Synthesis of 2-Alkylputrescines from 3-Alkylpyrroles

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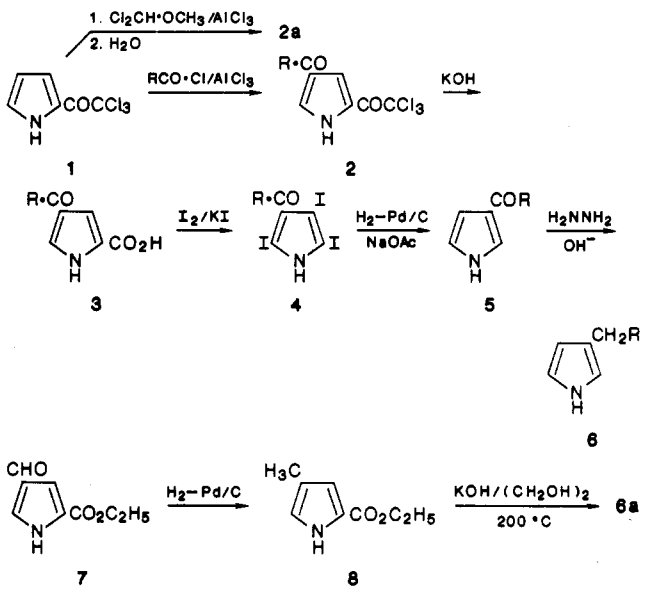
Acylation of 2-(trichloroacetyl)pyrrole gave the 4-acyl derivatives (from 4-formyl to 4-hexanoyl) in good yields. Alkaline treatment gave the corresponding 4-acyl-2-pyrrolecarboxylic acids, which were decarboxylated to the 3-acylpyrroles by prior conversion to the 3-acyl-2,4,5-triiodopyrroles followed by hydrogenolysis. The 3-acylpyrroles were reduced by treatment with hydrazine in alkaline medium to the 3-alkylpyrroles. The latter were ring-opened by treatment with hydroxylamine in the presence of bicarbonate to give the dioximes of the corresponding 2-alkylsuccinaldehydes, which were then reduced to the 2-alkylputrescines (1,4-diaminobutanes). Ring-opening of 2,3-dimethylpyrrole followed by reduction of the dioxime gave 1,2-dimethylputrescine; the same sequence gave 1,3-dimethylputrescine from 2,4-dimethylpyrrole, while 3,4-dimethylpyrrole did not ring-open and gave the dioxime of 3,4-dimethylmaleimide.

The natural polyamines putrescine (1,4-diaminobutane), spermidine (*N*-(3-aminopropyl)putrescine), and spermine (*N*,*N*′-bis(3-aminopropyl)putrescine) are known to be deeply involved in cell proliferation and "in vivo" protein synthesis.[1] Both spermidine and spermine are metabolically derived from putrescine, which in turn originates in the enzymatic decarboxylation of ornithine in a reaction catalyzed by ornithine decarboxylase. Major advances in the development of inhibitors of this enzyme have been made in the past few years.[2] Structural analogues of ornithine or putrescine have provided valuable information on the requirements for binding to the active site of the decarboxylase and on the nature of useful agents for modifying cellular polyamine levels.[2,3] We have recently reported the synthesis of *N*-alkylputrescines[4] and of 1-alkylputrescines,[5] some of which were found to be competitive inhibitors of ornithine decarboxylase,[6] as well as inhibitors of the diamine oxidases of plant and mammalian origin.[7] The 1-alkylputrescines (1,4-diaminoalkanes) were obtained by ring-opening of the corresponding 2-alkylpyrroles with hydroxylamine to give the dioximes of the 4-ketoalkanaldehydes. The dioximes were then reduced to the aforementioned 1-alkylputrescines.[5] Substituted pyrroles can therefore be considered as good synthons for the obtention of substituted putrescines that are not easily accesible by other routes. This will be further exemplified in this paper, where the synthesis of 2-alkylputrescines from 3-alkylpyrroles will be discussed (Scheme II).

Scheme I



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}.

While the synthesis of 2-alkylpyrroles can be accomplished by the direct electrophilic substitution of pyrrole,[8,5] the regioselective synthesis of 3-acyl- and 3-alkyl-pyrroles has been a difficult problem, requiring the use of indirect methods. Acylation or alkylation of pyrrole under conditions of the Friedel–Crafts reaction or the Vilsmeier–Haak reaction affords almost exclusively the 2-acyl or 2-alkylpyrroles. Two useful synthetic approaches are available for the synthesis of 3-acylpyrroles. One approach is based on the prior synthesis of 1-(arylsulfonyl)pyrrole, which on Friedel–Crafts acylation affords the 3-acyl derivatives.[9] Alkaline hydrolysis of the *N*-arylsulfonyl group leads to the obtention of the 3-acyl-1*H*-pyrroles. The method fails however when one-carbon acylations are attempted. Thus, acylation of 1-(phenylsulfonyl)pyrrole led

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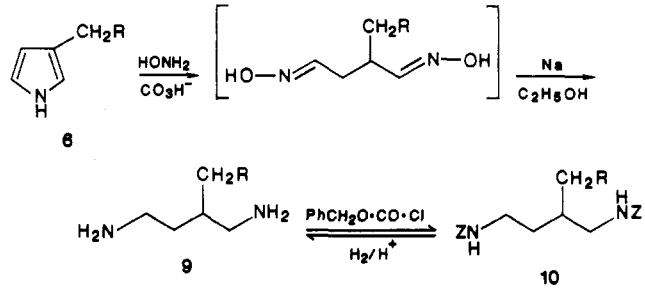
to the formation of its 2-formyl derivative.[9] The second approach is based on the introduction of an electron-withdrawing substituent at C-2, which directs the electrophilic substitution to C-4 (meta) and is then followed by the removal of the 2-substituent.[10] This last approach has been extensively explored. Anderson and co-workers first showed that Friedel–Crafts alkylation reactions of methyl 2-pyrrolecarboxylate or of 2-formyl- and 2-acetylpyrrole afforded the 4-alkyl as well as the 5-alkyl derivatives.[11] The latter were very likely produced by an acid-catalyzed rearrangement of the former.

