in 60 mL of dry benzene while the mixture was kept at 5–10 °C. The mixture was then stirred at 20 °C for 30 min and cooled again at 5 °C, and a solution of 33.5 g (0.5 mol) of pyrrole in 50 mL of dry benzene was then slowly added during 30 min. Stirring of the mixture under moisture exclusion conditions was continued during 18 h at 20 °C; it was then cooled at 5 °C, and 450 mL of ice water was added, followed by solid sodium bicarbonate to adjust it to pH 7 when a 40% sodium hydroxide solution was added, bringing the mixture to pH 12. The alkaline mixture was stirred for 1 h at 20 °C, the aqueous phase was separated and extracted with chloroform (3 × 300 mL), the chloroform extracts were pooled with the former benzene phase, and the solution was dried (Na_2SO_4) and evaporated to dryness in vacuo. The crude 2-acylpyrrole residue could be purified either by crystallization or by distillation in vacuo.

2-Acetylpyrrole (2b) was obtained (75%) from **1b** and pyrrole: mp 88–89 °C (petroleum ether) (lit.[9i] mp 90 °C); ^{13}C NMR ($CDCl_3$) δ 188.0 (CO), 131.8 (C-2), 125.2, 117.1 (CH pyrr).

2-Propionylpyrrole (2c) was obtained (78%) from **1c** and pyrrole: mp 51–52 °C (methanol–water) (lit.[9i] mp 52.5 °C); ^{13}C NMR ($CDCl_3$) δ 191.7 (CO), 131.5 (C-2), 110.2, 116.2, 125.0 (CH pyrr).

2-Butyrylpyrrole (2d) was obtained (97%) from **1d** and pyrrole: mp 43–45 °C (methanol–water); ^{13}C NMR ($CDCl_3$) δ 191.2 (CO), 132.0 (C-2), 125.0, 116.5, 110.6 (CH pyrr). Anal. Calcd for $C_8H_{11}NO$: C, 70.1; H, 8.0; N, 10.2. Found: C, 70.1; H, 8.1; N, 10.1.

2-Pentanoylpyrrole (2e) was obtained (80%) from **1e** and pyrrole: bp 86–87 °C (0.1 mm); ^{13}C NMR ($CDCl_3$) δ 191.3 (CO), 131.6 (C-2), 125.2, 116.5, 109.9 (CH pyrr). Anal. Calcd for $C_9H_{13}NO$: C, 71.5; H, 8.6; N, 9.3. Found: C, 71.3; H, 8.4; N, 9.5.

2-Hexanoylpyrrole (2f) was obtained (84%) from **1f** and pyrrole: bp 114–116 °C (0.75 mm); ^{13}C NMR ($CDCl_3$) δ 189.7 (CO), 130.9 (C-2), 124.1, 115.3, 108.8 (CH pyrr). Anal. Calcd for $C_{10}H_{15}NO$: C, 72.7; H, 9.1; N, 8.5. Found: C, 72.5; H, 9.0; N, 8.7.

2-Heptanoylpyrrole (2g) was obtained (89%) from **1g** and pyrrole: bp 92–95 °C (0.1 mm); ^{13}C NMR δ 190.9 (CO), 131.3 (C-2), 124.8, 116.2, 109.5 (CH pyrr). Anal. Calcd for $C_{11}H_{17}NO$: C, 73.7; H, 9.5; N, 7.8. Found: C, 73.9; H, 9.7; N, 7.5.

2-Decanoylpyrrole (2h) was obtained (77%) from **1h** and pyrrole: mp 52–53 °C (ethanol); ^{13}C NMR δ 190.9 (CO), 131.3 (C-2), 124.8, 116.2, 109.5 (CH pyrr). Anal. Calcd for $C_{14}H_{23}NO$: C, 76.0; H, 10.4; N, 6.3. Found: C, 76.1; H, 10.5; N, 6.2.

2-Lauroylpyrrole (2i) was obtained (76%) from **1i** and pyrrole: mp 65–66 °C (ethanol); ^{13}C NMR ($CDCl_3$) δ 191.3 (CO), 131.2 (C-2), 124.8, 116.2, 110.2 (CH pyrr). Anal. Calcd for $C_{16}H_{27}NO$: C, 77.1; H, 10.8; N, 5.6. Found: C, 77.0; H, 10.8; N, 5.6.

