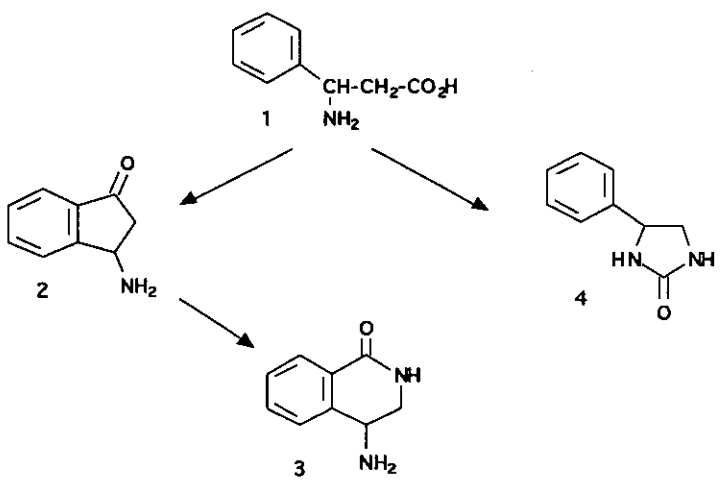
AN EFFICIENT SYNTHESIS OF NEW PHENYLPYRROLIZINE AND PHENYLPYRROLOPYRAZINE DERIVATIVES

Olivier Norbert Tembo, Patrick Dallemagne, Sylvain Rault, and Max Robba*

Centre d'Etudes et de Recherches sur le Médicament de Normandie
U.F.R. des Sciences Pharmaceutiques -1 rue Vaubénard-14032 CAEN cedex
France

Abstract - Synthesis of new 3-phenyl-2,3-dihydro-1*H*-pyrrolizine derivatives is achieved starting from 3-amino-3-phenylpropionic acid *via* an iminium salt. The reactivity of this system is studied and the new 4-phenyl-1,2,3,4-tetrahydropyrrolo-[1,2-*a*]pyrazin-1-one derivatives are synthesized, *via* a Beckmann's rearrangment.

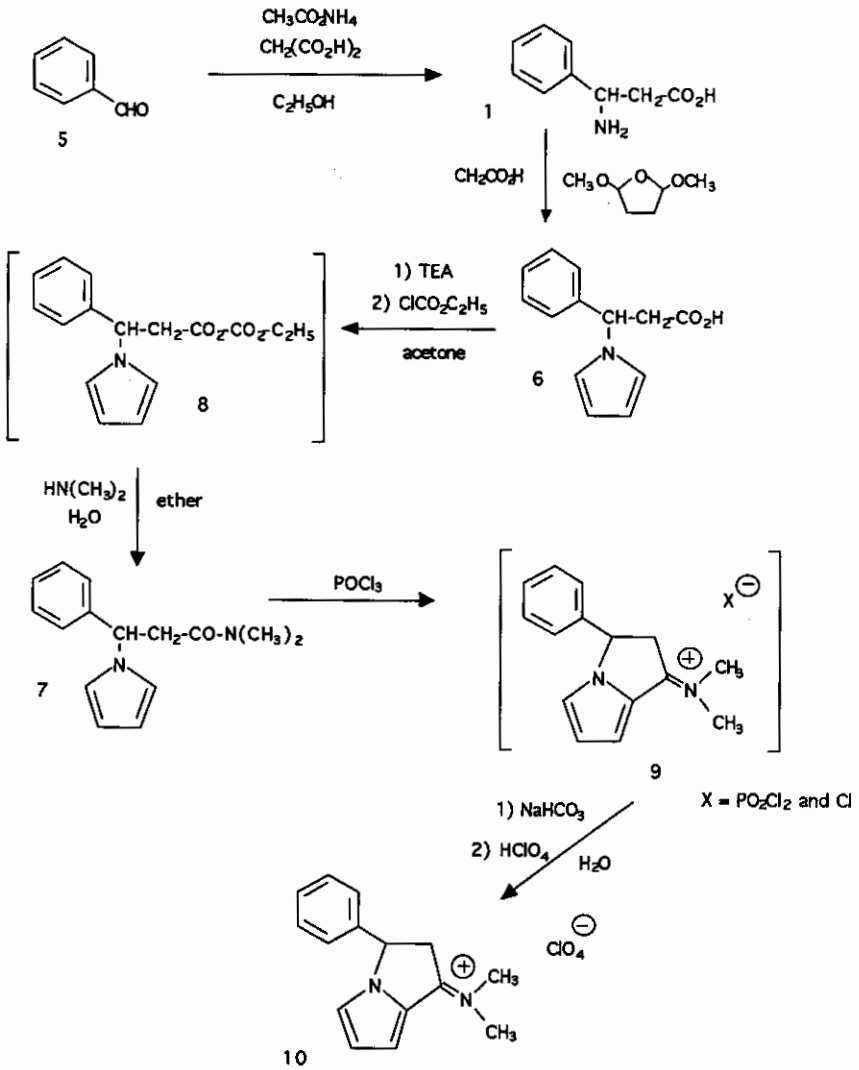
We recently described the reactivity of 3-amino-3-phenylpropionic acid (**1**) and its ability to lead to new series of compounds such as 3-aminoindan-1-one (**2**),[1] 4-aminoisoquinol-1-one (**3**)[2] and 4-phenylimidazolidin-2-one (**4**)[3] (Scheme 1).



