2-AMINOETHYLIMIDAZOLES. SYNTHESIS OF 1,4-DIMETHYL-5-PHENYL-2-[2-(4-PHENYLPIPERAZINYL)-ETHYL]IMIDAZOLE

Emilio Toja*, Pietro Ferrari, and Giorgio Tarzia

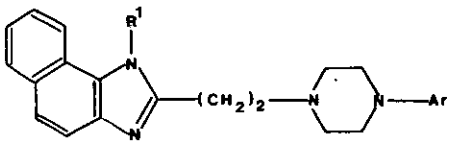
Lepetit Research Center, Via R. Lepetit, 34 - 21040 Gerenzano (VA), Italy

*Present address: Roussel Maestretti - Via Gran Sasso, 18 - 20131 Milano, Italy

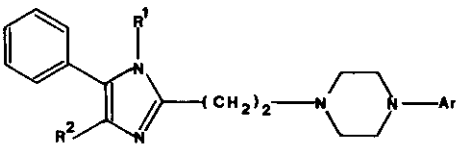
Abstract - A novel synthesis of N^1-methyl-1-phenyl-1,2-propanediamine (9) from 2-benzylamino-1-phenylpropanone (3) is reported. Condensation of this diamine with ethyl ethoxycarbonylacetimidate hydrochloride and dehydrogenation of the resulting imidazolidine (10) gives ethyl 2-(1,4-dimethyl-5-phenylimidazol-2-yl)acetate (11), suitable starting material for the synthesis of imidazoles with a 2-aminoethyl chain. The synthesis of the 2-[2-(4-phenylpiperazinyl)ethyl] derivative 14 is specifically reported.

We have recently reported that 1-alkylnaphth[1,2-d]imidazoles bearing an arylpiperazinoethyl chain in the 2-position 1 possess an oral and long-lasting antihypertensive activity in conscious normotensive and renal hypertensive dogs, without CNS depressant effects[1]. Information is available in the literature[2] on the adrenolytic and sedative properties of the structurally related 2-arylpiperazinoethylbenzimidazoles. Thus, in continuation of our program to investigate structures with possible dissociation between central effects and cardiovascular activity, we turned our attention to the non-condensed 2-arylpiperazinoethyl-1,4-dialkyl-5-phenylimidazoles 2.

We describe in this paper the synthesis of the parent compound of class 2 having $R^1=R^2=CH_3$ and $Ar=C_6H_5$ (14 in the Synthetic Scheme).



1



2

R^1,R^2 = alkyl groups; Ar = substituted phenyl

2-Benzylamino-1-phenylpropanone 3, prepared from 2-bromopropiophenone and benzylamine according to the reported procedure[3], was cyclized to the imidazol-2-one 4 with potassium cyanate and hydrochloric acid. Catalytic hydrogenation of the double bond required rather drastic conditions (acetic acid as solvent; 50°C and 20 bar) which however left unchanged the protecting benzyl group. The sodium salt of the imidazolidin-2-one 5 was methylated by means of methyl iodide in dimethylformamide to give 6. Methylation of 4 by this procedure gave 1-benzyl-3,5-dimethyl-4-phenylimidazole-2-one 4a, which remained unchanged under the same experimental conditions used for the hydrogenation of compound 4 to compound 5. Another unexpected finding was that 6 was recovered unchanged after prolonged reflux in ethanol containing excess 37% HCl. Thus, diamine 8 had to be prepared by prior reduction of 6 with lithium aluminum hydride in tetrahydrofuran and subsequent cleavage of the imidazolidine 7 by reflux in 10% aqueous hydrochloric acid. A controlled catalytic hydrogenation of 8 gave the diamine 9 in a practically quantitative yield without cleavage of the second benzylic bond present in the molecule. Reductive amination of 3 to 8 was not considered due to the drastic conditions (150°C, 12 h, autoclave) reported[4] for the synthesis of α-amino-isobutyrophenone-isopropylimine from isopropylamine and α-aminoisobutyrophenone.