(10) Ruhoff, J. R.; Reid, E. E. *J. Am. Chem. Soc.* **1937**, *59*, 401.

(11) Bedenbaugh, A. O.; Payton, A. L.; Bedenbaugh, J. H. *J. Org. Chem.* **1979**, *44*, 4703.

(12) Staudinger, H.; Rossler, K. *Ber. Deutsch. Chem. Ges.* **1936**, *69*, 73.

Preparation of 2-Alkylpyrroles 3a–3i. General Procedure. 2-Acylpyrrole **2** (0.5 mol, the crude product could be used) and 75 mL of 95% hydrazine hydrate were added to a solution of 100 g of potassium hydroxide in 600 mL of ethylene glycol. The mixture was slowly heated to 200 °C over a period of 1.5 h, while the distillate was collected. The latter was extracted with ether (3 × 80 mL), and the extracts were dried (Na_2SO_4) and evaporated to dryness in vacuo. The residue of 2-alkylpyrrole was purified by distillation in vacuo. This procedure was used for the preparation of **3a–g**. For the obtention of **3h–i** no distillate was collected from the ethylene glycol mixture. After the heating period was over (1.5 h), water (1 L) was added to the cooled mixture, and the latter was extracted with chloroform (3 × 300 mL). The chloroform extracts were dried (Na_2SO_4) and evaporated to dryness in vacuo, and the residue was distilled at reduced pressure.

2-Methylpyrrole (3a) was obtained (70%) from 2-formylpyrrole (**2a**):[13] bp 150 °C (758 mm) (lit.[14] bp 149 °C); ^{13}C NMR ($CDCl_3$) δ 127.1 (C-2), 115.9, 107.6, 105.2 (CH pyrr).

2-Ethylpyrrole (3b) was obtained (65%) from 2-acetylpyrrole (**2b**): bp 59–60 °C (15 mm) (lit.[15] bp 68 °C (14 mm)); ^{13}C NMR ($CDCl_3$) δ 134.7 (C-2), 116.7, 108.3, 104.4 (CH).

2-Propylpyrrole (3c) was obtained (93%) from 2-propionylpyrrole (**2c**): bp 111 °C (80 mm); ^{13}C NMR ($CDCl_3$) δ 133.0 (C-2), 116.6, 108.1, 105.1 (CH). Anal. Calcd for $C_7H_{11}N$: C, 77.1; H, 10.1; N, 12.8. Found: C, 77.0; H, 10.0; N, 13.0.

2-Butylpyrrole (3d) was obtained (60%) from 2-butyrylpyrrole (**2d**): bp 116 °C (20 mm); ^{13}C NMR δ 132.2 (C-2), 115.2, 107.2, 104.0 (CH). Anal. Calcd for $C_8H_{13}N$: C, 78.0; H, 10.6; N, 11.4. Found: C, 78.1; H, 10.7; N, 11.6.

2-Pentylpyrrole (3e) was obtained (70%) from 2-pentanoylpyrrole (**2e**): bp 133 °C (50 mm); ^{13}C NMR δ 132.8 (C-2), 115.8, 107.9, 104.6 (CH). Anal. Calcd for $C_9H_{15}N$: C, 78.8; H, 10.9; N, 10.2. Found: C, 78.6; H, 10.8; N, 10.2.

2-Hexylpyrrole (3f) was obtained (64%) from 2-hexanoylpyrrole (**2f**): bp 92 °C (1.5 mm); ^{13}C NMR δ 132.9 (C-2), 116.1, 108.0, 104.0 (CH); mass spectrum, *m/e* 151 (17, M^+). Anal. Calcd for $C_{10}H_{17}N$: C, 79.5; H, 11.2; N, 9.3. Found: C, 79.4; H, 11.1; N, 9.5.