In the present study, 2-(trichloroacetyl)pyrrole (1) was used as the intermediate to be β-acylated due to its facile large-scale synthesis.[12] Acylation of 1 with (dichloromethoxy)methane in the presence of $AlCl_3$ at −20 °C[13] afforded 4-formyl-2-(trichloroacetyl)pyrrole (**2a**) in 75% yield after hydrolysis of the resulting acetal. Acylation of 1 with acid chlorides under the same reaction conditions also afforded the 4-acyl derivatives **2** in good yields (Scheme I). The 4-acyl-2-(trichloroacetyl)pyrroles (**2**) could not be reduced with hydrogen to the corresponding 4-alkyl derivatives. On alkaline treatment they were easily transformed into the corresponding 2-pyrrolecarboxylic acids **3**. The attempted thermical decarboxylation of **3** either in solvents (quinoline, ethylene glycol) or in vacuo was unsuccesful or gave very low yields of the 3-acylpyrroles. However iodination of **3** with 3 mol of iodine per mole of the acids gave the 2,4,5-triiodopyrroles **4** in very good yields. Lesser amounts of iodine gave mixtures of mono-, di-, and triiodopyrroles. The triiodoacylpyrroles **4** were stable compounds, undoubtedly due to the presence of the 3-acyl residue. It is known[8] that iodol (2,3,4,5-tetraiodopyrrole) is an unstable compound which liberates iodine and polymerizes in solution, while in our hands triiodoalkylpyrroles behaved in a similar manner. Therefore, the iodination reaction could not be carried out if the 4-acyl residue in **3** was previously reduced to the corresponding 3-alkyl residue.

Hydrogenation of **4** over 10% palladium on charcoal gave the 3-acylpyrroles **5** in 75% yield. 3-Formylpyrrole (**5a**) could also be obtained in low yields by applying the Stephens–McFayden reaction to the *p*-tosylhydrazide of 3-pyrrolecarboxylic acid (although the same reaction carried out on the phenylhydrazide was unsuccesful[14]), but the multistep ring synthesis of 3-pyrrolecarboxylic acid[15] is certainly a drawback.

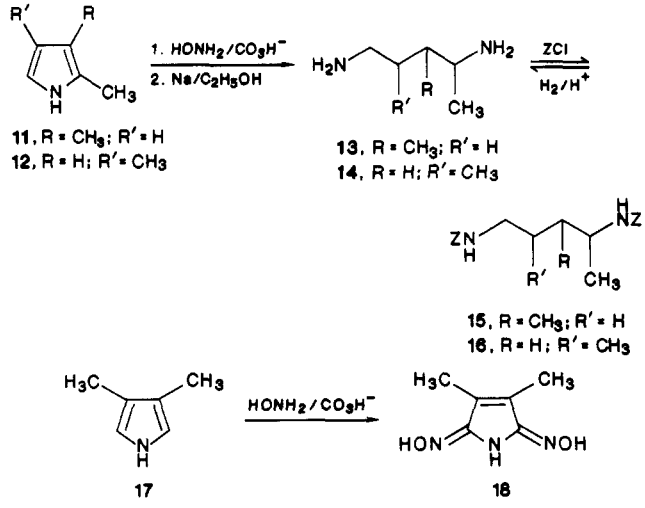
3-Acylpyrroles **5** could be easily reduced to 3-alkylpyrroles **6** by using the Huan–Minlon reaction, as was the case with the 2-acylpyrroles.[5] The catalytic hydrogenation of **5** (under a wide range of experimental conditions) gave only the 3-(hydroxyalkyl)pyrroles. An exception was the low-pressure catalytic reduction of 3-formylpyrrole **5a**, which gave 3-methylpyrrole (**6a**). This fact allowed a facile synthesis of **6a**. Acylation of the easily available ethyl 2-pyrrolecarboxylate[12] with (dichloromethoxy)methane as described above gave the 4-formyl derivative **7**, which was easily reduced to the 4-methylpyrrole **8**. The latter was saponified and decarboxylated to 3-methylpyrrole (**6a**) in 70% yield by being heated in a solution of potassium

Scheme II



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}.

Scheme III



hydroxide in ethylene glycol.

When the ring-opening of the 3-alkylpyrroles **6** with hydroxylamine was attempted, it was found that the reaction took place at much slower rates than with 2-alkylpyrroles,[5] while the long reaction times required led to the destruction of the 3-alkylpyrroles. Therefore the reaction was carried out under air-exclusion conditions over a long time period (168 h), which allowed to isolate the dioximes in around 40% yields (Scheme II). The latter could not be crystallized, undoubtedly due to the mixture of the syn and anti isomers which was evident in the ^1H NMR and ^{13}C NMR spectra. They were directly reduced with sodium and ethanol to the corresponding 1,4-diamines **9**. The latter were isolated and purified as their bis(benzyloxycarbonyl) derivatives **10**, following the procedures described for the obtention of the 1-alkylputrescines.[5] By hydrogenolysis of **10** over PtO_2 in ethanol–hydrochloric acid, the dihydrochlorides of the diamines **9** were obtained. They were highly hygroscopic and rather unstable when stored at 20 °C, but their high solubility in aqueous media was suitable for biological assays.[16] The carbamates **10** were suitable for storage of the 1,4-diaminoalkanes **9**.

