dripped (6 h) into 300 mL of boiling acetone. Reflux was maintained for 16 h, acetone was evaporated, and the suspension filtered. The solid material was purified by column chromatography (silica gel, ethyl ether) to afford 3.80 g (43%) of **1b**: mp 127–128 °C (MeCN); ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 6 H), 1.0–1.6 (m, 24 H), 3.2–3.7 (m, 30 H); mass spectrum, m/z 742 (M^+); $m/2z$ 371 ($M^+/2$). The same procedure was applied in the synthesis of triazinophane **1g** (Table IV).

10,23-Dichloro-1,7,14,20-tetrabutyl-1,4,7,9,11,13,14,17,20,22,24,26-dodecaaza[7.7](2,6)triazinophane (1f). A sample of 834 mg (1 mmol) of **1e** dissolved in 40 mL of 95% ethanol containing 2 drops of concentrated HCl was hydrogenated for 20 h at 25 °C in the presence of $PdCl_2$ (71 mg, 0.4 mmol). After filtration of the catalyst, the solvent was evaporated and the residue dissolved in $CHCl_3$ and extracted with 3 N HCl. The aqueous phase was made alkaline with NaOH and extracted with $CHCl_3$ to afford 360 mg (55%) of **1f**: mp 220 °C (benzene–*n*-hexane); ^{1}H NMR ($CDCl_3$) δ 0.9 (t, 12 H), 1.35 (m, 8 H), 1.55 (m, 8 H), 2.75 (t, 6 H), 3.45–3.65 (m, 14 H).

13,29-Bis(octylamino)-4,7,20,23-tetraoxa-1,10,12,14,16,17,26,28,30,32-decaaza[10.10](2,6)triazinophane (1h). A solution of 2.08 g (4 mmol) of **1g** and 1.14 g (8.8 mmol) of *n*-octylamine in 50 mL of Me_2SO was stirred at 160 °C for 5 h in the presence of 2.76 g (20 mmol) of K_2CO_3. The solvent was distilled in vacuo, and the residue dissolved in $CHCl_3$ and washed with H_2O, 3 N HCl, and H_2O. Evaporation of the solvent and column chromatography (silica gel, EtOAc–MeOH) afforded 1.97 g (70%) of **1h**: mp 178–180 °C (benzene–hexane); ^{1}H NMR ($CDCl_3$) δ 0.9 (t, 6 H), 1.1–1.7 (m, 24 H), 3.2–3.8 (m, 28 H), 4.9–5.2 (br s, 2 H), 7.4–8.2 (br s, 4 H).

1,7,14,20,27,33-Hexabutyl-4,17,30-trioxa-1,7,9,11,13,14,20,22,24,26,27,33-dodecaaza[7.7.7](2,4,6)triazinophane (2a). Solutions A and B [A, 2.16 g (3.3 mmol) of **1a** in 80 mL of Me_2SO; B, 0.713 g (3.3 mmol) of **5a** in 80 mL of Me_2SO] were simultaneously dripped (6 h) into a stirred suspension of 1.83 g (13.2 mmol) of K_2CO_3 in 50 mL of Me_2SO at 170 °C, and the mixture was refluxed for another 15 h. The solvent was distilled in vacuo, the residue dissolved in $CHCl_3$, and washed with brine. Evaporation of the solvent and column chromatography (silica gel, ethyl ether–light petroleum) afforded 368 mg (14%) of **2a**: mp 88–90 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 18 H), 1.20 (m, 12 H), 1.45 (m, 12 H), 2.5–4.5 (m, 36 H); mass spectrum, m/z 798 (M^+), $m/2z$ 399 ($M^+/2$). The same procedure was applied in the synthesis of triazinophanes **2b–d** (Table V).

Kinetic Measurements. Kinetics were run in a 10-mL flask, equipped with a teflon-lined screw cap, thermostated at 60 °C with circulating butyl phthalate and magnetic stirrer. The temperature was controlled to within ±0.01 °C by a Exacal 200 Bath Circulator. Stirring speed (1300 ± 50 rpm) was controlled by using a strobe light. The flask was charged with 2.5 mL of a 4 M aqueous solution of the appropriate iodide, 0.5 mL of a 0.1 M solution of catalyst in toluene, and tetradecane as internal standard (0.5 mL of a 0.1 M solution in toluene). *n*-Octyl methanesulfonate (1 mL of a 1M solution in toluene) was added at zero time. Kinetics were followed by GLC analysis, and the pseudo-first-order rate constants (k_{obsd}) were obtained by plotting ln [substrate] vs. time and determining the slope of the straight lines.

Extent of Complexation of Triazinophane 2b. A mixture of a 2.5×10^{-2} M toluene solution (6 mL) of **2b** and a 4 M aqueous solution (5 mL) of NaI was stirred for 2 h in a flask thermostated at 60 °C. The mixture was left without stirring for an additional 2 h to allow good separation of the two phases. Potentiometric titration of a 2-mL sample of the organic phase with 0.01 N aqueous silver nitrate showed that 11.5% of the ligand was complexed (average of three measurements).

Acknowledgment. This paper was supported by a grant from the Progetto Finalizzato di Chimica Fine e Secondaria of Consiglio Nazionale delle Ricerche (CNR), Roma. ^{13}C NMR spectra were recorded at the high-field NMR Service Center of the CNR, Bologna; technical assistance of D. Macciantelli, Bologna, is gratefully acknowledged. Thanks are due to BASF (Ludwigshafen, German Federal Republic) for a generous gift of diethylenetriamine and 1,13-diamino-4,7,10-trioxatridecane. In addition we are grateful to Prof. A. Fiecchi, Milano, and Dr. G. Podda, Cagliari, for mass spectra of triazinophanes **2a**, **2b**, and **2d**.

Registry No. **1a**, 86577-71-1; **1b**, 86577-69-7; **1c**, 86577-70-0; **1d**, 91817-02-6; **1e**, 91817-03-7; **1f**, 91817-04-8; **1g**, 91817-05-9; **1h**, 91817-06-0; **2a**, 86577-74-4; **2b**, 86577-72-2; **2c**, 86577-73-3; **2d**, 91817-07-1; **3**, 108-77-0; **4a**, 31353-28-3; **4b**, 32775-05-6; **4c**, 23243-82-5; **4d**, 91817-08-2; **4e**, 91817-09-3; **5a**, 2620-28-2; **5b**, 86577-64-2; **5c**, 86577-65-3; **5d**, 91817-10-6; **5e**, 91817-11-7; **5f**, 23539-10-8; **5g**, 929-59-9; **6a**, 86577-68-6; **6b**, 86577-66-4; **6c**, 86577-67-5; **6d**, 91817-12-8; **6e**, 91817-13-9; **6f**, 91841-55-3; **6g**, 4700-88-3; **6h**, 18426-53-4; Na^+, 17341-25-2; K^+, 24203-36-9; Cs^+, 18459-37-5; 3,6-dioxa-1,8-octanedioyl dichloride, 31255-09-1; butyric anhydride, 106-31-0; 4,7,10-trioxa-1,13-tridecanediamine, 4246-51-9; phthalic anhydride, 85-44-9; 1,5-diphthalimido-3-azapentane, 63563-83-7; 3-benzyl-1,5-diphthalimido-3-azapentane, 23538-88-7; octylamine, 111-86-4; diethylenetriamine, 111-40-0; benzyl bromide, 100-39-0; 1,8-dichloro-3,6-dioxaoctane, 112-26-5; ammonium, 14798-03-9.