2-Heptylpyrrole (3g) was obtained (61%) from 2-heptanoylpyrrole (**2g**): bp 160 °C (40 mm); ^{13}C NMR δ 132.9 (C-2), 116.4, 107.9, 104.9 (CH); mass spectrum, *m/e* (18, M^+). Anal. Calcd for $C_{11}H_{19}N$: C. 80.0; H, 11.5; N, 8.5. Found: C, 79.9; H, 11.4; N, 8.6.

2-Decylpyrrole (3h) was obtained (60%) from 2-decanoylpyrrole (**2h**): bp 102 °C (0.5 mm); ^{13}C NMR δ 132.7 (C-2), 115.8, 107.9, 104.6 (CH); mass spectrum, *m/e* 207 (25, M^+). Anal. Calcd for $C_{14}H_{25}N$: C, 81.1; H, 12.1; N, 6.8. Found: C, 81.0; H, 12.2; N, 6.7.

2-Lauroylpyrrole (3i) was obtained (57%) from 2-lauroylpyrrole (**2i**): bp 142 °C (0.2 mm); ^{13}C NMR δ 132.8 (C-2), 115.8, 108.1, 104.7 (CH); mass spectrum, *m/e* 235 (27, M^+). Anal. Calcd for $C_{16}H_{29}N$: C, 81.7; H, 12.3; N, 6.0. Found: C, 81.6; H, 12.3; N, 5.9.

Preparation of Dioximes of 4-Ketoalkyl Aldehydes 4a–i. General Procedure. Sodium bicarbonate (16.8 g, 0.2 mol) and hydroxylamine hydrochloride (20.8 g, 0.3 mol) were added to a solution of 2-alkylpyrrole (0.1 mol) in 100 mL of 96% ethanol. The mixture was heated under reflux with continuous stirring for 48 h; it was then cooled and filtered, the insoluble salts were washed with hot ethanol, and the pooled filtrate and washings were evaporated to dryness. The residue was dissolved in 200 mL of 10% sodium hydroxide, the solution was extracted with ethyl ether (3 × 100 mL) to eliminate any unreacted pyrrole, and the aqueous phase was adjusted to pH 6 with 10% hydrochloric acid and finally saturated with solid potassium carbonate. The mixture was extracted with ethyl ether (3 × 200 mL), and the extracts were dried (Na_2SO_4) and evaporated to dryness. The residue of crude dioxime could be used directly for reduction of 1,4-diaminoalkane. Purification of the dioxime (mixture of syn and anti forms) was achieved by chromatography on a TLC silica gel glass column (5 × 50 cm) packed under slight pressure, using 15% absolute ethanol in benzene. The dioxime was applied and eluted with use of the same solvent, the dioxime-containing fractions (identified by TLC on silica gel plates) were pooled and evaporated to dryness in vacuo, and the residue crystallized as indicated below.

4-Ketopentanal dioxime (4a) was obtained (50%) from 2-methylpyrrole (**3a**): mp 61–63 °C (benzene–hexane); ^{13}C NMR (D_2O) δ 155.0, 155.9, 150.1, 149.9, 149.4 (C=NOH); mass spectrum, *m/e* 130 (6, M^+). Anal. Calcd for $C_5H_{10}N_2O_2$: C, 46.2; H, 7.7; N, 21.5. Found: C, 46.1; H, 7.6; N, 21.6.

4-Ketohexanal dioxime (4b) was obtained (46%) from 2-ethylpyrrole (**3b**): mp 68–70 °C (benzene–hexane); ^{13}C NMR (Cl_3CD) δ 161.1, 160.9, 151.0, 150.6, 150.0 (C=NOH); mass spectrum, *m/e* 144 (10, M^+). Anal. Calcd for $C_6H_{12}N_2O_2$: C, 50.0; H, 8.3; N, 19.5. Found: C, 49.9; H, 8.2; N, 19.7.

4-Ketoheptanal dioxime (4c) was obtained (49%) from 2-propylpyrrole (**3c**): mp 55–57 °C (benzene–hexane); ^{13}C NMR (Cl_3CD) δ 160.1, 159.9, 150.9, 150.5, 149.7 (C=NOH); mass spectrum, *m/e* 158 (11, M^+). Anal. Calcd for $C_7H_{14}N_2O_2$: C, 53.1; H, 8.8; N, 17.7. Found: C, 53.0; H, 8.7; N, 17.8.