Scheme 1

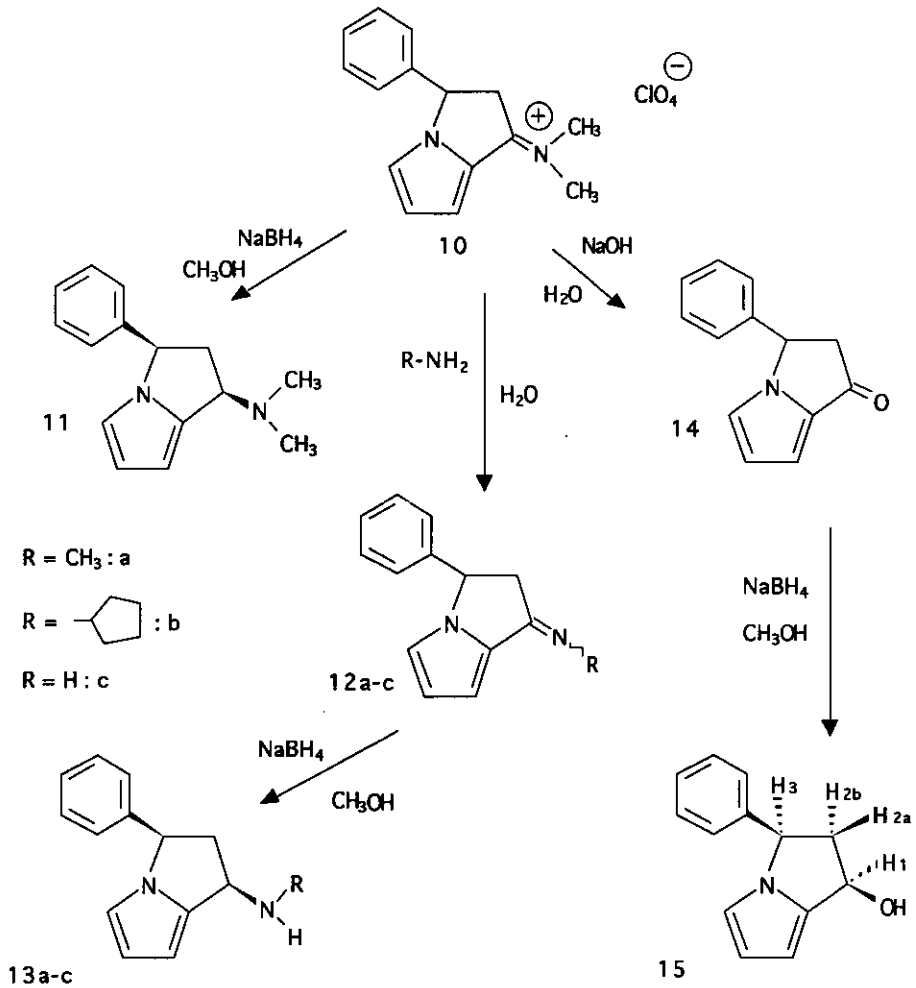
We wish to describe herein a further development of this β-amino acid in the synthesis of the phenylpyrrolizine and phenylpyrrolopyrazine systems.

β-Amino acid (**1**) was obtained in good yield from benzaldehyde (**5**) by treatment with ammonium acetate and malonic acid in refluxing ethanol, as previously described[1] (Scheme 2). Treatment of **1** with 2,5-dimethoxytetrahydrofuran in boiling acetic acid, according to the Clauson-Kaas method,[4,5] led to the pyrrolylphenylpropionic acid (**6**). Reaction of **6** with triethylamine followed by treatment with ethyl chloroformate and dimethylamine gave the dimethylamide (**7**) *via* the anhydride (**8**). Cyclization of **7** in boiling phosphoryl chloride afforded a mixture (**9**) of iminium chloride and phosphonodichloridate which was immediately treated with an aqueous solution of sodium hydrogenocarbonate. Acidification of the mixture with perchloric acid gave in 75% yield the phenylpyrrolizinyliminium perchlorate (**10**).



Scheme 2

The reactivity of this stable Vilsmeier salt was evaluated. Reduction of **10** with sodium borohydride gave the dimethylamine (**11**) (Scheme 3). Furthermore, treatment of **10** with an excess of primary amine led to the imines (**12a-c**) reduction of which with sodium borohydride gave the amines (**13a-c**). On the other hand, hydrolysis of **10** with sodium hydroxide led to the phenylpyrrolizinone (**14**) which was reduced with sodium borohydride to give the corresponding hydroxypyrrolizine (**15**) in quantitative yield.

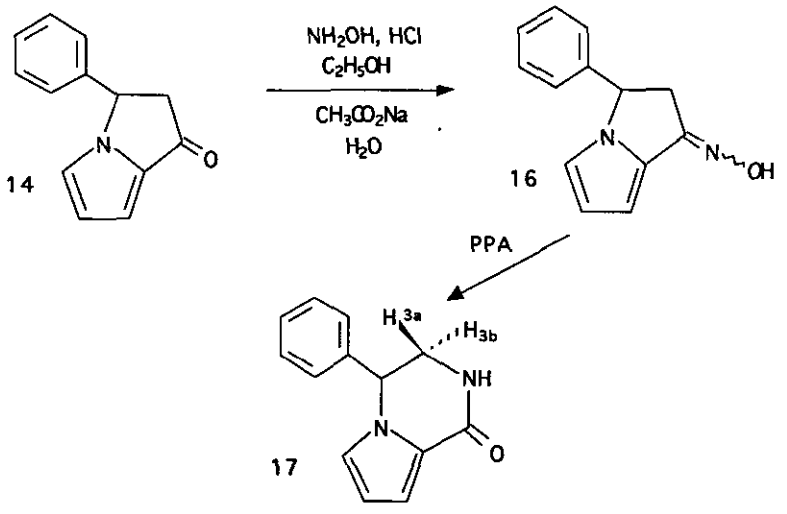


Scheme 3

The ^{1}H-nmr spectra of **11**, **13a-c** and **15** revealed the presence of only one *cis* or *trans* isomer for each compound. The values of the *cis* and *trans* coupling constants which affect the signals of protons H-1 and H-2 are equal (7.5 Hz) for **11** and **13a-c** and don't allow the attribution of the *cis* or *trans* structure. However, the analysis of the ^{1}H-nmr spectrum of **15** permits to clearly establish its structure. The signals of H-1 and H-3 are doublets of doublets exhibiting a *cis* coupling constant measured at 9 Hz and a *trans* coupling constant measured at 3 Hz for each signal. These values are in accordance with those recently reported for similar systems.[6]