Catalytic Hydrogenation of Pyrroles at Atmospheric Pressure[1]

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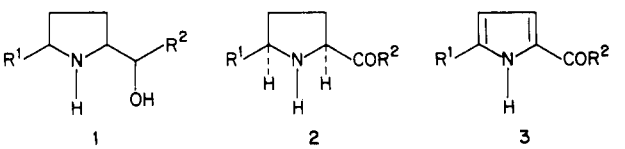
Received April 23, 1984

N-(*tert*-Butoxycarbonyl)pyrroles are catalytically hydrogenated to the corresponding pyrrolidines, over 5% platinum on carbon catalyst, at room temperature and atmospheric pressure. Under these conditions *O*-benzyl groups are retained and 2,5-disubstituted pyrroles are reduced predominantly or exclusively to the *cis*-2,5-disubstituted pyrrolidines. This facile catalytic reduction of pyrroles was the central feature of convenient, high yield syntheses of 2-acylpyrrolidines and 5-substituted proline derivatives.

It became necessary, in connection with several research programs, to devise syntheses of 2-(1-hydroxyalkyl)-5-substituted pyrrolidines 1 of a nature such that stereochemical control could be exercised in the side chain as well as at positions 2 and 5 of the heterocyclic ring. It was obvious that this objective was reducible to the development of a synthesis of *cis*-2-acyl-5-alkylpyrrolidines 2 which ought to be available by catalytic reduction of the corresponding pyrroles 3. Such reductions are known to be difficult[3,4] but facilitation of this process might be antic-



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(1) Contribution No. 633 from the Syntex Institute of Organic Chemistry.

(2) Syntex Post-doctoral Fellow, 1981–1982.

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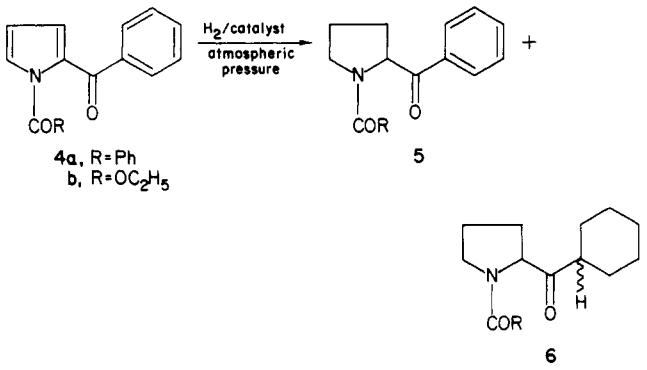
Table I. Catalytic Hydrogenation[a] of *N*-Acylpyrroles

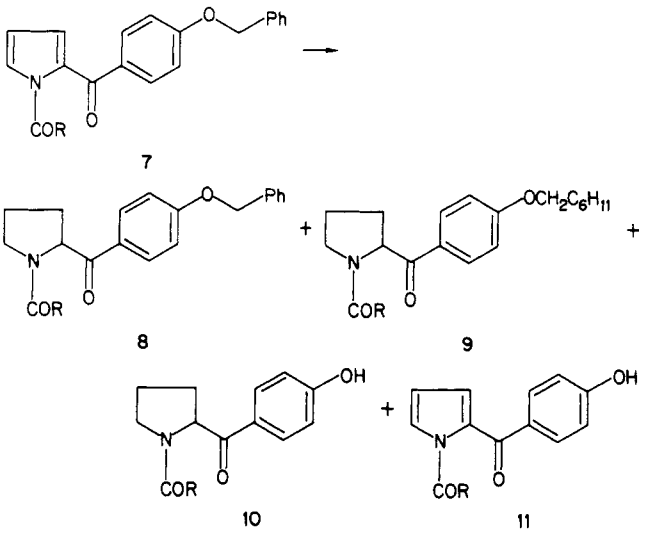
N-acylpyrrole	catalyst	amt cat, wt %	redn time, h	products (%)	purification process[b]
4a	5% Rh-C[c]	18[d]	24	**5a** (63)	CC; hexane–EtOAc (5:2) cryst
4a	5% Pt-C[e]	10	12	**5a** (84)	
4b	PtO_2[f]	9	24	**5b** (69), **6b** (10)	CC; hexane–EtOAc (10:3)
7a	5% Pt-C	20	8.5	**8a** (66), **9a** (≤5), **10a** (5)[g]	CA TLC; hexane–EtOAc (2:1 → 1:1)
7a	5% Rh-C[h]	20	6.5	**8a** (31), **9a** (10), **11a** (≤5)[i]	CC: hexane–EtOAc (1:1)
7a	PtO_2[f]	33[j]	72	**8a** (8), **9a** (8), **10a** (62), **11a** (10)	CA TLC; hexane–EtOAc (1:1)
7b	5% Rh-C	28	1.2	**8b** (41), **9b** (20), **10b** (21)	CA TLC; hexane–EtOAc (3:1 → 1:1)
7b	5% Pt-C	30	2.5	**8b** (64), **9b** (≤5), **10b** (8)	CA TLC; hexane–EtOAc (2:1)
12	5% Pt-C	10	2	**13** (85)	CA TLC; hexane–EtOAc (5:2) cryst
16a	5% Pt-C	20	1.5	**17a** (79)	
16b	5% Pt-C[k]	20	3	**17b** (74)	CA TLC; hexane–EtOAc (10:1)
22a	5% Pt-C	33	3	**23a** (88)	CC; hexane–EtOAc (95:5 → 90:10)
22b	5% Pt-C	20	3	**23b** (77)	CA TLC; hexane–EtOAc (95:5)
26	5% Pt-C	4	1.5	**27** (72), **28** (24)	CC; hexane–EtOAc (95:5)

[a] Hydrogenations conducted in methanol unless specified otherwise. [b] Stationary phase for chromatographic separations was silica gel. Solvent system, hexane–ethyl acetate (ratios in brackets). CC = column chromatography. CA TLC = centrifugally accelerated thin-layer chromatography. [c] Aldrich Chemical Co. [d] Reduction commenced with 10 wt % catalyst and a further 8% added after 16 h. [e] Matheson, Coleman and Bell. [f] The catalyst was prehydrogenated. [g] 2-[4-(Benzyloxy)benzoyl]pyrrole (5%) was also isolated. [h] Methanol–acetic acid (1:1) as solvent. [i] Characterized as 2-(4-hydroxybenzoyl)pyrrole. See footnote *b* Table II. [j] Reduction commenced with 22 wt% catalyst and a further 11% was added after 48 h. [k] Absolute ethanol as solvent.

Scheme I



Scheme II[a]



[a] a, R = Ph; b, R = $OC(CH_3)_3$.

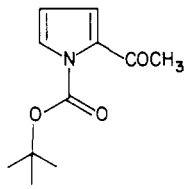
ipated if delocalization of the nitrogen electron pair is attenuated by N-acylation. Indeed, it was shown over forty years ago by Adkins et al.,[5] that the *N*-carbethoxy derivatives of substituted 2- and 3-acetyl and 2- or 3-carbethoxypyrroles were catalytically hydrogenated to the corresponding pyrrolidines, of unspecified stereochemistry, over Raney nickel at 70–200 °C and 70–350 atm. In contrast, nuclear hydrogenation of the N-unsubstituted analogues of the above compounds could not be effected under any known conditions.

In addition to the stereochemical criterion cited above, it was considered desirable that the process utilized to convert **3** into **2** be compatible with the use of benzyl protecting groups for phenolic moieties. This requirement eliminated Raney nickel catalyzed hydrogenation from contention.[6] Consequently, a study of the use of other catalysts, as well as the effect of other *N*-acyl groups on the catalytic reduction of 2-acylpyrroles was undertaken.[7] It was thus established that 1,2-dibenzoylpyrrole (**4a**) (Scheme I) could be catalytically reduced to 1,2-dibenzoylpyrrolidine (**5a**) over either 5% rhodium or platinum on carbon catalysts at *room temperature and atmospheric pressure* in 63% and 84% yields, respectively (Table I).[8] Similarly, 1-(ethoxycarbonyl)-2-benzoylpyrrole (**4b**) was hydrogenated over platinum oxide, but in this case the desired material **5b** (69%) was contaminated by about 10% of the over reduced product **6b** (unknown stereochemistry).