4-Ketooctanal dioxime (4d) was obtained (50%) from 2-butylpyrrole (**3d**): mp 76–78 °C (benzene–hexane); ^{13}C NMR (Cl_3CD) δ 160.1, 160.0, 159.9, 159.8, 150.7, 150.3 (C=NOH); mass spectrum, *m/e* 172 (12, M^+). Anal. Calcd for $C_8H_{16}N_2O_2$: C, 55.8; H, 9.3; N, 16.3. Found: C, 55.7; H, 9.2; N, 16.4.

4-Ketononanal dioxime (4e) was obtained (51%) from 2-pentylpyrrole (**3e**): mp 78–80 °C (benzene–hexane); mass spectrum, *m/e* 186 (11, M^+). Anal. Calcd for $C_9H_{18}N_2O_2$: C, 58.1; H, 9.7; N, 15.0. Found: C, 58.0; H, 9.6; N, 15.1.

4-Ketodecanal dioxime (4f) was obtained (45%) from 2-hexylpyrrole (**3f**): mp 80–81 °C (benzene–hexane); mass spectrum, *m/e* 200 (25, M^+). Anal. Calcd for $C_{10}H_{20}N_2O_2$: C, 60.0; H, 10.0; N, 14.0. Found: C, 60.1; H, 10.1; N, 13.9.

4-Ketoundecanal dioxime (4g) was obtained (40%) from 2-heptylpyrrole (**3g**): mp 82–84 °C (hexane); mass spectrum, *m/e* 214 (20, M^+). Anal. Calcd for $C_{11}H_{22}N_2O_2$: C, 61.7; H, 10.3; N, 13.1. Found: C, 61.5; H, 10.2; N, 13.0.

4-Ketotetradecanal dioxime (4h) was obtained (41%) from 2-decylpyrrole (**3h**): 86–88 °C (hexane); mass spectrum, *m/e* 256 (20, M^+). Anal. Calcd for $C_{14}H_{28}N_2O_2$: C, 65.6; H, 10.9; N, 10.9. Found: C, 65.5; H, 10.8; N, 11.0.

4-Ketohexadecanal dioxime (4i) was obtained (46%) from 2-lauroylpyrrole (**3i**): mp 87–89 °C (hexane); ^{13}C NMR (Me_2SO) δ 160.0, 159.9, 150.8, 150.4, 150.3 (C=NOH); mass spectrum, *m/e* 284 (15, M^+). Anal. Calcd for $C_{16}H_{32}N_2O_2$: C, 67.6; H, 11.3; N, 9.8. Found: C, 67.6; H, 11.2; N, 9.9.

Preparation of 1,4-Diaminoalkanes 5a–i. General Procedure. A solution of 6 g of crude dioxime **4** in 300 mL of anhydrous ethanol was slowly heated under reflux with constant stirring, while 30 g of sodium was added in small pieces. The mixture was heated under reflux during 4 h, it was then cooled, 600 mL of ice-water was added, and the solution was extracted with chloroform (5 × 200 mL). The extracts were dried (Na_2SO_4) and evaporated to dryness in vacuo, and the residue of crude 1,4-diamine **5** was dissolved in a mixture of 100 mL of 10% sodium hydroxide and 20 mL of chloroform. Benzyl chloroformate (10 mL) was added to the stirred mixture in five portions during 30 min, and the mixture was further stirred for 1 h. The chloroform layer was separated, and the aqueous layer was extracted with chloroform (4 × 20 mL). The organic solutions were pooled, washed with water (1 × 20 mL), dried (Na_2SO_4), and evaporated to dryness in vacuo. The residue of **6** was dissolved in a small volume of 3% methanol in benzene and was applied to a TLC silica gel column (5 × 50 cm) previously packed and washed with the same solvent. The bis(benzyloxycarbonyl) derivative **6** was eluted with use of the same solvent by applying a low pressure to the column. The fractions containing **6** were pooled and evaporated, and the residue was crystallized from benzene–hexane. It was dissolved in 150 mL of ethanol, 2 mL of concentrated hydrochloric acid was added, and it was reduced with hydrogen at 50 psi during 18 h over 20% its weight of PtO_2. The catalyst was filtered, and the filtrate was evaporated to dryness in vacuo, leaving behind the dihydrochloride of **5**, which was pure when analyzed by TLC. It could be crystallized from anhydrous ethanol–ether, but it was highly hygroscopic.