Our synthetic pathway leading to 9 substantially modifies the route reported for the isomeric N^2--methyl-1-phenyl-1,2-propanediamine[5,6]. Moreover, by properly choosing the starting bromoketone, any N^1-alkyl-1-aryl-1,2-propanediamine could in principle be obtained. An alternative procedure to synthesize a mixture of the threo and erythro forms of 9 from 2-amino-1-phenylpropanol has been proposed but without description of the experimental data[7]. It is worth mentioning that our route affords the erythro isomer of 9 only as the catalytic hydrogenation of the double bond of compound 4 leads to a cis disposition of the C_4-H and C_5-H protons in compound 5 and the subsequent transformations from 5 to 9, do not modify this situation. This is shown by the $J_{4,5}$ values of compounds 5

and 6 (8.5 Hz) and of compound 7 (9.5 Hz) which are consistent with those extimated from the Karplus equation [8] for a cis disposition of the C_4-H and C_5-H protons (J = 6-15 Hz; $\Phi_{4,5}$ = 5°-15°) but not with those expected for a trans disposition of the C_4-H and C_5-H protons (J = 1.3 Hz; $\Phi_{4,5}$ = 100°--120°). The erythro form of 9 is indicated also by its $J_{1,2}$ coupling constant value ($J_{1,2}$ = 5.0 Hz) which agrees with the values reported for the $J_{1,2}$ coupling constant of the erythro form of 1,2--methylamino-1-phenylethane and of 1,2-methylamino-1-phenylpropane ($J_{1,2}$ = 4.5 Hz) but not with the values reported for the $J_{1,2}$ coupling constant of the threo form ($J_{1,2}$ = 8.7 Hz) of these two compounds.[7]

Condensation of 9 with ethyl ethoxycarbonylacetimidate hydrochloride[9], according to Yamazaki's modification[10], gave the imidazolidine 10. No trace of the tautomeric imidazoline was evidentiated in the nmr spectrum, in which only the vinylic proton and NH were apparent. As a consequence, the dehydrogenation of 10 to imidazole 11 requires forcing conditions and was in fact obtained by reflux in acetic acid with 30% palladium on carbon. A concomitant thermal decarboxylation with formation of 12[11] in a 13% yield was observed. Nickel dioxide[12] in refluxing benzene and barium manganate[13] in refluxing dichloromethane were ineffective. Selenium powder[13] in diphenyl at 250°C gave predominantly 12 and dimeric products.

The transformation of 11 into 14 was obtained by two routes in about the same yield. In the first route, 11 was condensed with the lithium salt of N-phenylpiperazine and the resulting amide 13 was reduced by means of lithium aluminum hydride to 14. In the second route, 11 was reduced by means of lithium aluminum hydride to the 2-hydroxyethyl derivative 15 which was reacted with thionyl chloride and then with phenylpiperazine.

When submitted to a general pharmacological screening, 14 citrate showed marginal CNS depressant effects not accompanied however by cardiovascular activity. Moreover the acute oral toxicity was increased with respect to the corresponding compound 1. For these reasons, no other compound of this series was synthesized. Nonetheless the synthetic route presented in this paper could in principle be applied to the synthesis of whatever compound 2 by properly choosing the starting 2-bromoketone and the alkylating agent of the imidazole nitrogen.

EXPERIMENTAL

Melting points were determined on a Buchi 510 capillary apparatus and are uncorrected. The ir spectra were measured in nujol mull or as films with a Perkin-Elmer 157 spectrophotometer. ^1H nmr spectra were recorded on a Bruker WH 270 or WP 60 spectrometer. Differential scanning calorimetry

curves (DSC) were obtained on a TA 2000 Mettler thermal analyzer, in a normal pan, with nitrogen flow of 25 ml/min and a heating rate of 5°C/min. Tlc determinations were carried out on Merck silica gel plates 60 F254. Microanalyses were performed by the Analytical Department of Gruppo Lepetit.

1-Benzyl-5-methyl-4-phenylimidazol-2-one (4).