Ring-opening of the known 2,3-dimethylpyrrole (**11**) and 2,4-dimethylpyrrole (**12**) with hydroxylamine gave the corresponding dioximes in good yields which were reduced to the corresponding diamines **13** and **14** (Scheme III). The ^{13}C NMR spectra showed that they were, as expected, a mixture of diastereoisomers (see Experimental Section). When 3,4-dimethylpyrrole (**17**) was treated with hydroxylamine under the same reaction conditions, the product was not the expected dioxime but the dioxime of 3,4-di-

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methylmaleimide (18) (Scheme III). The latter could not be ring-opened by either acid or alkaline treatment. Its structure sheds light on the mechanism of the ring-opening of pyrrole with hydroxylamine and will be discussed elsewhere.

Experimental Section

Melting points were determined on a Köfler 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. Microanalysis were performed by UMYMFOR (University of Buenos Aires-CONICET). TLC was performed either on silica gel F-254 plates (Merck, 0.25 mm layer thickness) or on precoated cellulose plates (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 chloride 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 4-Acyl-2-trichloroacetylpyrroles 2. General Procedure. A solution of 290 mmol of the acyl chloride in 30 mL of dry dichloromethane was added at −20 °C to a mixture of 50 g (235 mmol) of 2-(trichloroacetyl)pyrrole (1) and 38 (289 mmol) of $AlCl_3$ in 200 mL of nitromethane and 200 mL of dichloromethane. The mixture was stirred during 18 h at −20 °C and poured over ice–water, the organic phase was separated, and the aqueous phase was extracted with ethyl ether. The pooled extracts were dried (Na_2SO_4) and evaporated to dryness, and the residue was crystallized from ethanol.

4-Formyl-2-(trichloroacetyl)pyrrole (2a) was obtained (75%) from 1 and (dichloromethoxy)methane: mp 137–138 °C; ^{13}C NMR (DMSO-d_6) δ 186.10 (CHO), 173.20 (CO), 94.60 (CCl_3). Anal. Calcd for $C_7H_4NO_2Cl_3$: C, 34.9; H, 1.7; N, 5.8. Found: C, 35.0; H, 1.7; N, 5.9.

4-Acetyl-2-(trichloroacetyl)pyrrole (2b) was obtained (81%) from 1 and acetyl chloride: mp 188–189 °C; ^{13}C NMR (DMSO-d_6) δ 193.20 (CO), 173.40 ($COCCl_3$), 94.80 (CCl_3), 27.70 (CH_3). Anal. Calcd for $C_8H_6NO_2Cl_3$: C, 37.7; H, 2.4; N, 5.5. Found: C, 37.8; H, 2.3; N, 5.4.

4-Propionyl-2-(trichloroacetyl)pyrrole (2c) was obtained (77%) from 1 and propionyl chloride: mp 180–181 °C; ^{13}C NMR ($CDCl_3$) δ 195.20 (CO), 172.70 ($COCl_3$), 32.00 (CH_2), 7.60 (CH_3). Anal. Calcd for $C_9H_8NO_2Cl_3$: 40.2; H, 3.0; N, 5.2. Found: C, 40.3; H, 2.9; N, 5.1.

4-Butyryl-2-(trichloroacetyl)pyrrole (2d) was obtained (80%) from 1 and butyroyl chloride: mp 121–122 °C; ^{13}C NMR ($CDCl_3$) δ 196.00 (CO), 172.70 ($COCl_3$), 41.60 (CH_2CO), 17.70 (CH_2), 13.60 (CH_3). Anal. Calcd for $C_{10}H_{10}NO_2Cl_3$: C, 42.5; H, 3.5; N, 4.9. Found: C, 42.4; H, 3.4; N, 5.0.

5-Pentanoyl-2-(trichloroacetyl)pyrrole (2e) was obtained (78%) from 1 and pentanoyl chloride: mp 90–91 °C; ^{13}C NMR ($CDCl_3$) δ 196.30 (CO), 173.60 ($COCCl_3$), 39.40, 26.40, 22.20 (CH_2), 13.60 (CH_3). Anal. Calcd for $C_{11}H_{12}NO_2Cl_3$: C, 44.5; H, 4.0; N, 4.7. Found: C, 44.4; H, 4.1; N, 4.8.

4-Hexanoyl-2-(trichloroacetyl)pyrrole (2f) was obtained (90%) from 1 and hexanoyl chloride: mp 82–84 °C. Anal. Calcd for $C_{12}H_{14}NO_2Cl_3$: C, 46.4; H, 4.5; N, 4.5. Found: C, 46.3; H, 4.4; N, 4.6.

Preparation of 4-Acyl-2-pyrrolecarboxylic Acids 3. General Procedure. 4-Acyl-2-(trichloroacetyl)pyrrole 2 (300 mmol) was slowly added to 1 L of 20% sodium hydroxide, and the solution was heated under reflux during 1 h. The solution was cooled, and adjusted to pH 2 with 6 N HCl. The pyrrole acids **3a** and **3b** were extracted repeatedly into ether. The acids **3c–f** precipitated at this stage. They were recovered either by evaporation of the ether extracts or by filtration and were crystallized from ethanol–water. They could be used in the next step without further purification.

4-Formyl-2-pyrrolecarboxylic acid (3a) was obtained (86%) from **2a**: mp 212–214 °C; ^{13}C NMR (DMSO-d_6) δ 186.4 (CHO), 162.3 (CO_2H), 131.2 (C-3), 127.3 (C-4), 126.3 (C-5), 113.6 (C-2). Anal. Calcd for $C_6H_5NO_3$: C, 51.8; H, 3.6; N, 10.1. Found: C, 51.6; H, 3.7; N, 10.2.