(13) "Organic Synthesis"; Wiley: New York, 1963; Collect. Vol. IV, p 831.
(14) Reference 9i, p 40.
(15) Reference 9i, p 45.

1,4-Diaminopentane Dihydrochloride (5a). Reduction of crude **4a** gave (50%) pure biscarbamate **6a**: mp 130–131 °C. Anal. Calcd for $C_{21}H_{26}N_2O_4$: C, 68.1; H, 7.1; N, 7.6. Found: C, 68.2; H, 7.2; N, 7.5. Hydrogenolysis of **6a** afforded 98% of **5a** dihydrochloride:[16] mass spectrum, *m/e* 102 (4, M^+), 44 (100, $M^+ - CH_2CH_2NH_2$); ^{13}C NMR (D_2O) δ 39.8 (CH_2NH_2), 48.1 ($CHNH_2$).

1,4-Diaminohexane Dihydrochloride (5b). Reduction of crude **4b** gave 51% of **6b**: mp 117–118 °C. Anal. Calcd for $C_{22}H_{28}N_2O_4$: C, 68.7; H, 7.3; N, 7.3. Found: C, 68.6; H, 7.2; N, 7.4. Hydrogenolysis of **6b** afforded 98% of **5b** dihydrochloride:[16] mass spectrum, *m/e* 116 (4, M^+), 58 (100, $M^+ - CH_2CH_2NH_2$); ^{13}C NMR δ 40.1 (CH_2NH_2), 53.6 ($CHNH_2$).

1,4-Diaminoheptane Dihydrochloride (5c). Reduction of crude **4c** gave 48% of **6c**: mp 117–118 °C. Anal. Calcd for $C_{23}H_{30}N_2O_4$: C, 69.3; H, 7.5; N, 7.0. Found: C, 69.2; H, 7.4; N, 7.1. Hydrogenolysis of **6c** gave 95% of **5c** dihydrochloride: mass spectrum, *m/e* 130 (4, M^+), 70 (100, pyrrolenine cation); ^{13}C NMR δ 39.8 (CH_2NH_2), 51.9 ($CHNH_2$).

1,4-Diaminooctane Dihydrochloride (5d). Reduction of crude **4d** gave 46% of **6d**: mp 110–111 °C. Anal. Calcd for $C_{24}H_{32}N_2O_4$: C, 69.9; H, 7.7; N, 6.8. Found: C, 70.0; H, 7.8; N, 6.7. Hydrogenolysis of **6d** gave 98% of **5d** dihydrochloride: mass spectrum, 144 (4.5, M^+), 70 (100); ^{13}C NMR δ 40.1 (CH_2NH_2), 52.3 ($CHNH_2$).

1,4-Diaminononane Dihydrochloride (5e). Reduction of crude **4e** gave 42% of **6e**: mp 104–105 °C. Anal. Calcd for $C_{25}H_{34}N_2O_4$: C, 70.4; H, 8.0; N, 6.5. Found: C, 70.4; H, 7.9; N, 6.5. Hydrogenolysis of **6e** gave 98% of **5e**: mass spectrum, *m/e* 158 (4.7, M^+), 70 (100); ^{13}C NMR δ 41.8 (CH_2NH_2), 54.1 ($CHNH_2$).

1,4-Diaminodecane Dihydrochloride (5f). Reduction of crude **4f** gave 52% of **6f**: mp 112–113 °C. Anal. Calcd for $C_{26}H_{36}N_2O_4$: C, 70.9; H, 8.2; N, 6.4. Found: C, 70.8; H, 8.1; N, 6.3. Hydrogenolysis of **6f** gave 98% of **5f**: mass spectrum, *m/e* 172 (8, M^+); ^{13}C NMR δ 39.8 (CH_2NH_2), 52.1 ($CHNH_2$).