The signals of protons H-2a and H-2b are furthermore complicated with a *geminal* coupling constant measured at 18 Hz. H-2b is a doublet of doublet of doublet showing a *geminal* and two *cis* coupling constants. The signal of H-2a is similar and exhibits a *geminal* and two *trans* coupling constants. These data are in favor of a *cis* structure for **15** which is confirmed by the remarkable difference of chemical shift between H-2a (3.20 ppm) and H-2b (2.17 ppm) translating an important steric hindrance for H-2a which is in a *cis* relationship between the phenyl and hydroxyl substituents. This difference of chemical shift is already observed on the spectra of **11** and **13a-c** and seems to indicate also a *cis* structure for these compounds.

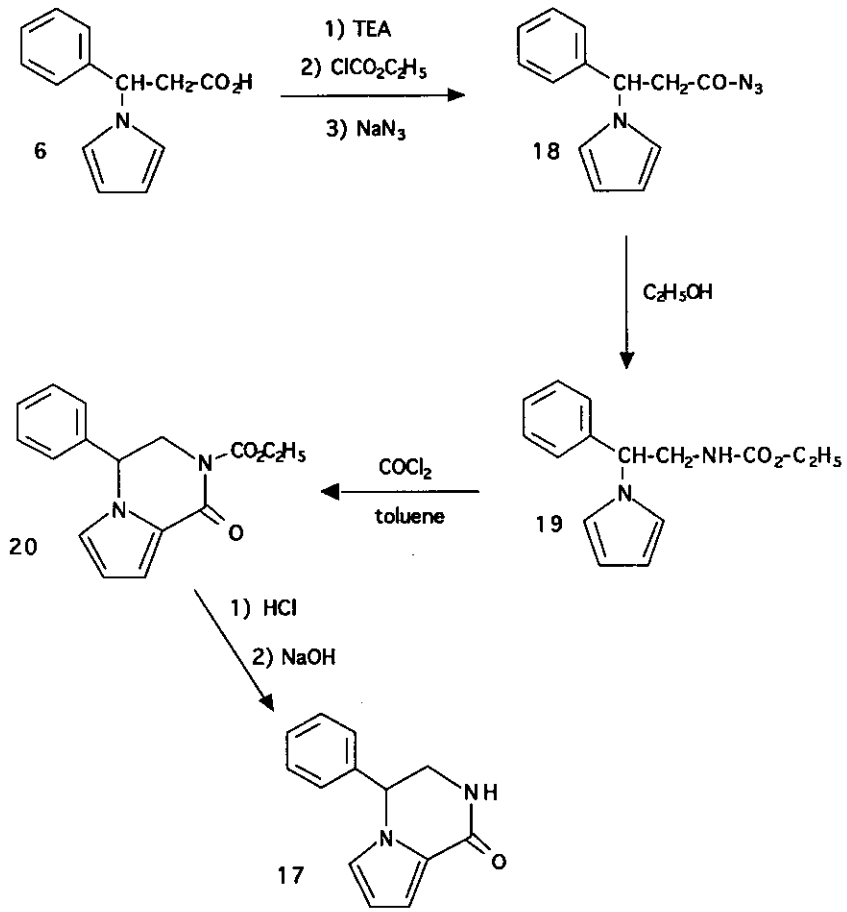
The phenylpyrrolizinone (**14**) was also treated under the conditions for a Beckmann's rearrangment (Scheme 4). Reaction with hydroxylamine hydrochloride afforded oxime (**16**). The study of the ^{1}H-nmr spectrum of the latter revealed the presence of only one isomer but it was not possible to establish clearly the E or Z structure. Treatment of **16** with polyphosphoric acid at 120°C led to a unique phenylpyrrolopyrazinone (**17**) in 63% yield. Its ^{1}H-nmr spectrum exhibits a coupling constant (4 Hz) between the proton of the amino grouping and H-3b, constant which disappears after deuteriation. This is in favor of the structure (**17**).



Scheme 4

However in order to confirm the position of the nitrogen insert, we undertook the unequivocal synthesis of the latter compound (Scheme 5).

The phenylpyrrolylpropionic acid (**6**) was treated with triethylamine followed by treatment with ethyl chloroformate and sodium azide to give the intermediate (**18**). Azide (**18**) was heated in ethanol to give the carbamate (**19**) which was cyclized with phosgene in refluxing toluene giving the ethoxycarbonylpyrazinone (**20**). Acidic hydrolysis of **20** afforded the expected phenylpyrrolopyrazinone (**17**) whose analytical data were identical to those of the compound synthesized by the Beckmann's rearrangment.



Scheme 5

Further investigation on these products and related compounds are in progress.

EXPERIMENTAL

General Methods. Melting points were taken on a Köfler bank and are uncorrected. Infrared spectra were recorded on a Philips PU 9716 apparatus. Nmr spectra were recorded on a Jeol FX 200 in DMSO-d_6 solution using TMS as an internal standard. Chemical shift are reported in ppm downfield (δ) from TMS.