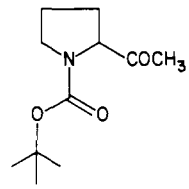
Whereas the reduction of 1-benzoyl-2-[4-(benzyloxy)benzoyl]pyrrole (**7a**) with Pt–C gave the desired pyrrolidine **8a** as the major product, serious selectivity problems were encountered when the hydrogenation was effected over Rh–C or PtO_2. When the rhodium catalyst was used (in methanol, containing acetic acid to increase the rate of hydrogen absorption) the required product **8a** (31%) was accompanied by the cyclohexylmethoxy compound **9a** (10%) and a small amount of the debenzylated starting

(3) Jones, R. A.; Bean, G. P. "The Chemistry of Pyrroles"; Academic Press: New York, 1977; pp 241–243.
(4) Weinstein, B.; Craig, A. R. *J. Org. Chem.* **1976**, *41*, 875.
(5) Signaigo, F. K.; Adkins, H. *J. Am. Chem. Soc.* **1936**, *58*, 709. Rainey, J. L.; Adkins, H. *Ibid.* **1939**, *61*, 1104.
(6) Greene, T. W. "Protective Groups in Organic Synthesis"; John Wiley and Sons: New York, 1981; p 296.
(7) Greenhouse, R.; Tallabs, R., carried out studies of a preliminary nature on 2-benzoylpyrrole and 1-(methoxycarbonyl)-2-benzoylpyrrole with a variety of hydrogenation catalysts under acidic and neutral conditions. The results were of much value in that they provided some insight as to which methods of catalytic reduction were less likely to be useful.
(8) It was recently reported that during the reduction (PtO_2, acetic anhydride, atmospheric pressure) of ethyl 1-benzoyl-2-cyano-4-(carbethoxyvinyl)pyrrol-3-acetate to ethyl 1-benzoyl-2-(acetamidomethyl)-4-(carbethoxyethyl)pyrrol-3-acetate, hydrogenation of the pyrrole nucleus was a competing reaction (Demopoulos, B. J.; Anderson, H. J.; Loader, C. E.; Faber, K. *Can. J. Chem.* **1983**, *61*, 2415).

material **11a**. The reduction of **7a** in the presence of platinum oxide occured very slowly (72 h) and gave the reduced debenzylated compound **10a** as the major (62%) product as well as lesser amounts of **8a**, **9a**, and **11a**. Inasmuch as the eventual facile removal of the *N*-acyl group was an important requisite, 1-(*tert*-butoxycarbonyl)-2-[4-(benzyloxy)benzoyl]pyrrole (**7b**), which was readily prepared by the potassium *tert*-butoxide promoted acylation of 2-[4-(benzyloxy)benzoyl]pyrrole with di-*tert*-butyl dicarbonate, was next subjected to catalytic reduction. Remarkably, the rate of hydrogen absorbtion for this compound, with either rhodium or platinum on carbon, was considerably greater than for the *N*-benzoyl compound **7a**. Nevertheless, with the rhodium catalyst the selectivity was still not improved, as indicated by the isolation of **8b**, **9b**, and **10b** in a 2:1:1 ratio. In contrast, with platinum on carbon **8b** was the major product while compounds **9b** and **10b** were formed in much smaller amounts. As a consequence, all of the subsequent hydrogenations were effected on the *N*-(*tert*-butoxycarbonyl) derivatives of the pyrroles using the 5% platinum on carbon catalyst. In this manner, 1-(*tert*-butoxycarbonyl)-2-acetylpyrrole (**12**) and



12



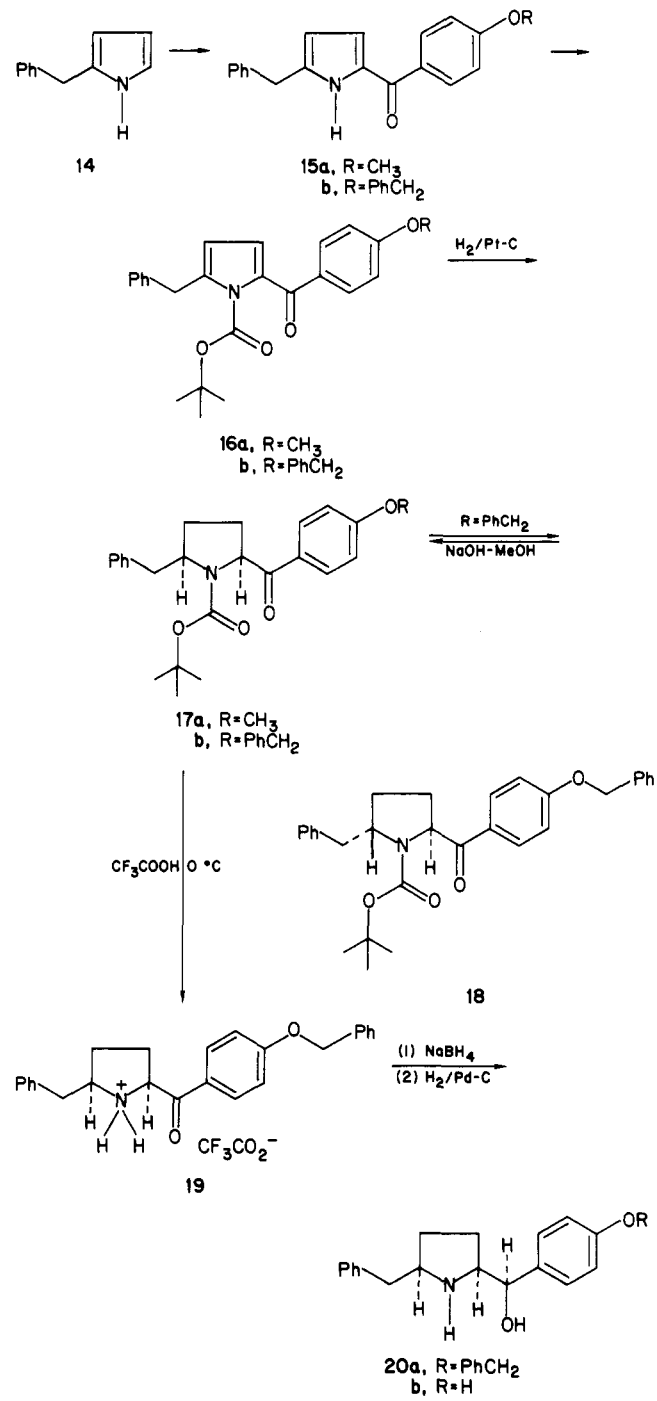
13

the 2-aroyl-5-benzyl compounds (**16a** and **11b** [synthesised by Vilsmeier-Haack acylation of 2-benzylpyrrole **14** and subsequent N-acylation of the 2-aroylpyrroles **15a** and **15b** obtained thereby with di-*tert*-butyl dicarbonate (Scheme III)] were reduced to the corresponding pyrrolidines **13**, **17a**, and **17b**[9] in good yields. A single stereoisomer was obtained from both **16a** and **16b** and this was demonstrated to be the cis isomer, in the case of the benzyloxy compound **17b**, by methanolic sodium hydroxide induced isomerization to a mixture rich (92%) in the trans compound **18**.