1,4-Diaminoundecane Dihydrochloride (5g). Reduction of crude **4g** gave 57% of **6g**: mp 112–113 °C. Anal. Calcd for $C_{27}H_{38}N_2O_4$: C, 71.4; H, 8.4; N, 6.2. Found: C, 71.2; H, 8.3; N, 6.1. Hydrogenolysis of **6g** gave 95% of **5g**; mass spectrum, *m/e* 186 (8, M^+), 70 (100); ^{13}C NMR δ 40.0 (CH_2NH_2), 52.3 ($CHNH_2$).

1,4-Diaminotetradecane Dihydrochloride (5h). Reduction of crude **4h** gave 50% of **6h**: mp 109–110 °C. Anal. Calcd for $C_{30}H_{44}N_2O_4$: C, 72.6; H, 8.9; N, 5.6. Found: C, 72.4; H, 8.8; N, 5.7. Hydrogenolysis of **6h** gave 97% of **5h**: mass spectrum, *m/e* 228 (8, M^+), 70 (100); ^{13}C NMR δ 40.0 (CH_2NH_2), 52.3 ($CHNH_2$).

1,4-Diaminohexadecane Dihydrochloride (5i). Reduction of crude **4i** gave 45% of **6i**: mp 109–110 °C. Anal. Calcd for $C_{32}H_{48}N_2O_4$: C, 73.3; H, 9.2; N, 5.3. Found: C, 73.4; H, 9.2; N, 5.3. Found: C, 73.4; H, 9.3; N, 5.2. Hydrogenolysis of **6i** gave 98% of **5i**: mass spectrum, *m/e* 256 (7, M^+), 70 (100); ^{13}C NMR δ 39.9 (CH_2NH_2), 52.3 ($CHNH_2$).

Acknowledgment. This work was made possible by a grant (GM-11973) from the National Institutes of Health (PHS).

Registry No. **1b**, 127-19-5; **1c**, 758-96-3; **1d**, 760-79-2; **1e**, 6225-06-5; **1f**, 5830-30-8; **1g**, 1115-96-4; **1h**, 14433-76-2; **1i**, 3007-53-2; **2a**, 1003-29-8; **2b**, 1072-83-9; **2c**, 1073-26-3; **2d**, 61480-97-5; **2e**, 89789-53-7; **2f**, 89789-54-8; **2g**, 73252-31-0; **2h**, 89789-55-9; **2i**, 89789-56-0; **3a**, 636-41-9; **3b**, 1551-06-0; **3c**, 1551-08-2; **3d**, 1551-10-6; **3e**, 1551-12-8; **3f**, 1551-14-0; **3g**, 878-12-6; **3h**, 89789-57-1; **3i**, 1216-25-7; **4a**, 89789-58-2; **4b**, 89789-59-3; **4c**, 89789-60-6; **4d**, 89789-61-7; **4e**, 89789-62-8; **4f**, 89789-63-9; **4g**, 89789-64-0; **4h**, 89789-65-1; **4i**, 89789-66-2; **5a**, 89789-67-3; **5b**, 89789-68-4; **5c**, 89789-69-5; **5d**, 89789-70-8; **5e**, 89789-71-9; **5f**, 89789-72-0; **5g**, 89789-73-1; **5h**, 89789-74-2; **5i**, 89789-75-3; **6a**, 89789-76-4; **6b**, 89789-77-5; **6c**, 89789-78-6; **6d**, 89789-79-7; **6e**, 89789-80-0; **6f**, 89789-81-1; **6g**, 89789-82-2; **6h**, 89789-83-3; **6i**, 89789-84-4; $CH_3CH_2C(O)Cl$, 79-03-8; $CH_3(CH_2)_2C(O)Cl$, 141-75-3; $CH_3(CH_2)_3C(O)Cl$, 638-29-9; $CH_3(CH_2)_4C(O)Cl$, 142-61-0; $CH_3(CH_2)_5C(O)Cl$, 2528-61-2; $CH_3(CH_2)_8C(O)Cl$, 112-13-0; $CH_3(CH_2)_{10}C(O)Cl$, 112-16-3; Me_2NH, 124-40-3; $NH_2OH{\cdot}HCl$, 5470-11-1; pyrrole, 109-97-7.

