CONVERSION OF IMIDAZO[1,2-a]PYRIDINES INTO PYRIDO[1,2-e]PURINES

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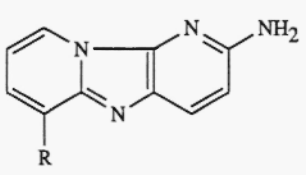
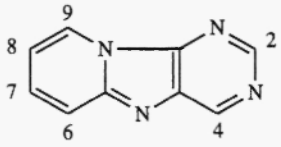
Abstract- Intramolecular cyclization of 2-acylated amine, carbamoyl and 3-aminoimidazo[1,2-*a*]pyridine-2-carbonitrile allows access to pyrido[1,2-*e*]purines.

Aminodipyrido[1,2-*a*:3',2'-*d*]imidazoles (Glu-P-1 and Glu-P-2 1a.b), isosteric compounds of 2-aminofluorene, were recently identified as highly mutagenic compounds (1). These molecules modify DNA by intercalation between base pairs or covalent binding to C-8 of guanine (2). They also induce transformation of embryonic hamster cells (3). Recently it was demonstrated that *N*-acetyl derivative of Glu-P-1 is the major active metabolite in rat bile (4). In a series of studies on the heterocyclization of the novel compounds having the imidazopyridine skeleton, we have studied the structural conversion of azaindolizine derivatives to the pyridopurine skeleton 2.



1a R = CH_3
1b R = H

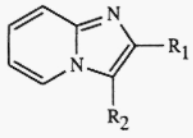


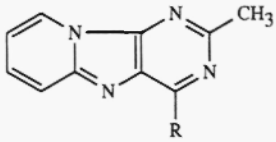
2

Attempts to convert 3 to the aminomethylderivative 4 were accomplished in high yield from catalytic reduction of the azide 5 (obtained from 3) with 5 % palladium on charcoal. The acylated compound 6 was subsequently nitrated to give 7.

Reaction of 7 with tin and bromhydric acid at -10°C gave the amino derivative 8. The presence of the adjacent amine and methylacetamido groups provided suitable substrate for formation of the fused pyrimidine ring system. When 8 was allowed to react overnight at room temperature, under nitrogen, with thionyl chloride/chloroform in the presence of pyridine according the procedure described by Geyer et al (5), a set of

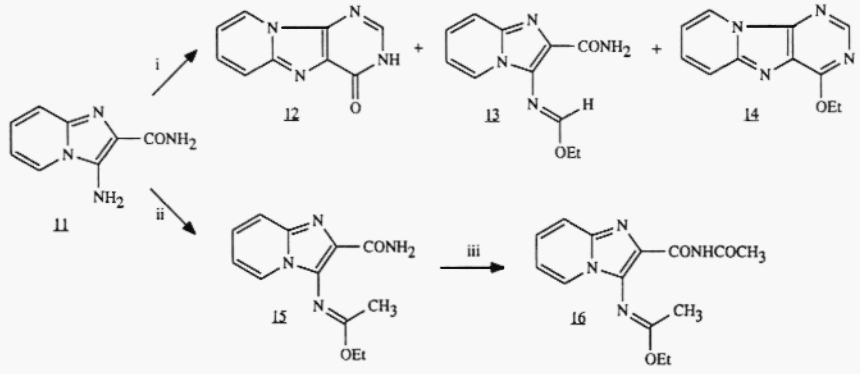
two products was obtained. The tricyclic compound 9 was easily separated from a product air and light-sensitive supposed to be the chloro derivative 10 according to the analysis of its mass and ^{1}H NMR spectra.