With the benzyloxy compound **17b** in hand it was a simple matter to establish that pyrrolidine derivatives analogous to **1** could be derived therefrom. The N-protecting group was removed with trifluoroacetic acid at 0 °C and the amino ketone **19** thus obtained was reduced with ethanolic sodium borohydride to the cis erythro amino alcohol **20a**,[10] which was catalytically hydrogenated to the phenol **20b** (83% overall from **17b**). That **20a** did indeed possess the erythro configuration was supported by the small value (3.2 Hz) of the NMR spectral coupling constant between the proton α to the hydroxyl group and the adjacent hydrogen on the pyrrolidine ring.[11]

The facility with which the above hydrogenations occurred suggested that 5-substituted prolines might be preparable in an analogous manner. Therefore, methyl

Scheme III[a]



5-methyl- or 5-benzylpyrrole-2-carboxylates **21a** or **21b** (synthesised by phosgenation and subsequent methanolysis of the appropriate 2-alkylpyrrole (Scheme IV)] were N-protected and then subjected to catalytic reduction over Pt–C. In each case a methyl ester **23a** or **23b**, which was at least 96% isomerically pure,[12] was isolated, and these compounds were converted into the corresponding methyl 5-substituted prolinate **24** or **24b** with trifluoroacetic acid. Amino acid analysis (after hydrolysis with 6 N hydrochloric acid) showed that **24a** was at least 96% cis and that the hydrolyzate had a retention time identical with natural *cis*-5-methylproline.[13] In addition, ammonolysis of **24a** gave an amide **25** for which the NMR spectrum was

(9) The *N*-acylpyrrolidines showed the expected spectral properties, including, in most instances, the phenomenon of restricted rotation about the NCO bond. For example, the NMR spectrum of **17a** had two ca. equiintense singlets at δ 1.29 and 1.49 at ambient temperature, for the *tert*-butyl group, which collapsed to a singlet absorption at δ 1.47 at 87 °C. See Table III for detailed NMR spectra.

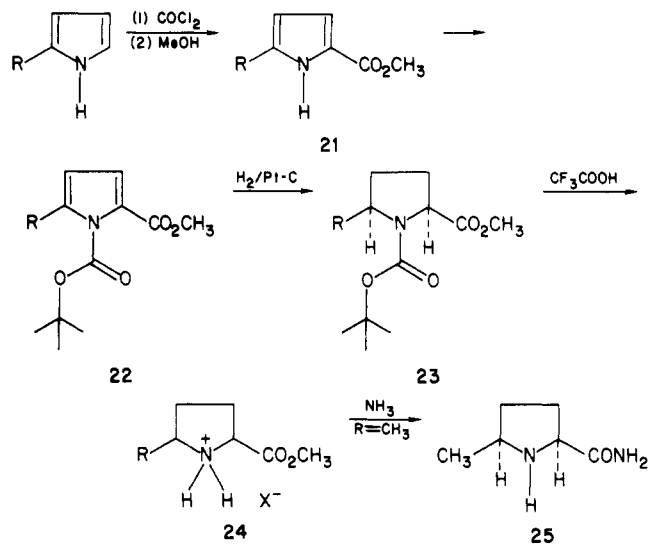
(10) It is well-known that the hydride reduction of α-amino ketones having an hydrogen bearing amino group gives a predominance of the erythro amino alcohol. See: Kaiser, C.; Colella, D. F.; Schwartz, M. S.; Garvey, E.; Wardell, J. R. *J. Med. Chem.* **1974**, *17*, 49 and references therein.

(11) Uloth, R. H.; Kirk, J. R.; Gould, W. A.; Larsen, A. A. *Ibid.* **1966**, *9*, 88 and references therein.

(12) The NMR spectra of the crude hydrogenation products indicated that 2–3% of an isomeric product was present.

(13) Katz, E.; Mason, K. T.; Mauger, A. B. *Biochem. Biophys. Res. Commun.* **1973**, *52*, 819.

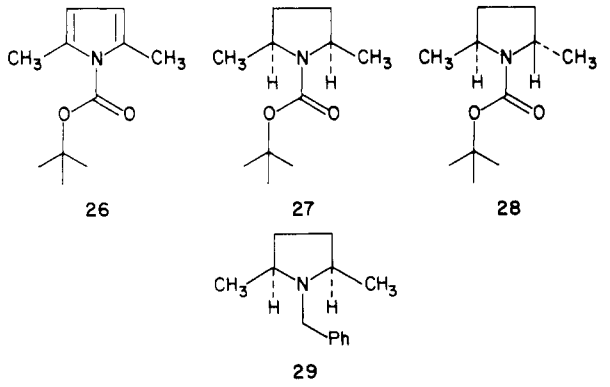
Scheme IV[a]



[a] a, R = CH_3; b, R = CH_2Ph

identical with natural *cis*-5-methylprolineamide.[14] 5-Substituted prolines have not heretofore been readily available;[15] the process described herein should give access to a wide variety of these interesting amino acids.

Finally, the reduction of 1-(*tert*-butoxycarbonyl)-2,5-dimethylpyrrole (**26**) took place to give a nearly quantitative yield of a mixture (3:1) of isomeric pyrrolidines **27** and **28**, which had identical GLPC retention times (3% SE-30, 80 °C) to an authentic sample prepared from the commercially available mixture of *cis*- and *trans*-2,5-dimethylpyrrolidines. Furthermore, the major component of the mixture was shown to be the cis compound by conversion into 1-benzyl-*cis*-2,5-dimethylpyrrolidine (**29**).[16] The high proportion of the trans isomer produced in this case seems to be peculiar to **26** because the reduction of other 1-(*tert*-butoxycarbonyl)-2,5-disubstituted pyrroles gave almost exclusively (≥95%) the cis compound.[17]



Experimental Section

The melting points were determined in a Mel-Temp melting point apparatus and are not corrected. The IR spectra were measured with a Pye-Unicam SP-3-200 Infrared Spectrophotometer. The NMR spectra were recorded with a Varian EM-360, Varian EM-390, Varian HA-100, or a Bruker WM 300 spectrometer and are expressed in parts per million (δ) from internal tetramethylsilane. The high-resolution mass spectra were obtained with a Varian-MAT 311A mass spectrometer. The low-resolution mass spectrum was measured on a Varian-MAT 1125 mass spectrometer by the direct inlet technique.

The centrifugally accelerated TLC separations were effected on a Model 7924 Chromatotron (Harrison Research, Palo Alto, CA). The GLPC analyses were carried out with a Hewlett-Packard Model 402 gas chromatograph on a 5 ft 3% SE-30 column (H_2).

The term "dried" signifies dried over anhydrous magnesium sulfate throughout the Experimental Section.

1,2-Dibenzoylpyrrole (4a). This compound was synthesised in a manner similar to that described by Jacob et al.[18] Triethylamine (5.2 g, 58 mmol) and freshly distilled benzoyl chloride (8.5 g, 58 mmol) were added to a solution of 2-benzoylpyrrole[18] (2.0 g, 11.7 mmol) in chloroform (100 mL, dried over 4A molecular sieves) and the solution was heated at reflux temperature for 48 h. The mixture was diluted with dichloromethane and then was washed successively with sulfuric acid (1 N), sodium hydroxide (1 N), and saturated salt solution. The organic phase was dried, the solvent was removed in vacuo, and the residue was subjected to distillation in vacuo (140–150 °C (~1 mm), Kugelrohr). The distillate crystallized spontaneously (2.13 g, 67%) and after crystallization from ethanol it had mp 74 °C: IR (KBr) 1722, 1628, 1600, 1578, 1565 sh, 1532 cm^{-1}; NMR ($CDCl_3$) δ 6.36 (t, 1 H), 6.88 (q, 1 H, $J_{3,4}$ = 3.4 Hz, $J_{3,5}$ = 1.2 Hz), 7.37–7.57 (m, 7 H), 7.68–7.93 (m, 4 H).

Anal. Calcd for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.23; H, 4.63; N, 5.03.