A solution of potassium cyanate (113.55 g, 1.4 mol) in water (250 ml) was dropped into a stirred solution of 2-benzylamino-1-phenylpropanone hydrochloride[3] (3) (193 g, 0.7 mol) in water (3750 ml). The reaction was heated at reflux for 1 h then 37% HCl (69 ml, 0.7 mol) was added slowly during 1 h while maintaining the reflux. The resulting precipitate was collected by filtration at room temperature, washed with water and vacuum dried to yield 147 g (79%) of 4:mp 219-226 °C which was used as such in the next step. An analytical sample was obtained by recrystallization from 95% ethanol:mp 227-229 °C; ir (nujol) 1690 (CO)cm^{-1}; ^1H nmr (DMSO-d_6) δ 2.10 (s, 3H, CH_3), 4.88 (s, 2H, CH_2), 7.20-7.60 (m, 10H, aromatic), 10.57 (s, 1H, NH). Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.36; H, 6.13; N, 10.69.

1-Benzyl-3,5-dimethyl-4-phenyl-4-phenylimidazol-2-one (4a)

A 55% dispersion of sodium hydride (1.59 g, 0.037 mol) was added portionwise to a cooled (0+5°C solution of 4 (7.0 g, 0.026 mol) in dimethylformamide (250 ml) 30 min. After completing the addition of the sodium hydrate, a solution of methyl iodide (2.12 ml, 4.83 g, 0.037 mol) in dimethylformamide (25 ml) was added (0+5°C) during 30 min, and the resulting mixture was allowed to react for 1 h at room temperature. The reaction mixture was quenched with ice-water (2 kg) and then extracted with ethyl acetate (300 x 3 ml). The organic layer was washed with water (300 x 3) dried over $MgSO_4$, filtered and evaporated under vacuum to yield 5.9 g (80% y) of an oily compound, ir (film) 1695 (CO)cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.97 (s, 3H, NCH_3), 4.97 (s, 2H, CH_2), 7.37 m, 10H, aromatic). This material was submitted without further purification to catalytic hydrogenation with 30% palladium on carbon in acetic acid as described for 5 and it was recovered unchanged under these conditions.

1-Benzyl-5-methyl-4-phenylimidazolidin-2-one (5).

A solution of 4 (45 g, 0.17 mol) in glacial acetic acid (500 ml) was hydrogenated at 50 °C and 20 bar in the presence of 10% palladium on carbon (20 g) for 6 h. The catalyst was filtered out and the solvent was evaporated under reduced pressure. The residue was taken up with toluene (100 ml) and the solvent again evaporated. The residue was triturated with water, recovered by filtration and vacuum dried to yield 37.5 g (82%) of 5 which was used as such in the next step. An analytical sample was obtained by recrystallization from acetone:mp 151-152 °C; ir (nujol) 3220, 3100 (NH), 1700 (CO)cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.67 (d, 3H, J= 7.0 Hz, CH_3), 3.87 (m, 1H, C_5-H), 4.80 (d, 1H, J= 8.5 Hz,

C_4-H), 4.00 and 4.93 (2d, 2H, J= 15.0 Hz, CH_2), 5.34 (br s, 1H, NH), 7.33 (m, 10H, aromatic). Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.63; H, 6.92; N, 10.64.

1-Benzyl-3,5-dimethyl-4-phenylimidazolidin-2-one (6).

A 55% dispersion of sodium hydride in mineral oil (12.9 g, 0.29 mol) was repeatedly washed with dry benzene under argon to remove the oil. Dimethylformamide (670 ml) was added under stirring at 0-5 °C followed by portionwise addition of 5 (71.37 g, 0.26 mol). The reaction was stirred under argon at 0-5 °C for 2 h, until the evolution of hydrogen ceased. A solution of methyl iodide (17 ml, 0.27 mol) in DMF (80 ml) was dropped and the mixture was allowed to reach the room temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed on a silica gel column eluted with ethyl acetate: methylene chloride 1:1 to yield 67.8 g (93%) of 6. An analytical sample was obtained by addition of petroleum ether to a solution of 6 in ether:mp 62-64 °C; ir (nujol) 1690 (CO)cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 0.67 (d, 3H, J= 7.0 Hz, CH_3), 2,72 (s, 3H, NCH_3), 3.71 (m, 1H, C_5-H), 4.44 (d, 1H, J=8.5 Hz, C_4-H), 4.00 and 4.89 (2d, 2H, J=15.0 Hz, CH_2), 7.07-7.44 (m, 10H, aromatic). Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.03; H, 7.30; N, 10.11.