4-Acetyl-2-pyrrolecarboxylic acid (3b) was obtained (84%) from **2b**: mp 213–214 °C (sealed capillary); ^{13}C NMR (DMSO-d_6) δ 193.4 (CO), 162.3 (CO_2H), 27.5 (CH_3). Anal. Calcd for $C_7H_7NO_3$: C, 54.9; H, 4.6; N, 9.2. Found: C, 54.8; H, 4.7; N, 9.3.

4-Propionyl-2-pyrrolecarboxylic acid (3c) was obtained (71%) from **2c**: mp 202–203 °C (sealed capillary); ^{13}C NMR (DMSO-d_6), δ 196.1 (CO), 162.2 (CO_2H), 32.4 (CH_2), 8.7 (CH_3). Anal. Calcd for $C_8H_9NO_3$: C, 57.5; H, 5.4; N, 8.4. Found: C, 57.4; H, 5.5; N, 8.5.

4-Butyryl-2-pyrrolecarboxylic acid (3d) was obtained (79%) from **2d**: mp 191–192 °C (sealed capillary); ^{13}C NMR (DMSO-d_6) δ 41.1, 18.1 (CH_2CH_2), 14.0 (CH_3). Anal. Calcd for $C_9H_{11}NO_3$: C, 59.7; H, 6.1; N, 7.7. Found: C, 59.6; H, 6.2; N, 7.8.

4-Pentanoyl-2-pyrrolecarboxylic acid (3e) was obtained (72%) from **2e**; mp 174–175 °C (sealed capillary). Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.5; H, 6.7; N, 7.2. Found: C, 61.6; H, 6.8; N, 7.3.

4-Hexanoyl-2-pyrrolecarboxylic acid (3f) was obtained (90%) from **2f**: mp 176–177 °C (sealed capillary). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.1; H, 7.2; N, 6.7. Found: C, 63.0; H, 7.1; N, 6.6.

Preparation of 3-Acyl-2,4,5-triiodopyrroles 4. General Procedure. 4-Acyl-2-pyrrolecarboxylic acid 3 (0.1 mol) was added to a stirred suspension of 168 g (2 mol) of sodium bicarbonate in 1.5 L of water. After total dissolution of the acid, a solution of 84 g (0.33 mol) of iodine and 110 g (0.66 mol) of potassium iodide in 0.5 L of water was slowly added to the stirred mixture over a period of 1 h. The mixture was then heated at 80 °C (only 60 °C in the case of **4a**) during 2 h with constant stirring; it was then cooled at 5 °C during 20 h and filtered, and the residue was recrystallized twice from ethanol.

2,4,5-Triiodo-3-formylpyrrole (4a) was obtained (82%) from **3a**: mp 221–222 °C; ^{13}C NMR (DMSO-d_6) δ 186.3 (CO), 126.2, 88.3, 83.8, 77.8 (Ar); mass spectrum, m/e 474 (12, $M^+ + 1$), 473 (100, M^+). Anal. Calcd for $C_5H_2NOI_3$: C, 12.7; H, 0.4; N, 3.0; I, 80.5. Found: C, 12.7; H, 0.4; N, 2.9; I, 80.6.

2,4,5-Triiodo-3-acetylpyrrole (4b) was obtained (87%) from **3b**; mp 161–163 °C; ^{13}C NMR (DMSO-d_6) δ 191.7 (CO), 130.4, 87.2, 77.0, 75.6 (Ar), 29.7 (CH_3); mass spectrum, m/e 488 (10, $M^+ + 1$), 487 (98, M^+). Anal. Calcd for $C_6H_4NOI_3$: C, 14.8; H, 0.8; N, 2.9; I, 78.2. Found: C, 14.7; N, 0.7; N, 2.9; N, 78.1.

2,4,5-Triiodo-3-propionylpyrrole (4c) was obtained (81%) from **3c**; mp 139–141 °C; ^{13}C NMR (DMSO-d_6) δ 195.3 (CO), 130.60, 86.80, 76.40, 74.90 (Ar), 34.1 (CH_2), 8.5 (CH_3); mass spectrum, m/e 501 (28, M^+). Anal. Calcd for $C_7H_6NOI_3$: C, 16.8; H, 1.2; N, 2.8; I, 76.0. Found: C, 16.9; H, 1.2; N, 2.7; I, 75.8.

2,4,5-Triiodo-3-butyrylpyrrole (4d) was obtained (79%) from **3d**; mp 106–108 °C; ^{13}C NMR (DMSO-d_6) δ 195.0 (CO), 130.70, 86.20, 76.30, 73.70 (Ar), 48.50 ($COCH_2$), 17.80 (CH_3CH_2), 13.70 (CH_3); mass spectrum, m/e 515 (29, M^+). Anal. Calcd for $C_8H_8NOI_3$: C, 18.6; H, 1.5; N, 2.7; I, 74.0. Found: C, 18.7; H, 1.6; N, 2.8; I, 73.9.

2,4,5-Triiodo-3-pentanoylpyrrole (4e) was obtained (86%) from **3e**; mp 135–136 °C; ^{13}C NMR (DMSO-d_6) δ 195.10 (CO), 130.50, 86.60, 76.40, 74.90 (Ar), 41.80 ($COCH_2$), 27.00 ($CH_2C_2H_5$), 22.10 (CH_2CH_3), 14.00 (CH_3); mass spectrum, m/e 529 (23, M^+). Anal. Calcd for $C_9H_{10}NOI_3$: C, 20.4; H, 1.9; N, 2.6; I, 72.0. Found: C, 20.5; H, 2.0; N, 2.5; I, 72.1.