1-(Ethoxycarbonyl)-2-benzoylpyrrole (4b). Potassium metal (0.50 g, 12.8 mmol) was added in small pieces to a solution of 2-benzoylpyrrole (2.0 g 11.7 mmol) in dry tetrahydrofuran (100 mL) maintained in a nitrogen atmosphere. The mixture was heated at reflux temperature until the potassium was consumed (2 h), the solution was cooled to 0 °C, and ethyl chloroformate (1.33 g, 1.21 mL, 12.7 mmol) was added. The solution was stirred at room temperature for 1.5 h, ether was added, and the mixture was washed with saturated salt solution. The organic phase was dried and evaporated in vacuo. The residue was subjected to column chromatography on silica gel using hexane–ethyl acetate (10:1) to elute the product (1.47 g, 77%). An analytical sample was obtained by distillation at 120 °C (1 mm): IR ($CHCl_3$) 1752, 1650 cm^{-1}; NMR ($CDCl_3$) δ 1.18 (t, 3 H, J = 7.2 Hz), 4.26 (q, 2 H, J = 7.2 Hz), 6.27 (q, 1 H, $J_{2,3}$ = 2.5 Hz, $J_{3,4}$ = 3.9 Hz), 6.69 (q, 1 H, $J_{1,4}$ = 1.4 Hz, $J_{3,4}$ = 3.9 Hz), 7.40–7.62 (m, 4 H), 7.78–7.96 (m, 2 H).

Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.96; H, 5.61, N, 5.68.

[4-(Benzyloxy)benzoyl]morpholide. A suspension of 4-(benzyloxy)benzoic acid (50 g, 0.22 mol) in thionyl chloride (100 mL) was heated at reflux temperature for 1 h. The volatile material was distilled off and the solid residue was dried in vacuo. The acid chloride, dissolved in toluene (500 mL), was added to a mixture of morpholine (17.1 g, 0.22 mol) and triethylamine (21.7 g, 29.8 mL, 0.22 mol). After the reaction had stirred for 1 h, the precipate was removed by filtration and the filtrate was evaporated in vacuo. The residual oil was dissolved in ether, and it was washed successively with saturated solutions of sodium carbonate and salt and then dried. The residue was purified by column chromatography on silica gel with dichloromethane and increasing amounts (3–7%) of methanol as the eluting solvents. The product (41 g, 63%) was obtained as a solid mp 72 °C: IR (KBr) 1622, 1608 cm^{-1}; NMR ($CDCl_3$) δ 3.60 (s, 8 H), 5.05 (s, 2 H), 6.94 (d, 2 H, J = 8.8 Hz), 7.22–7.42 (m, 5 H), 7.36 (d, 2 H, J = 8.8 Hz); exact mass (high-resolution mass spectrum) calcd for $C^{18}H_{19}NO_3$ 297.1365, found 297.1363.

2-[4-(Benzyloxy)benzoyl]pyrrole. This compound was synthesized by the method of White and McGillivray.[19] Thus, a mixture of the above morpholide (10.0 g, 33.7 mmol) and freshly distilled phosphorus oxychloride (12.4 g, 7.4 mL, 81 mmol) was left at room temperature in a nitrogen atmosphere for 5 h. A solution of distilled pyrrole (2.26 g, 2.34 mL, 33.7 mmol) in dry 1,2-dichloroethane (300 mL) was added and after stirring for 16

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h, excess 10% sodium carbonate solution was added. The mixture was stirred for 1 h, and the organic phase was separated, washed with saturated salt solution, and dried. The solvent was removed in vacuo and the residue was subjected to column chromatography on silica gel with hexane–ethyl acetate (5:2) as the eluting solvent. The product (7.0 g, 75%), after crystallization from ethanol, had mp 102 °C: IR (KBr) 3265, 1605, 1565, 1538 cm^{-1}; NMR ($CDCl_3$) δ 5.10 (s, 2 H), 6.21–6.37 (m, 1 H), 6.77–7.83 (m, 1 H), 7.01 (d, 2 H, J = 8.4 Hz), 7.33–7.50 (m, 6 H), 7.90 (d, 2 H, J = 8.4 Hz).

Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.54; N, 5.05. Found: C, 77.71; H, 5.53; N, 5.11.

1-Benzoyl-2-[4-(benzyloxy)benzoyl]pyrrole (7a). A solution of 2-[4-(benzyloxy)benzoyl]pyrrole (3.0 g, 10.8 mmol), benzoyl chloride (15.1 g, 10.8 mmol), and triethylamine (10.8 g, 15 mL, 10.8 mmol) in dry 1,2-dichloroethane was heated at 80 °C for 22 h. The reaction mixture was worked up as described for **4a** and the crude product was purified by column chromatography on silica gel with hexane–ethyl acetate (10:3) as the eluting solvent. The solid product (3.63 g, 89%) had mp 128 °C after crystallization from ethanol: IR (KBr) 1720, 1622, 1600, 1572 cm^{-1}; NMR ($CDCl_3$) δ 5.22 (s, 2 H), 6.47 (t, 1 H), 6.94 (dd, 1 H, $J_{3,4}$ = 3.4 Hz, $J_{3,5}$ = 1.3 Hz), 7.14 (d, 2 H, J = 8.6 Hz), 7.33–7.51 (m, 7 H), 7.59 (dd, 1 H, $J_{3,5}$ = 1.3 Hz, $J_{4,5}$ = 2.8 Hz), 7.61–7.74 (m, 3 H), 7.84 (d, 2 H, J = 8.6 Hz).

Anal. Calcd for $C_{25}H_{19}NO_3$: C, 78.72; H, 5.02; N, 3.67. Found: C, 78.51; H, 5.09; N, 3.73.

1-(*tert*-Butoxycarbonyl)-2-[4-(benzyloxy)benzoyl]pyrrole (7b). A mixture of 2-[4-(benzyloxy)benzoyl]pyrrole (0.800 g, 2.89 mmol), di-*tert*-butyl dicarbonate (0.700 g, 3.2 mmol), potassium *tert*-butoxide (0.032 g, 2.85 mmol), and anhydrous tetrahydrofuran (50 mL) was heated at reflux temperature for 1.5 h. The mixture was diluted with ether, washed with saturated salt solution, and dried. The solvent was removed in vacuo and the residue on crystallization from ether–hexane gave the product (0.840 g, 77%): mp 102 °C; IR (KBr) 1745, 1630, 1608, 1578 cm^{-1}; NMR ($CDCl_3$) δ 1.37 (s, 9 H), 5.13 (s, 2 H), 6.18–6.28 (m, 1 H), 6.53–6.63 (m, 1 H), 7.01 (d, 2 H, J = 8.8 Hz), 7.37 (s, 5 H), 7.85 (d, 2 H, J = 8.8 Hz).

Anal. Calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71. Found: C, 73.11; H, 6.21; N, 3.80.

2-Benzylpyrrole (14). A solution of 2-benzoylpyrrole (0.500 g) in dry tetrahydrofuran (25 mL) containing lithium aluminum hydride (0.330 g) was heated at reflux temperature for 48 h. The excess hydride was destroyed by addition of 5% ammonium chloride solution and ether was added to the mixture. The organic phase was separated and dried, and the solvent was removed in vacuo. The residual oil was distilled at 90 °C (1 mm) to give 2-benzylpyrrole (0.332 g, 72%) identical with an authentic specimen prepared from pyrrolylmagnesium bromide and benzyl bromide.[20]

2-(4-Methoxybenzoyl)-5-benzylpyrrole (15a). This compound was synthesised from 4-(methoxybenzoyl)morpholide[19] (7.03 g, 32 mmol), phosphorus oxychloride (10.7 g, 70 mmol), and 2-benzylpyrrole (32 mmol) in 1,2-dichloroethane (200 mL) as described for 2-[4-(benzyloxy)benzoyl]pyrrole, except that the reaction time was 15 h and the hydrolysis with sodium carbonate solution required 1.5 h. The crude product was dissolved in hot ethanol from which the product (5.5 g) crystallized. Chromatography of the mother liquor on silica gel with hexane–ethyl acetate as the eluant gave additional (1.38 g) product (total yield, 6.88 g, 74%): mp 111 °C; IR (KBr) 3445, 3255, 1608, 1595, 1562 cm^{-1}; NMR ($CDCl_3$) δ 3.86 (s, 3 H), 4.06 (s, 2 H), 6.07 (t, 1 H, $J_{1,4}$ = 2.4 Hz, $J_{3,4}$ = 3.7 Hz), 6.81 (dd, 1 H, $J_{1,3}$ = 2.4 Hz, $J_{3,4}$ = 3.7 Hz), 6.95 (d, 2 H, J = 8.9 Hz), 7.23–7.33 (m, 5 H), 7.88 (d, 2 H, J = 8.9 Hz), 8.87 (s, 1 H, W_H = 15 Hz).

Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.17; H, 6.13; N, 4.71.

1-(*tert*-Butoxycarbonyl)-2-acetylpyrrole (12). A solution of 2-acetylpyrrole[21] (3.0 g, 28 mmol) and di-*tert*-butyl dicarbonate (6.6 g, 30 mmol) in dry tetrahydrofuran (100 mL) containing potassium *tert*-butoxide (0.314 g, 2.8 mmol) was heated at reflux temperature for 2 h. The reaction mixture was worked up as described for **7b** to give the crude product which was passed through a short column of silica gel with hexane–ethyl acetate (10:1) as the solvent. The product (5.1 g, 89%) was obtained as a low melting solid: mp 27 °C; IR ($CHCl_3$) 1745, 1662 cm^{-1}; NMR ($CDCl_3$) δ 1.57 (s, 9 H), 2.43 (s, 3 H), 6.14 (t, 1 H), 6.83 (dd, 1 H, $J_{3,4}$ = 3.0 Hz, $J_{3,5}$ = 1.0 Hz), 7.31 (dd, 1 H, $J_{3,5}$ = 1.0 Hz, $J_{4,5}$ = 3.0 Hz).

Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14f H, 7.23; N, 6.69. Found: C, 63.12; H, 7.26; N, 6.66.

2-[4-(Benzyloxy)benzoyl]-5-benzylpyrrole (15b). This compound was prepared as described for **15a** except that the ratio of the morpholide (23.6 mmol) to phosphorus oxychloride (10 mmol) and 2-benzylpyrrole (25.2 mmol) and the hydrolysis time (24 h) were somewhat different. The crude product crystallized on trituration with hexane and after crystallization from hexane, the pure material (6.1 g, 71%) was obtained: mp 129 °C; IR (KBr) 3445, 3280, 1604, 1590, 1560 cm^{-1}; NMR ($CDCl_3$) δ 4.07 (s, 2 H), 5.10 (s, 2 H), 6.05 (dd, 1 H, $J_{1,4}$ = 2.4 Hz, $J_{3,4}$ = 3.8 Hz), 6.80 (dd, 1 H, $J_{1,3}$ = 2.4 Hz, $J_{3,4}$ = 3.8 Hz), 6.99 (d, 2 H, J = 8.7 Hz), 7.20 (s, 5 H), 7.35 (s, 5 H), 7.86 (d, 2 H, J = 8.7 Hz).

Anal. Calcd for $C_{25}H_{21}NO_2$: C, 81.72; H, 5.76; N, 3.81. Found: C, 81.66; H, 5.86; N, 3.85.

1-(*tert*-Butoxycarbonyl)-2-(4-methoxybenzoyl)-5-benzylpyrrole (16a). A mixture of the pyrrole **15a** (2.0 g, 6.8 mmol), di-*tert*-butyl dicarbonate (2.0 g, 9.2 mmol), potassium *tert*-butoxide (0.076 g, 0.68 mmol), and dry tetrahydrofuran (50 mL) was heated at reflux temperature in a nitrogen atmosphere for 3 h. The reaction mixture was worked up as described for **7b** to give the product (2.61 g, 97%) which, after crystallization from hexane or ethanol had mp 82 °C: IR (KBr) 1746, 1622, 1593 cm^{-1}; NMR ($CDCl_3$) δ 1.33 (s, 9 H), 3.86 (s, 3 H), 4.20 (s, 2 H), 5.86 (d, 1 H, $J_{3,4}$ = 3.7 Hz), 6.54 (d, 1 H, $J_{3,4}$ = 3.7 Hz), 6.95 (d, 2 H, J = 9.0 Hz), 7.18–7.33 (m, 5 H), 7.92 (d, 2 H, J = 9.0 Hz).

Anal. Calcd for $C_{24}H_{25}NO_4$: C, 73.64; H, 6.44; N, 3.58. Found: C, 73.74; H, 6.22; N, 3.69.

1-(*tert*-Butoxycarbonyl)-2-[4-(benzyloxy)benzoyl]-5-benzylpyrrole (16b). A mixture of the pyrrole **15b** (5.5 g, 11.8 mmol), di-*tert*-butyl dicarbonate (3.09 g, 14 mmol), and potassium *tert*-butoxide was heated at reflux temperature for 3 h in dry tetrahydrofuran (150 mL). After the usual workup and recrystallization from ethanol, the product (6.78 g, 88%) had mp 106 °C: IR (KBr) 1745, 1606, 1572 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (s, 9 H), 4.22 (s, 2 H), 5.10 (s, 2 H), 5.84 (d, 1 H, $J_{3,4}$ = 3.6 Hz), 6.52 (d, 1 H, $J_{3,4}$ = 3.6 Hz), 6.99 (d, 2 H, J = 8.6 Hz), 7.20 (s, 5 H), 7.35 (s, 5 H), 7.88 (d, 2 H, J = 8.6 Hz).

Anal. Calcd for $C_{30}H_{29}NO_4$: C, 77.07; H, 6.25; N, 3.00. Found: C, 77.23; H, 6.36; N, 2.95.

Methyl 5-Benzylpyrrole-2-carboxylate (21b). A solution of 2-benzylpyrrole (1.0 g, 6.37 mmol) in toluene (60 mL), which was 12.5 wt % in phosgene, was heated at reflux temperature for 6 h. The solution was evaporated in vacuo, and the dark colored residue was dissolved in methanol. After 1 h at room temperature, the methanol was removed in vacuo and the solid residue was purified by column chromatography on silica gel. The product (0.65 g, 47%) was eluted with hexane–ethyl acetate (5:1) and after crystallization from ethanol or hexane it had mp 103 °C: IR (KBr) 3285, 1678, 1602 cm^{-1}; NMR ($CDCl_3$ + D_2O) δ 3.85 (s, 3 H), 4.07 (s, 2 H), 6.08 (d, 1 H, J = 3.6 Hz), 6.93 (d, 1 H, J = 3.6 Hz), 7.37 (s, 5 H).

Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.45; H, 6.29; N, 6.48.

Methyl 1-(*tert*-Butoxycarbonyl)-5-methylpyrrole-2-carboxylate (22a). A solution of methyl 5-methylpyrrole-2-carboxylate[22] (0.410 g, 2.95 mmol) and di-*tert*-butyl dicarbonate (0.708 g, 3.24 mmol) in dry tetrahydrofuran (25 mL) containing potassium *tert*-butoxide (0.033 g, 0.3 mmol) was heated at reflux temperature for 19 h under nitrogen. At this point, further quantities of di-*tert*-butyl dicarbonate (0.100 g, 0.46 mmol) and potassium *tert*-butoxide (0.030 g, 0.26 mmol) were added and heating at reflux temperature was continued for a further 5 h. The reaction mixture was worked up as previously described and the crude product was purified by column chromatography on

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silica gel with hexane–ethyl acetate (20:1) as the eluting solvent. The product (0.601 g, 85%) was obtained as a colorless oil: IR ($CHCl_3$) 1750, 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.57 (s, 9 H), 2.38 (s, 3 H), 3.83 (s, 3 H), 5.90 (d, 2 H, J = 3.6 Hz), 6.79 (d, 1 H, J = 3.6 Hz); exact mass (high-resolution mass spectrum) calcd for $C_{12}H_{17}NO_4$ 239.1158, found 239.1161.