(16) Previously obtained from aliphatic precursors: Vita, G.; Bucher, G. *Chem. Ber.* **1966**, *99*, 3387.

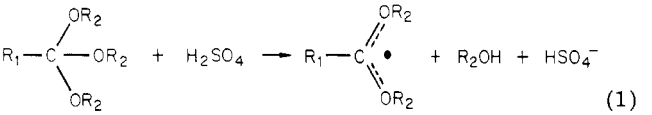
Heats of Formation of 1,3-Dioxolenium Ions from Ortho Ester Precursors in Sulfuric Acid Solution: Methyl vs. Phenyl Substitution at the *pro*-Acyl Carbon Atom

R. A. Burt,[1a] C. A. Chambers,[1b] Y. Chiang,[1a] C. S. Hillock,[1a] A. J. Kresge,*[1a] and J. W. Larsen*[1b]

Department of Chemistry, Scarborough Campus, University of Toronto, Scarborough, Ontario M1C 1A4, Canada, and Department of Chemistry, University of Tennessee, Knoxville, Tennessee 37916

Received December 27, 1983

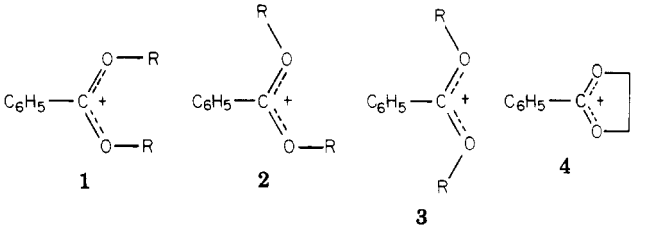
Recent calorimetric measurements have shown that the formation of methyl-substituted oxocarbonium ions in strongly acidic media is generally more exothermic than the formation of their phenyl-substituted analogues, contrary to the widely held idea that phenyl is a better carbocation-stabilizing group than methyl.[2] Among the substrates examined in this work were the ortho esters, trimethyl and triethyl orthoacetate and orthobenzoate; these substances, upon introduction into concentrated sulfuric acid, react to give the corresponding methyl- and phenyldialkoxycarbonium ions, eq 1. The heat evolved



$R_1 = CH_3, C_6H_5; R_2 = CH_3, C_2H_5$ (1)

in these exothermic reactions was found in each case to be greater for the methyl than for the phenyl analogue, by 3.8 kcal mol^{-1} in the methyl ortho ester series and by 4.6 kcal mol^{-1} in the ethyl ortho ester series.

These results, however, could have been complicated by steric interactions which inhibit the normal resonance effect of the phenyl group. Such steric inhibition of resonance has been demonstrated in the hydrolysis of trialkyl orthobenzoates under conditions where generation of dialkoxycarbonium ion intermediates is rate determining.[3] In these reactions, substitution of phenyl for hydrogen at the *pro*-acyl carbon atom produces rate retardations, in contrast to the strong acceleration shown by the phenyl group in the analogous hydrolysis reactions of acetals. This phenomenon was interpreted as the consequence of unfavorable interactions in all three of the completely planar conformations of the phenyldialkoxycarbonium ion: in the cis,cis conformation **1**, there is interference between the



1 **2** **3** **4**

alkoxy alkyl groups, and in the cis,trans **2** and trans,trans **3** conformations, there is interference between these alkyl groups and the ortho hydrogens of the benzene ring. When the steric interaction in the cis,cis conformation is relieved by joining the interfering alkyl groups together in a small

(1) (a) University of Toronto. (b) University of Tennessee. The new address of J.W.L. is Department of Chemistry, Lehigh University, Bethlehem, PA 18015.

(2) Larsen, J. W.; Bouis, P. A.; Riddle, C. A. *J. Org. Chem.* **1980**, *45*, 4969.

(3) Chiang, Y.; Kresge, A. J.; Salomaa, P.; Young, C. I. *J. Am. Chem. Soc.* **1974**, *96*, 4494.

0022-3263/84/1949-2622$01.50/0