1-Benzyl-3,5-dimethyl-4-phenylimidazolidine (7).

To a stirred dispersion of lithium aluminum hydride (2.4 g, 60 mmol) in dry tetrahydrofuran (180 ml) at 0-5 °C was added in portions 6 (16.6 g, 59 mmol). The reaction mixture was cautiously heated at 40 °C and then immediately cooled in order to control the exothermic reaction which suddenly started and maintain the temperature around 40 °C. Decomposition of the hydride was carried out at 0°C by subsequent additions of water (2.4 ml), 20% NaOH (2.4 ml), and again water (7.2 ml). The inorganic precipitate was filtered off and washed with ether. The solution was evaporated and the residue was chromatographed on a silica gel column eluted with ethyl acetate:cyclohexane 1:1 to yield 13.8 g (88%) of 7 as an oil, ir (film) 3050, 3030, 2980, 2910, 2840, 2800, 2650 (C-H and C-N)cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 0.64 (d, 3H, J=7.0 Hz, CH_3), 2.29 (s, 3H, NCH_3), 3.18 (m, 1H, C_5-H), 3.69 (d, 1H, J= 9.5 Hz, C_4-H), 3.62 and 4.04 (2d, 2H, J= 13.5 Hz, CH_2Ph), 3.02 and 4.11 (2d, 2H, J= 4.5 Hz, NCH_2N), 7.38-7.64 (m, 10H, aromatic). Anal. Calcd for $C_{18}H_{22}N_2$: C, 81.16; H, 8.32; N, 10.52. Found: C, 81.22; H, 8.40; N, 10.40.

N^2-Benzyl-N^1-methyl-1-phenyl-1,2-propanediamine (8).

A solution of 7 (13.2 g, 49 mmol) in 10% HCl (1300 ml) was heated at reflux under nitrogen for 14 h. The solution was evaporated to dryness, the residue taken up with methylene chloride (250 ml) and basified with 32% NH_4OH at 0 °C. The organic phase was dried (K_2CO_3) and evaporated. Unreacted 7

(0.8 g) was recovered by chromatography on a silica gel column eluted with ethyl acetate:cyclohexane 1:1, while 8 (11.2 g, 89%) was eluted with methanol as an oil, ir (film) 3350 (NH)cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.96 (d, 3H, J= 6 Hz, CH_3), 1.67 (br s, 2H, NH), 2.26 (s, 3H, NCH_3), 2.89 (m, 1H, C_2-H), 3.56 (d, 1H, J= 6 Hz, C_1-H), 3.78 and 3.89 (2d, 2H, J 12 Hz, CH_2), 7.37 (m, 10H, aromatic). Anal. Calcd for $C_{17}H_{22}N_2$: C, 80.27; H, 8.72; N, 11.01. Found: C, 80.32; H, 8.80; N, 11.10.

N^1-Methyl-1-phenyl-1,2-propanediamine (9).

A solution of 8 (11.2 g, 44 mmol) in absolute ethanol (300 ml) was acidified with a 3.34 M solution of HCl in ethanol (26.5 ml, 88 mmol) and hydrogenated at room temperature and atmospheric pressure in the presence of 10% palladium on carbon (2.4 g). The hydrogenation was stopped when 1100 ml (46.1 mmol.) of hydrogen were absorbed. The catalyst was filtered out and the solvent was evaporated under reduced pressure. The residue was taken up in methylene chloride (250 ml) and basified with 32% NH_4OH. The organic phase was dried (K_2CO_3) and evaporated to give 7.2 g (99%) of 9 as an oil. A sample was distilled at 60-63 °C (0.8 mm Hg), ir (film) 3300 (NH), 1600 (NH_2)cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.00 (d, 3H, J= 6 Hz, CH_3), 1.30 (br s, 3H, NH and NH_2), 2.27 (s, 3H, NCH_3), 3.13 (m, 1H, C_2-H), 3.33 (d, 1H, J= 5.0 Hz, C_1-H), 7.30 (br s, 5H, aromatic). The dihydrochloride of 9 was crystallized from ethanol-ether and melted at 244 °C with decomposition. Anal. Calcd for $C_{10}H_{18}Cl_2N_2$: C, 50.64; H, 7.65; N, 11.81; Cl, 29.90. Found: C, 50.35; H, 7.59; N, 11.49; Cl, 29.51.