2,4,5-Triiodo-3-hexanoylpyrrole (4f) was obtained (90%) from **3f**; mp 131–133 °C; ^{13}C NMR (DMSO-d_6) δ 195.20 (CO), 130.80, 86.50, 76.50, 74.30 (Ar); 40.60 ($COCH_2$), 30.80 ($CH_2C_3H_7$), 23.90 ($CH_2C_2H_5$), 22.0 (CH_2CH_3), 13.90 (CH_3); mass spectrum, m/e 543 (24, M^+). Anal. Calcd for $C_{10}H_{12}NOI_3$: C, 22.1; H, 2.2; N, 2.6; I, 70.1. Found: C, 22.0; I, 2.1; N, 2.5; I, 70.2.

Preparation of 3-Acylpyrroles 5. General Procedure. 2,4,5-Triiodo-3-acylpyrrole 4 (8 mmol) was dissolved in 150 mL of ethanol together with 20 g of sodium acetate trihydrate and was reduced over 1 g of 10% palladium on charcoal with hydrogen at 50 psi during 2 h. The catalyst was filtered, the filtrate was evaporated to dryness in vacuo, and the residue was partitioned between water (50 mL) and chloroform (50 mL). The latter was separated, the aqueous layer was extracted with chloroform (3 × 20 mL), the chloroform extracts were pooled, dried (Na_2SO_4), and evaporated to dryness, and the residue was crystallized from benzene-hexane.

3-Formylpyrrole (5a) was obtained (70%) from **4a**; mp 63–64 °C (lit.[14] mp 63–65 °C); ^{13}C NMR δ 186.30 (CO), 128.50, 125.80, 120.80, 106.50 (Ar); mass spectrum, *m/e* 95 (100, M^+). Anal. Calcd for C_5H_5NO: C, 63.2; H, 5.3; N, 14.7. Found: C, 63.1; H, 5.2; N, 14.4.

3-Acetylpyrrole (5b) was obtained (74%) from **4b**; mp 112–113 °C (lit.[9b] mp 112–114 °C; lit.[14] mp 114–115 °C); ^{13}C NMR δ 194.90 (CO), 125.40, 124.30, 119.80, 108.10 (Ar), 26.80 (CH_3); mass spectrum, *m/e* 109 (99, M^+). Anal. Calcd for C_6H_7NO: C, 66.1; H, 6.4; N, 12.8. Found: C, 66.0; H, 6.5; N, 12.8.

3-Propionylpyrrole (5c) was obtained (73%) from **4c**; mp 109–111 °C; ^{13}C NMR δ 198.10 (CO), 125.00, 123.50, 119.70, 108.10 (Ar), 32.40 (CH_2), 8.80 (CH_3); mass spectrum, *m/e* 123 (99, M^+). Anal. Calcd for C_7H_9NO: C, 68.3; H, 7.3; N, 11.4. Found: C, 68.2; H, 7.3; N, 11.3.

3-Butyrylpyrrole (5d) was obtained (75%) from **4d** as an oil, which could not be crystallized; ^1H NMR δ 9.55 (NH, 1 H, s), 7.43, 6.75, 6.65 (Ar, 3 H, m), 2.75 (CH_2CO, 2 H, t (J = 8 Hz)), 1.75 (CH_2CH_3, 2 H, m), 1.05 (CH_3, 3 H, t (J = 8 Hz)); ^{13}C NMR 197.20 (CO), 124.80, 123.70, 119.40, 107.60 (Ar), 40.70 ($ArCH_2$), 18.00 (CH_2CH_3), 13.10 (CH_3); mass spectrum, *m/e* 137 (85, M^+), 109 (31, $M^+ - C_2H_5$), 94 (100, $M^+ - C_3H_7$), 66 (37, C_4H_4N).

4-Pentanoylpyrrole (5e) was obtained (81%) from **4e**: mp 82–83 °C; ^{13}C NMR δ 197.90 (CO), 125.10, 123.90, 119.70, 108.80 (Ar), 39.10 ($ArCH_2$), 27.20 ($ArCH_2CH_2$), 22.20(CH_2CH_3), 13.50 (CH_3); mass spectrum, *m/e* 151 (73, M^+). Anal. Calcd for $C_9H_{13}NO$: C, 71.5; H, 8.6; N, 9.3. Found: C, 71.4; H, 8.5; N, 9.4.

3-Hexanoylpyrrole (5f) was obtained (78%) from **4f**: mp 49–50 °C; ^{13}C NMR δ 198.10 (CO), 125.20, 123.90, 119.70, 108.10 (Ar), 39.40 ($ArCH_2$), 31.40 ($CH_2C_3H_7$), 24.80 ($CH_2C_2H_5$), 22.20 (CH_2CH_3), 13.60 (CH_3); mass spectrum, *m/e* 165 (67, M^+). Anal. Calcd for $C_{10}H_{15}NO$: C, 72.7; H, 9.1; N, 8.5. Found: C, 72.6; H, 9.0; N, 8.7.

Preparation of 3-Alkylpyrroles 6. General Procedure. 3-Acylpyrrole **5** (0.2 mol) and 35 mL of 80% hydrazine hydrate were added to a solution of 45 g of potassium hydroxide in 300 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 (4 × 80 mL) after prior dilution with 100 mL of water, the pooled extracts were dried (Na_2SO_4) and evaporated to dryness in vacuo, and the residue was distilled at reduced pressure.

3-Methylpyrrole (6a) was obtained (42%) from 3-formylpyrrole (**5a**): bp 62–64 °C (30 mm) (lit.[17] bp 142–143 °C); ^{13}C NMR δ 117.70, 117.40, 115.20, 108.80 (Ar), 11.10 (CH_3); mass spectrum, *m/e* 81 (40, M^+). Anal. Calcd for C_5H_7N: C, 74.1; H, 8.6; N, 17.3. Found: C, 74.1; H, 8.8; N, 17.4.