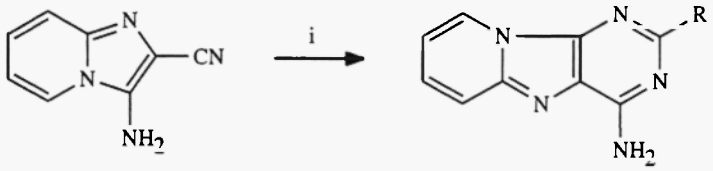
3	R_1=CH_2Cl	R_2=H		9 R=H	70%
4	R_1=CH_2NH_2	R_2=H	75%	10 R=Cl	1%
5	R_1=CH_2N_3	R_2=H	75%		
6	R_1=$CH_2NHCOCH_3$	R_2=H	60%		
7	R_1=$CH_2NHCOCH_3$	R_2=NO_2	31%		
8	R_1=$CH_2NHCOCH_3$	R_2=NH_2	25%		

Another direct route of the pyridopurine ring system based on the model compound 11 was developed in order to functionalize this ring system. The aminoamide (11) was treated with triethyl orthoformate in glacial acetic acid with molecular sieves (4Å) at reflux for 48 h to afford 12 (50%), 13 (6%) and 14 (2%). When the reaction was carried out under reflux for 17 h, the yield of 12 increased to 81%. Treatment of 11 in refluxing triethyl orthoacetate in the presence of molecular sieves (4Å) for 15 h, followed by evaporation of the remaining triethyl orthoacetate, gave 15 (14%) which was further converted into the non-cyclised acetylderivative 16 (84%) by the reaction with hot acetic anhydride.



Reagents and conditions: i: $(EtO)_3CH$, AcOH, molecular sieves 4Å, reflux (48 h); ii: $CH_3C(OEt)_3$, molecular sieves 4Å, reflux (15 h); iii: Ac_2O, Δ

The aminoimidazopurine derivatives 18 (84%), and 19 (74%) were conveniently prepared from 3-aminoimidazo[1,2-*a*]pyridine-2-carbonitrile 17 by the action of formamidine (or acetamidine) acetate in refluxing ethoxyethanol.



17

18 R = H
19 R = CH_3

Reagents and conditions: (i) AcOH, formamidine or acetamidine acetate, ethoxyethanol, reflux

The antineoplastic activity of some compounds are currently under investigation.

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EXPERIMENTAL

Melting points were determinated on a kofler hotstage apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian EM360A or a Brüker AC 100 or 250. ^{13}C-NMR spectra were recorded on a Brüker WM 360 spectrometer. The chemical shifts are reported in ppm downfield from TMS as internal reference or using the signal of the small amount of residual chloroform. With regard to ^{13}C-NMR, the center resonance of deuteriochloroform was used as reference. Mass spectra were recorded by electron impact on a LKB 2091 spectrometer. All new compounds gave satisfactory elemental analysis

2-Chloromethylimidazo[1,2-a]pyridine 3: To a solution of chloroacetone (27 g, 0.212 mol) in 1,2-dimethoxyethane was added 2-aminopyridine (18.8 g, 0.204 mol). The mixture was stirred at room temperature for 2 hours. The precipitate was collected, washed with 1,2-dimethoxyethane and suspended in ethanol (500 ml). The suspension was refluxed for 2 hours and evaporated to dryness. The residue was dissolved in water (50 ml), made alkaline with sodium carbonate and extracted with dichloromethane. The organic layers were dried over calcium chloride and after usual work up chromatographed on neutral alumina (eluent dichloromethane) to give 22 g (66%) of 3 as white plates; mp: 91-93°C; ^{1}H-NMR ($CDCl_3$), δ: 4.77 (s, 2H, CH_2), 6.77 (pseudo t, 1H, 6-H), 7.17 (pseudo t, 1H, 7-H), 7.53 (d, 1H, 8-H), 8.07 (dd, 1H, 5-H).