Ethyl 1,4-Dimethyl-5-phenyl-2-imidazolidinylideneacetate (10).

Sodium hydroxide (3.9 g, 97 mmol) was added under nitrogen at 0-5 °C to a stirred solution of 9 dihydrochloride (23.08 g, 97 mmol) in absolute ethanol (150 ml) and the stirring was continued up to the complete dissolution of the resulting monohydrochloride. Ethyl ethoxycarbonylacetimidate hydrochloride[8] (19.6 g, 0.1 mol) was added in one portion and the stirring was continued at 0-5 °C for 6 h, at room temperature for 20 h and at 40 °C for 30 min. The reaction mixture was cooled to room temperature and the inorganic salts were removed by filtration. The filtrate was evaporated under reduced pressure and the residue redissolved in water (40 ml) and basified with 32% NH_4OH. The solid which precipitated was collected by filtration and vacuum dried to give 20.14 g (79%) of 10. The analytical sample was recrystallized from cyclohexane: mp 103-104 °C; ir (nujol) 3400 (NH) 1640, 1590 (C=C-CO)cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.78 (d, 3H, J= 7.0 Hz, CH_3), 1.29 (t, 3H, J= 6 Hz, CH_3 ester), 2.64 (s, 3H, NCH_3), 4.10 (q, 2H, J=6 Hz, CH_2 ester), 4.10 (s, 1H, HC=CO), 4.13 (m, 1H, C_4-H), 4.53 (d, 1H, J= 8.5 Hz, C_5-H), 7.16 and 7.38 (2m, 5H, aromatic), 7.51 (br s, 1H, NH). Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.23; H, 7.91; N, 10.83.

Ethyl 2-(1,4-Dimethyl-5-phenylimidazol-2-yl)acetate (11) and 5-Phenyl-1,2,4-trimethylimidazole Hydrochloride (12).

Imidazolidine 10 (19 g, 73 mmol) was added under nitrogen to a dispersion of 30% palladium on carbon (10 g) in glacial acetic acid (60 ml) and the reaction was stirred at reflux for 80 min until tlc (chloroform:methanol 9:1) revealed disappearance of the starting compound. The catalyst was quickly filtered out under nitrogen at about 80 °C and the solvent was evaporated under reduced pressure. The residue was taken up with water (40 ml), the resulting solution brought to pH 7 with 32% NH_4OH and let stand at 5 °C overnight. The precipitate was collected by filtration and vacuum dried to give 14.3 g of 11. The remaining solution was basified to pH 9 with 32% NH_4OH and extracted with ether. The residue of the evaporation of the solvent was chromatographed on a silica gel column eluted with cyclohexane:acetone 1:1 to give 1 g of 11 and 1.73 g (13%) of 12 as an oil. Overall yield for 11:81%. An analytical sample of 11 was obtained by recrystallization from pentane:mp 60-61 °C; ir (nujol) 1720 (CO)cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.27 (t, 3H, J= 6 Hz, CH_3 ester), 2.20 (s, 3H, CH_3), 3.47 (s, 3H, NCH_3), 3.84 (s, 2H, CH_2CO), 4.22 (9, 2H, J= 6 Hz, CH_2 ester), 7.27-7.56 (m, 5H, aromatic). Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.75; H, 7.02; N, 10.84. Found: C, 69.89; H, 7.05; N, 10,75.