3-Ethylpyrrole (6b) was obtained (49%) from 3-acetylpyrrole (**5b**): bp 65–66 °C (30 mm); ^{13}C NMR δ 125.20, 117.30, 114.00, 107.10 (Ar), 19.50 (CH_2), 14.80 (CH_3); mass spectrum, *m/e* 95 (18, M^+), 80 (81, $M^+ - CH_3$). Anal. Calcd for C_6H_9N: C, 75.8; H, 9.5; N, 14.7. Found: C, 75.7; H, 9.4; N, 14.8.

3-Propylpyrrole (6c) was obtained (46%) from 3-propionylpyrrole (**5c**): bp 75–76 °C (30 mm); ^{13}C NMR δ 124.60, 118.30, 115.70, 108.80 (Ar), 29.80 ($CH_2C_2H_5$), 25.10 (CH_2CH_3), 14.60 (CH_3); mass spectrum, *m/e* 109 (16, M^+), 80 (64, $M^+ - C_2H_5$). Anal. Calcd for $C_7H_{11}N$: C, 77.1; H, 10.1; N, 12.8. Found: C, 77.2; H, 10.2; N, 12.9.

3-Butylpyrrole (6d) was obtained (53%) from 3-butyrylpyrrole (**5d**): bp 98–100 °C (30 mm); ^{13}C NMR δ 124.70, 118.20, 115.50, 108.70 (Ar), 34.10 ($ArCH_2$), 27.30 ($CH_2C_2H_5$), 23.10 (CH_2CH_3), 14.50 (CH_3); mass spectrum, *m/e* 123 (25, M^+), 80 (100, $M^+ - C_3H_7$). Anal. Calcd for $C_8H_{13}N$: C, 78.0; H, 10.6; N, 11.4. Found: C, 78.1; H, 10.5; N, 11.5.

3-Pentylpyrrole (6e) was obtained (45%) from 3-pentanoylpyrrole (**5e**); bp 79–80 °C (2.5 mm); ^{13}C NMR δ 123.90, 117.20, 114.50, 107.80 (Ar), 31.40 ($ArCH_2$), 30.60 ($CH_2C_3H_7$), 26.60 ($CH_2C_2H_5$), 22.20 (CH_2CH_3), 13.60 (CH_3); mass spectrum, *m/e* 137 (12, M^+), 80 (28, $M^+ - C_4H_9$), 41 (100, aziridine cation). Anal. Calcd for $C_9H_{15}N$: C, 78.8; H, 10.9; N, 10.2. Found: C, 78.7; H, 10.8; N, 10.1.

3-Hexylpyrrole (6f) was obtained (44%) from 3-hexanoylpyrrole (**5f**): bp 54–56 °C (0.2 mm): ^{13}C NMR δ 124.00, 117.30, 114.50, 108.90 (Ar), 31.50 (Ar CH_2), 31.00 ($CH_2C_4H_9$), 28.90 ($CH_2C_3H_7$), 26.60 ($CH_2C_2H_5$), 22.30 (CH_2CH_3), 13.70 (CH_3); mass spectrum, *m/e* 151 (18, M^+), 94 (10, $M^+ - C_4H_9$), 80 ($M^+ - C_3H_7$, 100), 41 (12, aziridine cation). Anal. Calcd for $C_{10}H_{17}N$: C, 79.5; H, 11.3; N, 9.3. Found: C, 79.4; H, 11.2; N, 9.4.

Ethyl 4-formyl-2-pyrrolecarboxylate (7) was obtained (80%) from ethyl 2-pyrrolecarboxylate (70 g, 0.5 mol) by alkylation with (dichloromethoxy)methane (75 g, 0.65 mol) in the presence of $AlCl_3$ (173 g, 1.3 mol) following the procedure described for the preparation of **2a**: mp 101–102 °C (benzene–hexane) (lit.[18] mp 104–106 °C); ^{13}C NMR δ 185.90 (CHO), 161.00 (CO), 129.20, 127.00, 124.90, 114.00 (Ar), 60.90 (CH_2), 14.00 (CH_3). Anal. Calcd for $C_8H_9NO_3$: C, 57.5; H, 5.4; N, 8.4. Found: C, 57.4; H, 5.5; N, 8.3.

Ethyl 4-methyl-2-pyrrolecarboxylate (8) was obtained (90%) by hydrogenation of **7** (10 g) in ethanol (150 mL) over 2 g of 10% Pd/C at 50 psi during 16 h: mp 37–38 °C (ethanol–water); ^{13}C NMR δ 161.9 (CO), 122.4, 122.0, 120.6, 116.2 (Ar), 60.2 (CH_2), 14.4 (CH_3), 11.6 (4-CH_3). Anal. Calcd for $C_8H_{11}NO_2$: C, 62.7; H, 7.2; N, 9.1. Found: C, 62.8; H, 7.3; N, 9.2.

3-Methylpyrrole (6a). A mixture of 50 g of **8** and 100 g of potassium hydroxide in 600 mL of ethylene glycol was slowly heated to 200 °C over a 1-h period, while the distillate was collected. The mixture was then cooled to 20 °C, 500 mL of water was added, and heating to 200 °C was resumed while the distillate was collected. The pooled distillates were diluted with 200 mL of water, and the aqueous mixture was extracted with 200 mL of chloroform first and subsequently with further three portions of 50 mL of chloroform. The pooled extracts were dried (Na_2SO_4) and evaporated in vacuo; the residue was distilled in vacuo, and the fraction distilling at 62–64 °C (30 mm) was collected; 19.3 g (73%) of methylpyrrole **6a** was obtained.