Methyl 1-(*tert*-Butoxycarbonyl)-5-benzylpyrrole-2-carboxylate (22b). A solution of the pyrrole **21b** (0.300 g, 1.40 mmol) and di-*tert*-butyl dicarbonate (0.335 g, 1.53 mmol) in anhydrous tetrahydrofuran (10 mL) containing potassium *tert*-butoxide (0.050 g, 0.45 mmol) was heated at reflux temperature under nitrogen for 19 h. At this time, additional di-*tert*-butyl dicarbonate (0.300 g) and potassium *tert*-butoxide (0.050 g) were added and after a further 5 h at reflux temperature the reaction mixture was worked up. The crude product was subjected to column chromatography on silica gel with hexane–ethyl acetate (95:5) to elute the solid product (0.408 g, 93%). After crystallization from hexane it had mp 59 °C: IR (KBr) 1755, 1710, 1608 cm^{-1}; NRM ($CDCl_3$) δ 1.40 (s, 9 H), 3.78 (s, 3 H), 4.14 (s, 2 H), 5.89 (d, 1 H, J = 3.5 Hz), 6.82 (d, 1 H, J = 3.5 Hz), 7.22 (m, 5 H).

Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.49; H, 6.91; N, 4.56.

1-(*tert*-Butoxycarbonyl)-2,5-dimethylpyrrole (26). A mixture of 2,5-dimethylpyrrole (5.0 g, 52.5 mmol), di-*tert*-butyl dicarbonate (13.0 g, 60 mmol), and potassium *tert*-butoxide (1.0 g, 9.8 mmol) was heated at reflux temperature (nitrogen atmosphere) in dry tetrahydrofuran (100 mL). Additional quantities of di-*tert*-butyl dicarbonate (4.0 g, 18 mmol) and potassium *tert*-butoxide (0.42 g, 3.8 mmol) were added in three equal portions at the end of 24, 48, and 72 h. After a total of 96 h the reaction mixture was worked up in the usual way to give a brown colored oil which was subjected to column chromatography on silica gel with hexane–ethyl acetate (95:5) as the eluting solvent. An oily mixture (15.5 g) of the product and di-*tert*-butyl dicarbonate (65:35 by NMR) was obtained which was used as such for the hydrogenation reaction. An analytical specimen of **26** was obtained by subjecting the crude material (1.0 g) to centrifugally accelerated TLC on silica gel with hexane as the eluting solvent. The desired material (0.507 g) was then distilled in vacuo: bp 60–70 °C (0.1 mm); IR ($CHCl_3$) 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.43 (s, 9 H), 2.43 (s, 6 H), 4.20 (s, 2 H).

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.44; H, 8.85; N, 7.41.

Catalytic Hydrogenation of *N*-Acylpyrroles. The catalytic hydrogenations over the rhodium or platinum on carbon catalysts were all carried out in the same manner. A solution of the *N*-acylpyrrole in the desired solvent (10–50 mL/mmol substrate, see Table I), containing the suspended catalyst (sometimes added in two portions), was hydrogenated at room temperature and atmospheric pressure for the time specified in Table I (reduction followed by TLC). The mixture was filtered through Celite, the filtrate was evaporated, and the residue was submitted to the purification procedure indicated in Table I. The physical constants, IR, and NMR spectra of the products are found in Tables II and III (supplementary material section).

For the hydrogenations over platinum oxide, the catalyst was prereduced with hydrogen, the sample of the *N*-acylpyrrole was added, and the reaction was then carried out as described above.

Isomerization of *cis*-1-(*tert*-Butoxycarbonyl)-2-[4-(benzyloxy)benzoyl]-5-benzylpyrrolidine (17b) to the Trans Isomer (18). A solution of **17b** (0.100 g, 0.21 mmol) in methanol (8 mL) containing 1 N sodium hydroxide (4 mL) was heated at reflux temperature for 65 h. The solution was evaporated in vacuo, water was added to the residue, and the product was extracted into ether. The extract was washed with saturated salt solution, dried, and evaporated in vacuo. The residue was shown by NMR spectroscopy to consist of a 92:8 trans:cis mixture of isomers. One crystallization from hexane gave the pure trans isomer with mp 120 °C.

Anal. Calcd for $C_{30}H_{33}NO_4$: C, 76.41; H, 7.05; N, 2.97. Found: C, 76.72; H, 7.13; N, 2.91.

2-[4-(Benzyloxy)benzoyl]-5-benzylpyrrolidine Trifluoroacetic Acid Salt (19). Trifluoroacetic acid (2 mL) was added to the *tert*-butoxy compound **17b** (0.100 g, 0.21 mmol) at 0 °C. After 5 min the solution was evaporated in vacuo to give an oil which crystallized on trituration with ether. Crystallization of this material from ethyl acetate gave the product (0.081 g, 79%): mp 151 °C dec.

Anal. Calcd for $C_{25}H_{25}NO_2 \cdot CF_3COOH$: C, 66.80; H, 5.40; N, 2.89. Found: C, 66.90; H, 5.57; N, 2.88.

Table II. Melting Points and Recrystallization Solvents of *N*-Acylpyrrole Hydrogenation Products[a]

compd	mp, °C	recryst solvent
5a	85	toluene
5b	oil	
6b	oil	
8a	111	ether
8b	116	ethanol
9a	75	hexane
9b	104	ethanol
10a	188	ethanol
10b	201	acetone
11a[b]	194	ethanol
13	85 (1 mm)	
17a	112	ethanol
17b	101	hexane
23a	oil	
23b	oil	
27, 28	60 (0.1 mm)	

[a] All compounds except **6b** and **23a** had acceptable (±0.3) elemental analyses for C, H, and N. Compounds **6b** and **23a** were characterized by a low- and a high-resolution mass spectrum, respectively. This data is available as a part (Table IV) of the supplementary material. [b] Compound **11a** was somewhat unstable. Therefore it was N-debenzoylated, by crystallization from ethanol, to 2-(4-hydroxybenzoyl)pyrrole. The melting point corresponds to this compound.

Synthesis of the Erythro Cis Alcohol (20a) by Sodium Borohydride Reduction of 19. Sodium borohydride (0.60 g, 15.8 mmol) was added to a solution of the crude trifluoroacetic acid salt **19**, obtained from **17b** (1.40 g, 2.97 mmol) in ethanol (150 mL) at 0 °C. After 1 h at 0 °C, the mixture was slowly poured into 10% ammonium chloride solution. The ethanol was removed in vacuo, the aqueous residue was diluted with saturated sodium carbonate solution, and the product was extracted into dichloromethane. The extract was washed with saturated salt solution, dried, and evaporated in vacuo. The solid residue was dissolved in methanolic hydrogen chloride solution, the solvent was evaporated in vacuo, and the solid material (1.14 g, 94%) was crystallized from ethyl acetate to give the product: mp 168 °C.

Anal. Calcd for $C_{25}H_{27}NO_2 \cdot HCl$: C, 73.24; H, 6.88; Cl, 8.65; N, 3.42. Found: C, 73.13; H, 6.92; Cl, 8.71; N, 3.46.

Synthesis of Phenolic Amine (20b) by Catalytic Hydrogenolysis of 20a. A solution of **20a** (0.740 g, 1.81 mmol) in methanol (40 mL) containing 10% palladium on carbon (0.074 g) was hydrogenated at room temperature and atmospheric pressure. After 5 h, the mixture was filtered through Celite, the filtrate was evaporated in vacuo, and the residue was crystallized from acetonitrile to give the product (0.510 g, 88%): mp 163 °C.

Anal. Calcd for $C_{18}H_{21}NO_2 \cdot HCl$: C, 67.60; H, 6.93; N, 4.38. Found: C, 67.58; H, 6.94; N, 4.35.

***cis*-Methyl 5-Methylprolinate Trifluoroacetic Acid Salt (24a, $X^- = F_3CCO_2^-$).** The *tert*-butoxy compound **23a** (0.180 g, 0.74 mmol) was left with trifluoroacetic acid (4 mL) at 0 °C for 20 min. The solution was evaporated in vacuo and the residue on crystallization from ethyl acetate–hexane gave the product (0.164 g, 86%): mp 102 °C.