3-Phenyl-3-(pyrrol-1-yl)propionic acid (**6**). To a solution of **1** (35 g, 0.22 mol) in acetic acid (100 ml) was added 2,5-dimethoxytetrahydrofuran (25 ml, 0.22 mol). The reaction mixture was refluxed for 1 h and then evaporated to dryness. The oily residue was crystallized by trituration in water. It was collected by filtration and washed with water to give **6** (35 g, 75%) : mp 120°C (ether); ir (KBr) 3050-2800 (OH), 1680 (CO); ^{1}H-nmr 9.6 (br, OH), 7.13 (s, H-Ø), 6.60 (m, 2H-αPyr), 6.03 (m, 2H-βPyr), 5.50 (t, $J_{CH\ CH2}$ = 9 Hz, CH), 3.08 (d, $J_{CH2\ CH}$ = 9 Hz, CH_2). Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 72.54; H, 6.09; N, 6.51. Found : C, 72.67; H, 6.04; N, 6.47.

N,N-Dimethyl-3-phenyl-3-(pyrrol-1-yl)propionic acid (**7**). To a stirred solution of **6** (20 g, 0.093 mol) in acetone (100 ml) at 0°C was added dropwise triethylamine (13 ml, 0.093 mol). After 30 min, ethyl chloroformate (9 ml, 0.093 mol) was added and the reaction mixture was stirred at 0°C for 30 min. The precipitate formed was filtered and the filtrate was evaporated to dryness. The oily residue was then dissolved in ether (50 ml) and dimethylamine (20 ml of 40% aqueous solution) was added. The reaction mixture was stirred at room temperature for 15 min and then poured into water (100 ml). The organic layer was washed with water (3 x 100 ml), dried over magnesium sulfate, and evaporated to dryness to give **7** as white crystals (16 g, 71%) : mp 122°C (ether); ir (KBr) 1630 (CO); ^{1}H-nmr 7.56 (s, H-Ø), 7.13 (m, 2H-αPyr), 6.05 (m, 2H-βPyr), 5.93 (t, $J_{CH\ CH2}$ = 9 Hz, CH), 3.53 (d, $J_{CH2\ CH}$ = 9 Hz, CH_2), 3.23 (s, CH_3), 3.00 (s, CH_3). Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found : C, 74.49; H, 7.48; N, 11.44.

N,N-Dimethyl-3-phenyl-2,3-dihydro-1*H*-pyrrolizin-1-yliminium perchlorate (**10**). A solution of **7** (5.5 g, 0.022 mol) in phosphoryl chloride (50 ml, 0.54 mol) was refluxed for 1 h and then evaporated to dryness. The oily residue was washed with petroleum ether (2 x 100 ml), poured into iced water (500 ml) and stirred for 30 min. The mixture was filtered and the filtrate was adjusted to pH = 9 with sodium hydrogen carbonate. Perchloric acid was then added to the solution until pH = 2. The precipitate was filtered, washed with water (50 ml) and dried to give **10** as green needles (4.1 g, 75%) : mp 160°C (methanol); ir (KBr) 1670 (CN); ^{1}H-nmr 7.49 (d, $J_{H\text{-}5\ H\text{-}6}$ = 2.5 Hz, H-5), 7.33 (m, 3H-Ø), 7.30 (d, $J_{H\text{-}7\ H\text{-}6}$ = 4 Hz, H-7), 7.16 (m, 2H-Ø), 6.77 (dd, $J_{H\text{-}6\ H\text{-}7}$ = 4 Hz, $J_{H\text{-}6\ H\text{-}5}$ = 2.5 Hz, H-6), 5.83 (dd, $J_{H\text{-}3\ H\text{-}2a}$ = 9 Hz, $J_{H\text{-}3\ H\text{-}2b}$ = 3 Hz, H-3), 4.30 (dd, $J_{H\text{-}2a\ H\text{-}2b}$ = 18 Hz, $J_{H\text{-}2a\ H\text{-}3}$ = 9 Hz, H-2a), 3.68 (dd, $J_{H\text{-}2b\ H\text{-}2a}$ = 18 Hz, $J_{H\text{-}2b\ H\text{-}3}$ = 3 Hz, H-2b), 3.60 (s, CH_3), 3.46 (s, CH_3). Anal. Calcd for $C_{15}H_{17}N_2O_4Cl$: C, 55.48; H, 5.28; N, 8.63. Found : C, 55.54; H, 5.36; N, 8.67.

cis-1-Dimethylamino-3-phenyl-2,3-dihydro-1*H*-pyrrolizine (**11**). To a stirred solution of **10** (2 g, 0.006 mol) in methanol (100 ml), was added sodium borohydride (0.7 g, 0.018 mol). The reaction mixture was refluxed for 1 h and the solvent was removed under reduced pressure. The solid residue was taken up in chloroform (70 ml) and filtered. The filtrate was washed with water (2 x 50 ml). The organic layer was dried over calcium chloride and evaporated to dryness to give **11** as white crystals (1.2 g, 87%) : mp 94°C (ether / petroleum ether); ^{1}H-nmr 7.17 (s, 5H-Ø), 6.26 (d, $J_{H\text{-}5\ H\text{-}6}$ = 2.5 Hz, H-5), 6.01 (dd, $J_{H\text{-}6\ H\text{-}7}$ = 4 Hz, $J_{H\text{-}6\ H\text{-}5}$ = 2.5 Hz, H-6), 5.83 (d, $J_{H\text{-}7\ H\text{-}6}$ = 4 Hz, H-7), 5.17 (dd, $J_{H\text{-}3\ H\text{-}2a}$ = $J_{H\text{-}3\ H\text{-}2b}$ = 7.5 Hz, H-3), 4.07 (dd, $J_{H\text{-}1\ H\text{-}2a}$ = $J_{H\text{-}1\ H\text{-}2b}$ = 7.5 Hz, H-1), 2.90 (ddd, $J_{H\text{-}2a\ H\text{-}2b}$ = 18 Hz, $J_{H\text{-}2a\ H\text{-}1}$ = $J_{H\text{-}2a\ H\text{-}3}$ = 7.5 Hz, H-2a), 2.20 (s, 2 CH_3), 2.18 (ddd, $J_{H\text{-}2b\ H\text{-}2a}$ = 18 Hz, $J_{H\text{-}2b\ H\text{-}1}$ = $J_{H\text{-}2b\ H\text{-}3}$ = 7.5 Hz, H-2b). Anal. Calcd for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.38. Found : C, 79.66; H, 8.03; N, 12.40.