Preparation of 2-Alkyl-1,4-diaminoalkanes 9. 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 3-alkylpyrrole **6** (0.1 mol) in 100 mL of 96% ethanol in a three-neck round-bottom flask equipped with a sealed stirrer, an efficient reflux condenser topped with a N_2-filled container, and a two-way gas inlet valve. The mixture was stirred at 15 °C during 30 min while it was purged by alternating vacuum and N_2 admission. It was then heated to reflux under air exclusion with constant stirring during 168 h (7 days). The mixture was then cooled and filtered, the filtrate was evaporated to dryness in vacuo, and the residue was partitioned between 100 mL of water and 100 mL of chloroform. The aqueous layer was further extracted with chloroform (4 × 20 mL), and the chloroform extracts were pooled, dried (Na_2SO_4), and evaporated to dryness. The residue (a mixture of the syn and anti isomers of the dioxime; (^{13}C NMR δ 154.50 and 149.50 (C=NOH)) was dissolved in 300 mL of anhydrous ethanol, 30 g of sodium was added, and the mixture was heated under reflux during 4 h. Ice–water (500 mL) was then added, and the solution was extracted with chloroform (5 × 75 mL). The extracts were dried (Na_2SO_4) and evaporated to dryness in vacuo, and the residue of crude 1,4-diamine **9** 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 **10** 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 **10** was eluted with use of the same solvent by applying a low pressure to the column. The fractions containing **10** 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 **9**, which was pure when analyzed by TLC. The

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dihydrochlorides were highly hygroscopic.

2-Methyl-1,4-bis[(benzyloxycarbonyl)amino]butane (10a) was obtained (30%) from 3-methylpyrrole (**6a**): mp 91–93 °C. Anal. Calcd for $C_{21}H_{26}N_2O_4$: C, 68.1; H, 7.1; N, 7.6. Found: C, 68.0; H, 7.2; N, 7.5. Hydrogenolysis of **10a** afforded (95%) of the dihydrochloride **9a**:[19] mass spectrum, *m/e* 102 (40, M^+); ^{13}C NMR (D_2O) δ 45.50 (C-4), 38.10 (C-1), 31.80 (C-2), 29.70 (C-3), 16.60 (CH_3).

2-Ethyl-1,4-bis[(benzyloxycarbonyl)amino]butane (10b) was obtained (30%) from 3-ethylpyrrole (**6b**): mp 76–77 °C. Anal. Calcd for $C_{22}H_{28}N_2O_4$: C, 68.7; H, 7.3; N, 7.3. Found: C, 68.8; H, 7.4; N, 7.2. Hydrogenolysis of **10b** afforded (90%) the dihydrochloride of **9b**; mass spectrum, *m/e* 116 (40, M^+); ^{13}C NMR (D_2O) δ 42.70 (C-4), 38.00 (C-1), 35.50 (C-2), 28.60 (C-3), 23.10 (CH_2CH_3), 10.0 (CH_3).

2-Propyl-1,4-bis[(benzyloxycarbonyl)amino]butane (10c) was obtained (34%) from 3-propylpyrrole **6c**: mp 71–72 °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 **10c** afforded (95%) of the dihydrochloride of **9c**: mass spectrum, *m/e* 130 (14, M^+); ^{13}C NMR (D_2O) δ 43.00 (C-4), 37.80 (C-1), 34.00 (C-2), 32.50 (C-3), 29.00 ($CH_2C_2H_5$), 19.00 (CH_2CH_3), 14.10 (CH_3).

2-Butyl-1,4-bis[(benzyloxycarbonyl)amino]butane (10d) was obtained (31%) from 3-butylpyrrole (**6d**): mp 85–86 °C. Anal. Calcd for $C_{24}H_{32}N_2O_4$: C, 69.9; H, 7.7; N, 6.8. Found: C, 69.8; H, 7.6; N, 6.9. Hydrogenolysis of **10d** afforded (90%) of the dihydrochloride of **9d**: mass spectrum, *m/e* 144 (10, M^+), 70 (100, pyrrolenine cation); ^{13}C NMR δ 43.20 (C-4), 38.00 (C-1), 34.30 (C-2), 30.10 (C-3), 29.10 ($CH_2C_3H_7$), 27.90 ($CH_2C_2H_5$), 22.90 (CH_2CH_3), 14.10 (CH_3).

2-Pentyl-1,4-bis[(benzyloxycarbonyl)amino]butane (10e) was obtained (30%) from 3-pentylpyrrole (**6e**): mp 84–85 °C. Anal. Calcd for $C_{25}H_{34}N_2O_4$: C, 70.4; H, 8.0; N, 6.5. Found: C, 70.3; H, 7.9; N, 6.4. Hydrogenolysis afforded (90%) of the dihydrochloride of **9e**: mass spectrum, *m/e* 158 (5, M^+), 70 (100); ^{13}C NMR (D_2O) δ 43.20 (C-4), 38.00 (C-1), 34.40 (C-2), 31.90 (C-3), 30.40 ($CH_2C_4H_9$), 29.10 ($CH_2C_3H_7$), 25.40 ($CH_2C_2H_5$), 22.70 (CH_2CH_3), 14.20 (CH_3).

2-Hexyl-1,4-bis[(benzyloxycarbonyl)amino]butane (10f) was obtained (26%) from 3-hexylpyrrole (**6d**): mp 67–68 °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, 8.3; N, 6.5. Hydrogenolysis afforded (95%) of the dihydrochloride of **9f**: mass spectrum, *m/e* 172 (18, M^+); ^{13}C NMR (D_2O) δ 43.10 (C-4), 37.90 (C-1), 34.30 (C-2), 31.80 (C-3), 30.40 ($CH_2C_5H_{11}$), 29.30 ($CH_2C_4H_9$), 29.00 ($CH_2C_3H_7$), 25.70 ($CH_2C_2H_5$), 22.80 (CH_2CH_3), 14.30 (CH_3).