An analytical sample of 12 hydrochloride was obtained by a double recrystallization from ethanol--ether:mp 216-218 °C; ir (nujol) 2500 (NH^+)cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.30 (s, 3H, CH_3-C4), 2.84 (s, 3H, CH_3-C2), 3.64 (s, 3H, NCH_3), 7.33 and 7.54 (2m, 5H, aromatic), 15.68 (brs, 1H, NH^+).

Anal. Calcd for $C_{12}H_{15}Cl\,N_2$:C, 64.71; H, 6.79; N, 12.58. Found: C, 64.99; H, 6.83; N, 12.64.

1-[2-(1,4-Dimethyl-5-phenyl-1H-imidazol-2-yl)acetyl]-4-phenylpiperazine (13).

A 15% solution of buthyl lithium in hexane (9.5 ml, 19 mmol) was dropped into a solution of N-phenylpiperazine (3 ml, 19 mmol) in dry ether (25 ml) and stirring was continued at 0-5 °C under nitrogen for 3 h. A solution of 11 (2.43 g, 9.4 mmol) in dry ether (25 ml) was added and stirring was continued for 21 h at room temperature. The solvent was evaporated, the residue was triturated with water and filtered to afford 2.66 g (75%) of 13 in the form of the monohydrate, used as such in the next step. A sample recrystallized from t-butyl methyl ether melted at 93-94 °C. An analytical sample was obtained by a second crystallization from ethyl acetate: mp 109-111 °C; ir (nujol) 1650 (NCO)$^{cm-1}$; ^1H nmr ($CDCl_3$) δ 2.16 (s, 3H, CH_3), 3.53 (s, 3H, NCH_3) 3.96 (s, 2H, CH_2CO), 3.16, 3.78 and 3.96 (3m, 8H, CH_2N), 6.93, 7.33 and 7.47 (3m, 10H, aromatic). Anal. Calcd for $C_{23}H_{26}N_4O$. H_2O:C, 70.38; H, 7.19; N, 14.27. Found: C, 70.51; H, 7.02; N, 14.26.

DSC analysis revealed that the hydrated form slowly loosed water in the interval 95-140 °C giving rise to the anhydrous compound which remelted at 146-148 °C.

1,4-Dimethyl-5-phenyl-2-[2-(4-phenylpiperazinyl)ethyl]imidazole (14).

Lithium aluminum hydride (15 g, 40 mmol) was added to a dispersion of 13 monohydrate (2.6 g, 6.6 mmol) in ether (50 ml) and the reaction was stirred at reflux under nitrogen for 3 h. Decomposition of the hydride was carried out at 0 °C by subsequent additions of water (1.5 ml), 20% NaOH (1.5 ml) and again water (4.5 ml). The inorganic precipitate was filtered off and washed with methylene chloride. The solvent was evaporated and the residue was chromatographed on a silica gel column eluted with chloroform:methanol 95:5 to yield 1.67 g (70%) of 14. An analytical sample was obtained by recrystallization from t-butyl methyl ether:mp 131-132 °C; ir (nujol) 1610, 1590, 1500 (C=C and C=N)cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.20 (s, 3H, CH_3), 2.76, 2.96 and 3.22 (3m, 12H, CH_2), 3.44 (s, 3H, NCH_3), 6.9-7.5 (m, 10H, aromatic). Anal. Calcd for $C_{23}H_{28}N_4$: C, 76.63; H, 7.83; N, 15.54. Found: C, 76.70; H, 8.00; N, 15.62.