1-Methylimino-3-phenyl-2,3-dihydro-1*H*-pyrrolizine (**12a**). A solution of **10** (2 g, 0.006 mol) in methylamine (20 ml of 40% aqueous solution) was stirred at room temperature for 5 min. The solution was then extracted with ether (75 ml). The organic layer was washed with water (2 x 100 ml), dried over magnesium sulfate and evaporated to dryness to give **12a** as white crystals (0.6g, 60%) : mp 133°C (ether); ir (KBr) 1650 (CN);

^{1}H-nmr 7.33 (m, 3H-Ø), 7.13 (m, 2H-Ø), 6.80 (d, $J_{H\text{-}5\,H\text{-}6}$ = 2.5 Hz, H-5), 6.33 (m, H-6 and H-7), 5.63 (dd, $J_{H\text{-}3\,H\text{-}2a}$ = 9 Hz, $J_{H\text{-}3\,H\text{-}2b}$ = 3 Hz H-3), 3.63 (dd, $J_{H\text{-}2a\,H\text{-}2b}$ = 18 Hz, $J_{H\text{-}2a\,H\text{-}3}$ = 9 Hz, H-2a), 3.13 (s, CH_3), 2.83 (dd, $J_{H\text{-}2b\,H\text{-}2a}$ = 18 Hz, $J_{H\text{-}2b\,H\text{-}3}$ = 3 Hz, H-2b). Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32. Found : C, 79.80; H, 6.65; N, 13.16.

1-Cyclopentylimino-3-phenyl-2,3-dihydro-1*H*-pyrrolizine (**12b**). To a stirred solution of **10** (2 g, 0.006 mol) in dimethylformamide (40 ml) was added cyclopentylamine (1 ml, 0.01 mol) and potassium carbonate (1.4 g, 0.01 mol). The reaction mixture was refluxed for 2 h, cooled and poured into water (250 ml). The solution was then extracted with ether (250 ml). The organic layer was washed with water (2 x 100 ml), dried over magnesium sulfate and evaporated to dryness. The oily residue crystallized by addition of hexane to give **12b** (1.2 g, 76%) : mp 80°C (ether / hexane); ir (KBr) 1650 (CN); ^{1}H-nmr 7.30 (m, 3H-Ø), 7.10 (m, 2H-Ø), 6.76 (d, $J_{H\text{-}5\,H\text{-}6}$ = 2.5 Hz, H-5), 6.53 (d, $J_{H\text{-}7\,H\text{-}6}$ = 4 Hz, H-7), 6.33 (dd, $J_{H\text{-}6\,H\text{-}7}$ = 4 Hz, $J_{H\text{-}6\,H\text{-}5}$ = 2.5 Hz, H-6), 5.57 (dd, $J_{H\text{-}3\,H\text{-}2a}$ = 9 Hz, $J_{H\text{-}3\,H\text{-}2b}$ = 3 Hz, H-3), 4.36 (m, CH), 4.26 (m, $2CH_2$), 3.73 (dd, $J_{H\text{-}2a\,H\text{-}2b}$ = 18 Hz, $J_{H\text{-}2a\,H\text{-}3}$ = 9 Hz, H-2a), 3.57 (dd, $J_{H\text{-}2b\,H\text{-}2a}$ = 18 Hz, $J_{H\text{-}2b\,H\text{-}3}$ = 3 Hz, H-2b), 1.67 (m, $2CH_2$). Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.78; H, 7.62; N, 10.60. Found : C, 81.55; H, 7.63; N, 10.59.

cis-1-Methylamino-3-phenyl-2,3-dihydro-1*H*-pyrrolizine (**13a**). To a stirred solution of **12a** (1 g, 0.0047 mol) in methanol (30 ml) was added sodium borohydride (0.5 g, 0.014 mol). The reaction mixture was then refluxed for 1 h and the solvent was removed under reduced pressure. The solid residue was taken up in water (50 ml) and extracted with ether (100 ml). The organic layer was dried over magnesium sulfate and evaporated to dryness to give **13a** as white crystals (0.7 g, 65%) : mp 68°C (ether / petroleum ether); ir (KBr) 3300 (NH); ^{1}H-nmr 7.30 (s, 5H-Ø), 6.25 (d, $J_{H\text{-}5\,H\text{-}6}$ = 2.5 Hz, H-5), 6.07 (dd, $J_{H\text{-}6\,H\text{-}7}$ = 4 Hz, $J_{H\text{-}6\,H\text{-}5}$ = 2.5 Hz, H-6), 5.87 (d, $J_{H\text{-}7\,H\text{-}6}$ = 4 Hz, H-7), 5.17 (dd, $J_{H\text{-}3\,H\text{-}2a}$ = $J_{H\text{-}3\,H\text{-}2b}$ = 7.5 Hz, H-3), 4.07 (dd, $J_{H\text{-}1\,H\text{-}2a}$ = $J_{H\text{-}1\,H\text{-}2b}$ = 7.5 Hz, H-1), 3.10 (ddd, $J_{H\text{-}2a\,H\text{-}2b}$ = 18 Hz, $J_{H\text{-}2a\,H1}$ = $J_{H\text{-}2a\,H\text{-}3}$ = 7.5 Hz, H-2a), 2.5 (br, NH), 2.30 (s, CH_3), 2.03 (ddd, $J_{H\text{-}2b\,H\text{-}2a}$ = 18 Hz, $J_{H\text{-}2b\,H1}$ = $J_{H\text{-}2b\,H\text{-}3}$ = 7.5 Hz, H-2b). Anal. Calcd for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20. Found : C, 79.48; H, 7.55; N, 12.57.