1,2-Dimethyl-1,4-bis[(benzyloxycarbonyl)amino]butane (15) was obtained (28%) from 2,3-dimethylpyrrole 11[21] following the general procedure described above: mp 94–97 °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, 7.4; N, 7.2. Hydrogenolysis afforded (85%) the dihydrochloride of **13**: mass spectrum, *m/e* 116 (14, M^+); ^{13}C NMR (D_2O) δ 57.70, 51.80 (C-1), 38.30 (C-4), 34.50, 33.80 (C-2), 30.90, 29.70 (C-3), 15.80, 14.70, 13.60, 12.80 (CH_3).

1,3-Dimethyl-1,4-bis[(benzyloxycarbonyl)amino]butane (16) was obtained (32%) from 2,4-dimethylpyrrole (**12**:[22] mp 164–176 °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, 7.4; N, 7.2. Hydrogenolysis afforded (90%) the dihydrochloride of **14**: mass spectrum, *m/e* 116 (13, M^+); ^{13}C NMR (D_2O) δ 46.50, 46.40, 46.00, 45.40 (C-1), 39.50, 38.90 (C-4 and C-3), 28.80, 28.70 (C-2), 19.40, 18.00, 17.10, 16.30 (CH_3).

3,4-Dimethylmaleimide Dioxime (18). 3,4-Dimethylpyrrole (**17**) (0.95 g) was brought into reaction with 2.1 g of hydroxylamine hydrochloride and 1.7 g of sodium bicarbonate following the general procedure described for the preparation of **8**. When the residue was partitioned between water and chloroform an insoluble solid remained, which was filtered and recrystallized from anhydrous ethanol (50 mg; 32%): mp above 300 °C dec; high-resolution mass spectrum, *m/e* 155.0723 (100, M^+); ^{13}C NMR (DMSO-d_3) δ 151.3 (C=N), 131.2 (C=C), 8.6 (CH_3). Anal. Calcd for $C_6H_9N_3O_2$: C, 46.4; H, 5.8; N, 27.1. Found: C, 46.5; 4,5.7; N, 27.0.

The chloroform extracts did not contain any aliphatic dioxime.

3-Formylpyrrole (5a) from 3-[(2-Tosylhydrazino)carbonyl]pyrrole. Methyl 3-pyrrolecarboxylate (2 g) was heated under reflux with hydrazine (5 mL, 80%) during 2 h, after which the solution was evaporated to dryness in vacuo. The residue was dissolved in dry pyridine (20 mL) and was treated at 0 °C with a solution of 3.5 g of *p*-toluensulfonyl chloride in 10 mL of dry pyridine. After being stirred during 30 min at 20 °C, the mixture was poured into 100 mL of ice-cold 2 N hydrochloric acid and filtered, and the hydrazide was recrystallized from ethanol–water: 1.34 g (30%); mp 247–248 °C (Anal. Calcd for $C_{12}H_3N_3O_3S$: N, 15.0. Found: N, 15.1). A mixture of the hydrazide (1 g), anhydrous sodium carbonate (1 g), and diethylene glycol (20 mL) was stirred under nitrogen at 170 °C for 5 min. The mixture was then poured into 50 mL of ice-cold water and was extracted with chloroform (3 × 20 mL). Removal of the solvent left a residue of **5a**, which was crystallized from benzene–hexane: 50 mg (15%); mp 63–64 °C.

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Registry No. **1**, 35302-72-8; **2a**, 67858-51-9; **2b**, 72652-34-7; **2c**, 111468-90-7; **2d**, 111468-91-8; **2e**, 111468-92-9; **2f**, 111468-93-0; **3a**, 7126-53-6; **3b**, 16168-93-7; **3c**, 111468-94-1; **3d**, 111468-95-2; **3e**, 111468-96-3; **3f**, 111468-97-4; **4a**, 35302-95-5; **4b**, 111468-98-5; **4c**, 111468-99-6; **4d**, 111469-00-2; **4e**, 111469-01-3; **4f**, 111469-02-4; **5a**, 7126-39-8; **5b**, 1072-82-8; **5c**, 1193-61-9; **5d**, 111469-03-5; **5e**, 111469-04-6; **5f**, 111469-05-7; **6a**, 616-43-3; **6b**, 1551-16-2; **6c**, 1551-09-3; **6d**, 933-08-4; **6e**, 1551-13-9; **6f**, 1551-07-1; **7**, 7126-57-0; **8**, 40611-85-6; **9a**·2HCl, 111469-11-5; **9b**·2HCl, 92238-42-1; **9c**·2HCl, 111469-12-6; **9d**·2HCl, 111469-13-7; **9e**·2HCl, 111469-14-8; **9f**·2HCl, 111469-15-9; **10a**, 111469-06-8; **10b**, 111495-43-3; **10c**, 111469-07-9; **10d**, 111469-08-0; **10e**, 111469-09-1; **10f**, 111469-10-4; **11**, 600-28-2; **12**, 625-82-1; **13**·2HCl, 111469-17-1; **14**·2HCl, 111469-19-3; **15**, 111469-16-0; **16**, 111469-18-2; **17**, 822-51-5; **18**, 14445-80-8; CH_3OCHCl_2, 4885-02-3; CH_3COCl, 75-36-5; CH_3CH_2COCl, 79-03-8; $CH_3(CH_2)_2COCl$, 141-75-3; $CH_3(CH_2)_3COCl$, 638-29-9; $CH_3(CH_2)_4COCl$, 142-61-0; ethyl 2-pyrrolecarboxylate, 2199-43-1; methyl 3-pyrrolecarboxylate, 2703-17-5; 3-pyrrolecarboxylic acid hydrazide, 50561-16-5; 3-pyrrolecarboxylic acid tosylhydrazide, 111469-20-6.

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