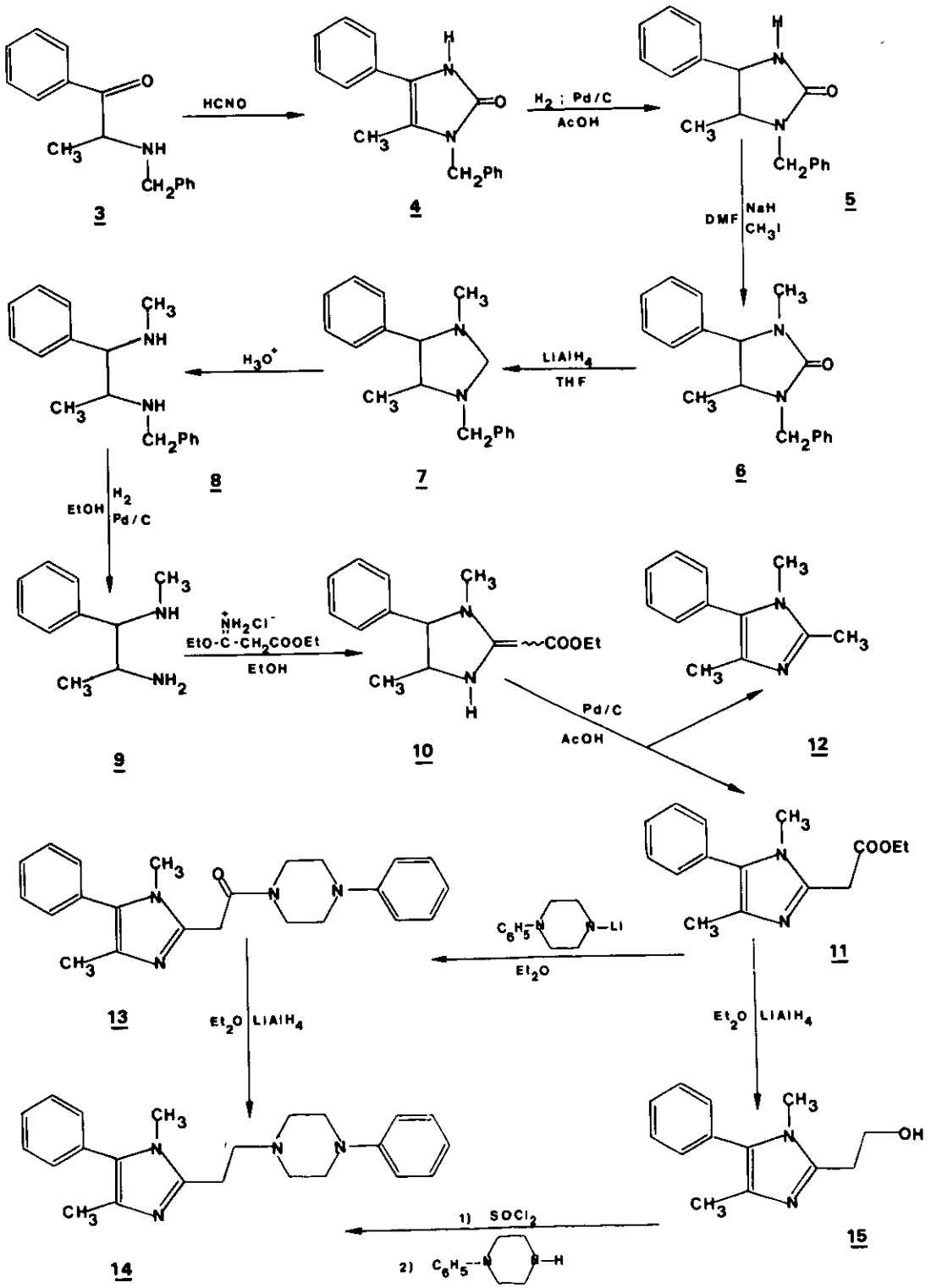
Compound 14 was submitted to the pharmacological screening in the form of citrate which was prepared in a 89% yield by addition of an equimolar amount of citric acid monohydrate, dissolved in the minimum volume of ethanol, to a boiling solution of 14 in ethanol (1 mmol in 5 ml); mp 162 °C with decomposition. Anal. Calcd for $C_{29}H_{36}N_4O_7$: C, 63.03; H, 6.57; N, 10.14. Found: C, 62.73; H, 6.55; N, 10.11.

Alternative Procedure for the Preparation of 14.