cis-1-Cyclopentylamino-3-phenyl-2,3-dihydro-1*H*-pyrrolizine (**13b**). By use of the same method outlined for the synthesis of **13a**, **13b** (0.5 g, 71%) was obtained from a reaction of **12b** (0.7 g, 0.002 mol) with sodium borohydride (0.2 g, 0.006 mol): mp 50°C (petroleum ether); ir (KBr) 3295 (NH); ^{1}H-nmr 7.30 (s, 5H-Ø), 6.23 (d, $J_{H\text{-}5\,H\text{-}6}$ = 2.5 Hz, H-5), 6.06 (dd, $J_{H\text{-}6\,H\text{-}7}$ = 4 Hz, $J_{H\text{-}6\,H\text{-}5}$ = 2.5 Hz, H-6), 5.90 (d, $J_{H\text{-}7\,H\text{-}6}$ = 4 Hz, H-7), 5.13 (dd, $J_{H\text{-}3\,H\text{-}2a}$ = $J_{H\text{-}3\,H\text{-}2b}$ = 7.5 Hz, H-3), 4.23 (dd, $J_{H\text{-}1\,H\text{-}2a}$ = $J_{H\text{-}1\,H\text{-}2b}$ = 7.5 Hz, H-1), 3.30 (m, $2CH_2$), 3.10 (ddd, $J_{H\text{-}2a\,H\text{-}2b}$ = 18 Hz, $J_{H\text{-}2a\,H1}$ = $J_{H\text{-}2a\,H\text{-}3}$ = 7.5 Hz, H-2a), 2.5 (br, NH), 2.10 (ddd, $J_{H\text{-}2b\,H\text{-}2a}$ = 18 Hz, $J_{H\text{-}2b\,H1}$ = $J_{H\text{-}2b\,H\text{-}3}$ = 7.5 Hz, H-2b), 1.40 (m, $2CH_2$). Anal. Calcd for $C_{18}H_{22}N_2$: C, 81.16; H, 8.32; N, 10.52. Found : C, 81.17; H, 8.15; N, 10.68.

cis-1-Amino-3-phenyl-2,3-dihydro-1*H*-pyrrolizine (**13c**). A solution of **10** (1.5 g, 0.004 mol) in methanol (50 ml) was bubbled for 2 min at room temperature with an ammonia flow. The reaction mixture was stirred for 10 min and sodium borohydride (0.6 g, 0.016 mol) was then added. The stirring was maintained 1 h at room temperature and the solvent was removed under reduced pressure. The solid residue was taken up in water (50 ml) and the solution was extracted with ether (100 ml). The organic layer was dried over magnesium sulfate and evaporated to dryness to give **13c** as white crystals (0.8 g, 87%): mp 66°C (ether); ir (KBr) 3450-3350 (NH_2); ^{1}H-nmr 7.27 (s, 5H-Ø), 6.17 (d, $J_{H\text{-}5\,H\text{-}6}$ = 2.5 Hz, H-5), 6.00 (dd, $J_{H\text{-}6\,H\text{-}7}$ = 4 Hz, $J_{H\text{-}6\,H\text{-}5}$ = 2.5 Hz, H-6),

5.80 (d, $J_{H\text{-}7\,H\text{-}6}$ = 4 Hz, H-7), 5.10 (dd, $J_{H\text{-}3\,H\text{-}2a} = J_{H\text{-}3\,H\text{-}2b}$ = 7.5 Hz, H-3), 4.27 (dd, $J_{H\text{-}1\,H\text{-}2a} = J_{H\text{-}1\,H\text{-}2b}$ = 7.5 Hz, H-1), 3.13 (ddd, $J_{H\text{-}2a\,H\text{-}2b}$ = 18 Hz, $J_{H\text{-}2a\,H1} = J_{H\text{-}2a\,H\text{-}3}$ = 7.5 Hz, H-2a), 2.9 (br, NH_2), 2.03 (ddd, $J_{H\text{-}2b\,H\text{-}2a}$ = 18 Hz, $J_{H\text{-}2b\,H1} = J_{H\text{-}2b\,H\text{-}3}$ = 7.5 Hz, H-2b). Anal. Calcd for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 13.12. Found : C, 78.60; H, 7.00; N, 13.12.