Anal. Calcd for $C_9H_{14}F_3NO_4$: C, 42.03; H, 5.49; N, 5.45. Found: C, 42.01; H, 5.52; N, 5.42.

***cis*-Methyl 5-Benzylprolinate Hydrochloride (24b, $X^- = Cl^-$).** The *tert*-butoxy compound **23b** was converted into the trifluoroacetic acid salt as described for **23a**. The crude salt was mixed with saturated sodium carbonate solution at 0 °C and the product was extracted into dichloromethane. The extract was dried and evaporated in vacuo, and a solution of hydrogen chloride in ethyl acetate was added to the residue. Evaporation of the solvent and crystallization of the residual solid from ethyl acetate gave the product (89% yield): mp 154 °C.

Anal. Calcd for $C_{13}H_{17}NO_2 \cdot HCl$: C, 61.05; H, 7.09; N, 5.48. Found: C, 61.00; H, 7.15; N, 5.48.

Trifluoroacetic Acid Salt of (±)-*cis*-5-Methylprolinamide (25). A solution of the trifluoroacetic acid salt **24a** (0.040 g, 0.16 mmol) in 4% methanolic ammonia (2 mL) was left at room temperature for 5 days. The solvent was removed in vacuo, trifluoroacetic acid was added to the residue, and after evaporation in vacuo the residue was purified by column chromatography on Sephadex LH-20 (1.4 × 40 cm) with methanol as the eluant. The product (0.035 g, 93%) on crystallization from ethyl acetate–hexane had mp 124 °C. The NMR spectrum and TLC [ethyl acetate–triethylamine (96:4)] were identical with L-*cis*-5-methylprolinamide trifluoroacetic acid salt:[14] exact mass (high-resolution mass spectrum) calcd for $C_6H_{12}N_2O$ 128.0950, found 128.0949.

***cis*-1-Benzyl-2,5-dimethylpyrrolidine (29).** A solution of the mixture of **27** and **28** (0.500 g, 2.5 mmol) in 2 N methanolic hydrochloric acid (10 mL) was heated at reflux temperature for 2.5 h. The solution was evaporated to dryness in vacuo and the crystalline solid which remained was washed with ethyl acetate. The solid thus obtained (0.34 g) was dissolved in acetone (10 mL) containing benzyl bromide (0.50 g, 2.9 mmol) and suspended sodium carbonate (0.50 g), and the mixture was heated at reflux temperature for 2 h. The solvent was evaporated in vacuo, the residue was triturated with ether, the mixture was filtered, and the filtrate was evaporated in vacuo. Methanolic hydrogen chloride was added to the residue, the solution was evaporated in vacuo and the residue was twice crystallized from ethyl acetate. The hydrochloride salt thus obtained was decomposed with saturated sodium carbonate solution and the free base was extracted into ether. The solvent was removed in vacuo and the residual oil was distilled in vacuo to give pure **29** (0.161 g, 34%): bp 60 °C (0.1 mm). The NMR spectrum of this material was identical with the published spectrum of *cis*-1-benzyl-2,5-dimethylpyrrolidine.[16]

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Registry No. **4a**, 92012-07-2; **4b**, 92012-08-3; **5a**, 92012-09-4; **5b**, 92012-10-7; **6b**, 92012-11-8; **7a**, 92012-12-9; **7b**, 92012-13-0; **8a**, 92012-14-1; **8b**, 92012-15-2; **9a**, 92012-16-3; **9b**, 92012-17-4; **10a**, 92012-18-5; **10b**, 92012-19-6; **11a**, 92012-20-9; **11a** (*N*-debenzyl deriv), 92012-21-0; **12**, 75400-61-2; **13**, 92012-22-1; **14**, 33234-48-9; **15a**, 92012-23-2; **15b**, 92012-24-3; **16a**, 92012-25-4; **16b**, 92012-26-5; **17a**, 92012-27-6; **17b**, 92012-28-7; **18**, 92012-29-8; **19**, 92012-31-2; **20a**, 92012-32-3; **20a**·HCl, 92077-34-4; **20b**, 92012-33-4; **20b**·HCl, 92077-35-5; **21a**, 1194-97-4; **21b**, 92012-34-5; **22a**, 92012-35-6; **22b**, 92012-36-7; DL-**23a**, 92012-37-8; DL-**23b**, 92012-38-9; DL-**24a** (X = CF_3CO_2), 92012-44-7; DL-**24b** (X = CF_3CO_2), 92012-40-3; DL-**24b** (X = Cl), 92012-41-4; (±)-**25**·CF_3CO_2H, 92077-37-7; **26**, 50585-36-9; **27**, 92012-42-5; **28**, 92012-43-6; **29**, 4209-68-1; **29**·HCl, 4209-69-2; PhCOCl, 98-88-4; C_2H_5OCOCl, 541-41-3; NH_3, 7664-41-7; $PhCH_2Br$, 100-39-0; Rh, 7440-16-6; Pt, 7440-06-4; PtO_2, 1314-15-4; 2-benzoylpyrrole, 7697-46-3; [4-(benzyloxy)benzoyl]morpholide, 92012-45-8; 4-(benzyloxy)benzoic acid, 1486-51-7; morpholine, 110-91-8; 2-[4-(benzyloxy)benzoyl]pyrrole, 92012-46-9; pyrrole, 109-97-7; di-*tert*-butyl dicarbonate, 24424-99-5; [4-(methoxy)-benzoyl]morpholide, 7504-58-7; 2-acetylpyrrole, 1072-83-9; 2,5-dimethylpyrrole, 625-84-3.

Supplementary Material Available: Table III, giving the IR and NMR spectral data of the pyrrolidine derivatives, and Table IV, giving the C, H, and N analytical figures for the compounds listed in Table II (4 pages). Ordering information is given on any current masthead page.

Stereoconservative Reductive Methyl- and Dimethylamination of Isomeric 3,3-Diarylpropenals. Synthetic and Mechanistic Studies on Control of the Stereochemistry

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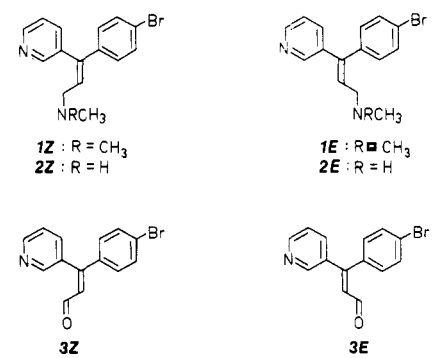
The tertiary allylic amine zimeldine (**1Z**) and the secondary amine **2Z** have been prepared by reductive aminations of (*Z*)-3-(4-bromophenyl)-3-(3-pyridyl)propenal (**3Z**) with sodium cyanoborohydride in the presence of dimethylammonium and methylammonium chloride. The reductive methylamination was largely stereoconservative, giving >96% of the *Z* isomer **2Z**, over a very large pH interval. However, the degree of isomerization in the reductive dimethylamination of **3Z** increased with higher pH. The isomerization showed a first-order dependence on free dimethylamine, inferring a Michael-induced isomerization of the intermediate iminium ion **8** by attack of amine. The rate of isomerization was identical for the two isomeric aldehydes **3Z** and **3E**. The reductive amination of both **3Z** and **3E** was completely stereoconservative (>99%) at low pH with both $MeNH_2$ and Me_2NH.

The antidepressant zimeldine[1] (**1Z**) and its primary metabolite norzimeldine (**2Z**) have been synthesized by several methods including dehydration,[2a] Wittig reaction,[2a] stereoselective allylic rearrangements,[2b,c] and palladium-catalyzed amination.[2d] The difference in biological effects of the *Z* isomers **1Z** and **2Z** and the *E* isomers **1E** and **2E** emphasizes the importance of controlling the stereochemistry of the double bond.[2c] In connection with metabolic studies we required a way of introducing various amine substituents in a stereospecific manner. The reaction should be applicable also for derivatives having the pyr-



(1) Revised rINN name. Earlier zimelidine.

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