Compound 11 (7.75 g, 30 mmol) was added in portions at 0-5 °C under nitrogen to a stirred dispersion of lithium aluminum hydride (3.6 g, 90 mmol) in dry ether (150 ml). The reaction was stirred as long as it reached room temperature. Decomposition of the hydride was carried out at 0 °C by subsequent additions of water (3.6 ml), 20% NaOH (3.6 ml) and again water (10.8 ml). The inorganic precipitate was filtered off and washed with methylene chloride. The solvents were evaporated to afford 6.3 g (97%) of 15. An analytical sample was obtained by recrystallization from ethyl acetate: mp 120-122 °C; ir (nujol) 3150 (OH)cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.18 (s, 3H, CH_3), 2.91 (t, 2H, J= 6 Hz, $CH_2C=N$), 3.42 (s, 3H, NCH_3), 4.09 (t, 2H, J= 6 Hz, CH_2OH), 5.28 (br s, 1H, OH), 7.27-7.51 (m, 5H, aromatic). Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.45; N, 12.95. Found: C, 72.07; H, 7.58; N, 12.90.

Thionyl chloride (1.84 ml, 24 mmol) was dropped into a solution of 15 (4.8 g, 22 mmol) in chloroform (85 ml) and the reaction was heated at reflux for 15 min. The solvent was evaporated under reduced pressure, the residue taken up with water (40 ml) and the solution was basified with 32% NH_4OH. The solid was collected by filtration, dried in vacuo and redissolved in n-amylalcohol (74 ml). N-phenylpiperazine (8.38 g, 49 mmol) was added and the solution was heated at reflux under nitrogen for 2 h. The solvent was evaporated under reduced pressure and the residue was triturated at about 90 °C with water (40 ml) up to obtaining a fine dispersion which was filtered to afford 7.14 g (89%) of 14.

Scheme


HCNO
H2 ; Pd/C
AcOH
DMF NaH CH3I
LiAlH4
THF
H3O+
EtOH H2 Pd/C
NH2Cl
EtO-C-CH2COOEt
EtOH
Pd/C
AcOH
Et2O LiAlH4
1) SOCl2
2)
3
4
5
6
7
8
9
10
11
12
13
14
15

REFERENCES AND NOTES

1. E. Toja, G. Di Francesco, D. Barone, E. Baldoli, N. Corsico and G. Tarzia, Eur. J. Med. Chem., in press.
2. S. Archer, US Patents 3362956 and 3472854; Chem. Abstr., 1968, 69, 10467 and 1970, 72, 55505.
3. S.D. Wilson and L. Sun, J. Chinese Chem. Soc., 1934, 2, 243; Chem. Abstr., 1935, 29, 758.
4. G. Bittner, H. Witte, G. Hesse, Liebig's Ann. Chem., 1983, 713, 1.
5. R. Duschinsky, L.A. Dolan, L.O. Randall and G. Lehmann, J. Am.C hem. Soc., 1947, 69, 3150.
6. R. Duschinsky, US Patent 2514380; Chem. Abstr., 1950, 44, 10734.
7. P. Savignac, M. Dreux and J. Chenault, C.R. Acad. Sci.,Ser. C, 1972, 274, 1099.
8. L.M. Jackman, S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Second Edition Pergamon Press Inc., New York, 1969.
9. D.J. Collins, J. Chem. Soc., 1963, 1337.
10. T. Yamazaki, K. Matoba, T. Imai and R.N. Castle, J.Heterocyclic Chem., 1979, 16, 517.
11. The picrate has been prepared from 2,5-dimethyl-4-phenyloxazole by quaternization with MeO_3SF and reaction of the product with EtOH-NH_3 as reported by: Y. Kikugawa and L.A. Cohen, Chem. Pharm. Bull., 1976, 24, 3205.
12. K.S. Balachandran, I. Bhatnagar and M.V. George, J.Org.Chem., 1968, 33, 3891.
13. J.L. Hughey, S. Knapp and H. Schugar, Synthesis, 1980, 489.
14. R.E. Klem, H.F. Skinner, H. Walba and R.W. Isensee, J.Heterocyclic Chem., 1970, 7, 403.

Received, 9th March, 1987