3-Phenyl-2,3-dihydro-1*H*-pyrrolizin-1-one (**14**). A solution of **10** (2 g, 0.006 mol) in water (100 ml) was adjusted to pH = 11 with sodium hydroxide in pellets. The reaction mixture was stirred at room temperature for 10 min and then extracted with ether (100 ml). The organic layer was washed with water (2 x 50 ml), dried over magnesium sulfate and evaporated to dryness to give **14** as white crystals (1 g, 95%): mp 104°C (ether / hexane); ir (KBr) 1680 (CO); ^{1}H-nmr 7.36 (m, 3H-Ø), 7.13 (m, 2H-Ø), 7.05 (d, $J_{H\text{-}5\,H\text{-}6}$ = 2.5 Hz, H-5), 6.70 (d, $J_{H\text{-}7\,H\text{-}6}$ = 4 Hz, H-7), 6.53 (dd, $J_{H\text{-}6\,H\text{-}7}$ = 4 Hz, $J_{H\text{-}6\,H\text{-}5}$ = 2.5 Hz, H-6), 5.73 (dd, $J_{H\text{-}3\,H\text{-}2a}$ = 9 Hz, $J_{H\text{-}3\,H\text{-}2b}$ = 3 Hz, H-3), 3.80 (dd, $J_{H\text{-}2a\,H\text{-}2b}$ = 18 Hz, $J_{H\text{-}2a\,H\text{-}3}$ = 9 Hz, H-2a), 2.77 (dd, $J_{H\text{-}2b\,H\text{-}2a}$ = 18 Hz, $J_{H\text{-}2b\,H\text{-}3}$ = 3 Hz, H-2b). Anal. Calcd for $C_{13}H_{11}NO$: C, 79.17; H, 5.62; N, 7.10. Found : C, 79.11; H, 5.70; N, 7.13.

cis-1-Hydroxy-3-phenyl-2,3-dihydro-1*H*-pyrrolizine (**15**). To a stirred solution of **14** (1.1 g, 0.006 mol) in methanol (20 ml) was added sodium borohydride (0.85 g, 0.024 mol). The reaction mixture was stirred at room temperature for 1 h and the solvent was removed under reduced pressure. The solid residue was taken up in water (10 ml) and the insoluble mass was filtered, washed with water (2 x 5 ml) and dried to give **15** as white crystals (0.95 g, 86%): mp 65°C (ether / petroleum ether); ir (KBr) 3240 (OH); ^{1}H-nmr 7.33 (s, 5H-Ø), 6.33 (d, $J_{H\text{-}5\,H\text{-}6}$ = 2.5 Hz, H-5), 6.13 (dd, $J_{H\text{-}6\,H\text{-}7}$ = 4 Hz, $J_{H\text{-}6\,H\text{-}5}$ = 2.5 Hz, H-6), 5.93 (d, $J_{H\text{-}7\,H\text{-}6}$ = 4 Hz, H-7), 5.3 (br, OH), 5.17 (m, H-1 and H-3), 3.20 (ddd, $J_{H\text{-}2a\,H\text{-}2b}$ = 18 Hz, $J_{H\text{-}2a\,H1} = J_{H\text{-}2a\,H\text{-}3}$ = 9 Hz, H-2a), 2.17 (ddd, $J_{H\text{-}2b\,H\text{-}2a}$ = 18 Hz, $J_{H\text{-}2b\,H1} = J_{H\text{-}2b\,H\text{-}3}$ = 3 Hz, H-2b). Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found : C, 78.23; H, 6.67; N, 7.08.

1-Oximino-3-phenyl-2,3-dihydro-1*H*-pyrrolizine (**16**). To a stirred solution of **14** (1.8 g, 0.009 mol) in ethanol (15 ml) was added a solution of hydroxylamine hydrochloride (2.5 g, 0.036 mol) in water (10 ml). The reaction mixture was refluxed for 1 h and ethanol was removed under reduced pressure. The precipitate appeared was filtered, washed with water and dried to give **16** as white crystals (1.8 g, 93%): mp 173°C (methanol); ir (KBr) 3280-3100 (OH), 1670 (CN); ^{1}H-nmr 10.50 (s, OH), 7.33 (m, 3H-Ø), 7.05 (m, 2H-Ø), 6.70 (d, $J_{H\text{-}5\,H\text{-}6}$ = 2.5 Hz, H-5), 6.54 (d, $J_{H\text{-}7\,H\text{-}6}$ = 4 Hz, H-7), 6.27 (dd, $J_{H\text{-}6\,H\text{-}7}$ = 4 Hz, $J_{H\text{-}6\,H\text{-}5}$ = 2.5 Hz, H-6), 5.64 (dd, $J_{H\text{-}3\,H\text{-}2a}$ = 9 Hz, $J_{H\text{-}3\,H\text{-}2b}$ = 3 Hz, H-3), 3.74 (dd, $J_{H\text{-}2a\,H\text{-}2b}$ = 18 Hz, $J_{H\text{-}2a\,H\text{-}3}$ = 9 Hz, H-2a), 2.91 (dd, $J_{H\text{-}2b\,H\text{-}2a}$ = 18 Hz, $J_{H\text{-}2b\,H\text{-}3}$ = 3 Hz, H-2b). Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.57; H, 5.70; N, 13.20. Found : C, 73.40; H, 5.72; N, 13.22.

4-Phenyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazin-1-one (**17**).

Method A : A solution of **16** (0.8 g, 0.004 mol) in polyphosphoric acid (20 ml) was heated at 90°C for 15 min. The reaction mixture was poured into iced water (60 ml) and the solution was extracted with chloroform (100 ml). The organic layer was dried over calcium chloride and evaporated to dryness to give **17** as white crystals (0.5 g, 63%): mp 166°C (chloroform); ir (KBr) 3200 (NH), 1630 (CO); ^{1}H-nmr 7.54 (d, $J_{NH\,H\text{-}3b}$ = 4 Hz, NH), 7.34 (m, 3H-Ø), 6.97 (m, 2H-Ø), 6.88 (d, $J_{H\text{-}8\,H\text{-}7}$ = 4 Hz, H-8), 6.77 (d, $J_{H\text{-}6\,H\text{-}7}$ = 2.5 Hz, H-6), 6.25 (dd, $J_{H\text{-}7\,H\text{-}8}$ = 4 Hz, $J_{H\text{-}7\,H\text{-}6}$ = 2.5 Hz, H-7), 5.57 (dd, $J_{H\text{-}4\,H\text{-}3a} = J_{H\text{-}4\,H\text{-}3b}$ = 4 Hz, H-4), 3.91 (dd, $J_{H\text{-}3a\,H\text{-}3b}$ = 14 Hz, $J_{H\text{-}3a\,H\text{-}4}$ = 4 Hz, H-3a), 3.63 (ddd, $J_{H\text{-}3b\,H\text{-}3a}$ = 14 Hz, $J_{H\text{-}3b\,H\text{-}4} = J_{H\text{-}3b\,NH}$ = 4 Hz, H-3b). Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.57; H, 5.70; N, 13.20. Found : C, 73.52; H, 5.72; N, 13.14.

Method B : A solution of **20** (0.5 g, 0.0018 mol) in a 10N aqueous hydrochloric acid solution (20 ml) was refluxed for 30 min. The solvent was then removed under reduced pressure and the oily residue was dissolved in a 1N aqueous sodium hydroxide solution. The solution was extracted with chloroform (100 ml). The organic layer was washed with water (2 x 50 ml), dried over calcium chloride and evaporated to dryness to give **17** (0.25 g, 65%).

3-Phenyl-3-(pyrrol-1-yl)propionyl azide (**18**). To a stirred solution of **6** (10 g, 0.047 mol) in acetone (100 ml) at 0°C was added dropwise triethylamine (6.5 ml, 0.047 mol). After 30 min ethyl chloroformate (4.5 ml, 0.047 mol) was added and 30 min later, a solution of sodium azide (3.1 g, 0.047 mol) in water (5 ml) was also added to the reaction mixture which was stirred at 0°C for 2 h. It was then poured into water (300 ml) and the precipitate appeared was filtered, washed with water (2 x 100 ml) and dried to give **18** which was immediately used without other purification (8.9 g, 80%): mp 100°C; ir (KBr) 2100 (N_3), 1675 (CO).

N-Ethyl-N-[(α-pyrrol-1-yl)phenetyl]carbamate (**19**). A solution of **18** (2 g, 0.008 mol) in ethanol (150 ml) was refluxed for 2 h. The solvent was removed under reduced pressure and the oily residue was crystallized to give **19** as white crystals (1.9 g, 88%) : mp 114°C (ether); ir (KBr) 3300 (NH), 1685 (CO); ^{1}H-nmr 7.27 (s, H-Ø), 7.2 (br, NH), 6.90 (m, 2H-αPyr), 6.03 (m, 2H-βPyr), 5.33 (t, $J_{CH\ CH2}$ = 9 Hz, CH), 4.00 (q, $J_{CH2\ CH3}$ = 7.5 Hz, OCH_2), 3.70 (dd, $J_{CH2\ CH}$ = $J_{CH2\ NH}$ = 9 Hz, CH_2N), 1.10 (t, $J_{CH3\ CH2}$ = 7.5 Hz, CH_3). Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.75; H, 7.02; N, 10.84. Found : C, 69.67; H, 6.90; N, 10.79.

2-Ethoxycarbonyl-4-phenyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazin-1-one (**20**). To a stirred solution of **19** (2 g, 0.008 mol) in toluene (20 ml) was added a 20% solution of phosgene in toluene (30 ml). The reaction mixture was refluxed for 90 min and then evaporated to dryness. The oily residue was crystallized to give **20** as white crystals (1.5 g, 68%): mp 122°C (ether); ir (KBr) 1750 and 1670 (CO); ^{1}H-nmr 7.33 (m, 3H-Ø), 7.02 (m, 2H-Ø, H-6 and H-8), 6.33 (dd, $J_{H\text{-}7\ H\text{-}8}$ = 4 Hz, $J_{H\text{-}7\ H\text{-}6}$ = 2.5 Hz, H-7), 5.71 (dd, $J_{H\text{-}4\ H\text{-}3a}$ = $J_{H\text{-}4\ H\text{-}3b}$ = 4 Hz, H-4), 4.46 (dd, $J_{H\text{-}3a\ H\text{-}3b}$ = 14 Hz, $J_{H\text{-}3a\ H\text{-}4}$ = 4 Hz, H-3a), 4.23 (dd, $J_{H\text{-}3b\ H\text{-}3a}$ = 14 Hz, $J_{H\text{-}3b\ H\text{-}4}$ = 4 Hz, H-3b), 4.06 (q, $J_{CH2\ CH3}$ = 5 Hz, CH_2), 1.09 (t, $J_{CH3\ CH2}$ = 5 Hz, CH_3). Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found : C, 67.64; H, 5.80; N, 9.74.

REFERENCES

1. P. Dallemagne, S. Rault, and M. Robba, Bull. Soc. Chim. Fr., 1987, 6, 1079.

2. P. Dallemagne, O.N. Tembo, S. Rault, and M. Robba, Bull. Soc. Chim. Fr., 1989, 1, 98.

3. S. Rault, O. N. Tembo, P. Dallemagne, and M. Robba, Heterocycles, 1991, 7, 1301.

4. N. Clauson-Kaas and Z. Tyle, Acta Chem. Scand., 1952, 6, 667.

5. N. Clauson-Kaas and N. Elming, Acta Chem. Scand., 1952, 6, 867.

6. P. Dallemagne, J. C. Pilo, S. Rault, M. Robba, M. Saux, and A. Carpy, Heterocycles, 1992, 34, 1317.

Received, 5th April, 1993