2-Azidomethylimidazo[1,2-a]pyridine 5: A mixture of 3 (5 g, 0.03 mmol) and sodium azide (9.75 g, 0.15 mmol) in dimethylformamide (70 ml) was stirred at 70°C during 4 hours. The solvent was removed under reduced pressure and the residue dissolved in dichloromethane. After drying, the organic layer was evaporated and the residue chromatographed on neutral alumina (eluent dichloromethane) to give 5 in 75% yield as a gum; ^{1}H-NMR ($CDCl_3$), δ: 4.55 (s, 2H, CH_2), 6.81 (pseudo t, 1H, 6-H), 7.21 (pseudo t, 1H, 7-H), 7.63 (dd, 1H, 8-H), 7.63 (s, 1H, 3-H), 8.20 (dd, 1H, 5-H).

(Imidazo[1,2-a]pyridin-2-yl)methylamine 4: A solution of azide 5 (15.5 g, 0.09 mol) in ethanol (200 ml) was hydrogenated for 6 hours in the presence of 5% palladium on charcoal (50 mg). After filtration and concentration, the residue was dissolved in dichloromethane. Usual work up followed by chromatography on neutral alumina gave the amine 4 (9.5 g, 73%) as an oil; ^{1}H-NMR ($CDCl_3$), δ: 1.90 (s, 2H, CH_2), 4.06 (s, 2H, NH_2), 6.73 (pseudo t, 1H, H-6), 7.16 (pseudo t, 1H, H-7), 7.58 (s, 1H, H-3), 7.60 (d, 1H, H-8), 8.08 (dd, 1H, H-5).

(Imidazo[1,2-a]pyridin-2-yl)methylacetamide 6: A solution of 4 (9.5 g, 65 mmol) in acetic anhydride (20 ml) was refluxed under stirring for 2 hours, then concentrated to dryness. The residue was made alkaline, extracted with dichloromethane and, after usual work up, chromatographed on neutral alumina (eluent dichloromethane) to give 6 (7.95 g, 60%) as white plates; mp 156-158°C; ^{1}H-NMR ($CDCl_3$), δ 1.20 (s, 3H, CH_3), 4.56 (d, 2H, CH_2), 6.83 (pseudo t, 1H, 6-H), 7.23 (pseudo t, 1H, 7-H), 7.56 (dd, 1H, 8-H), 7.63 (s, 1H, 3-H), 8.16 (dd, 1H, 5-H).

(3-Nitroimidazo[1,2-a]pyridin-2-yl)methylacetamide 7: the acetamide 6 (6g, 33 mmol) was dissolved in concentrated sulfuric acid (45 ml) previously cooled at -10°C. Nitric acid (d = 1.38, 3.5 ml) was slowly added without the temperature rose above 0°C. The mixture was allowed to stand at room temperature, stirred for further two hours, then poured onto ice. The obtained precipitate was filtered, washed with water and solubilized in dichloromethane. The organic layer was dried over calcium chloride, evaporated to dryness and chromatographed on neutral alumina eluting with dichloromethane to give 1.6 g (31%) of 7 as pale yellow plates; mp 179-181°C; ^{1}H-NMR ($CDCl_3$), δ: 2.13 (s, 3H, CH_3), 5.06 (d, 2H, CH_2), 6.60 (m, 1H, NH), 7.36 (dd, 1H, 6-H), 7.86 (m, 2H, 7-H, 8-H), 9.63 (dd, 1H. 5-H).

(3-Aminoimidazo[1,2-a]pyridin-2-yl)methylacetamide 8: A solution of 7 (0.5 g, 2.14 mmol) in ethanol (90 ml) was hydrogenated for 12 hours at room temperature in the presence of 5% palladium on charcoal. The solution was filtered and concentrated *in vacuo*. The residue was dissolved in dichloromethane. Usual work up followed by chromatography of the residue on neutral alumina (eluent dichloromethane) gave the amine 8 (120 mg, 25%) as a brown gum; ^{1}H-NMR (methanol-d_4), δ: 2.12 (s, 3H, CH_3), 4.62 (s, 2H, CH_2), 7.06 (pseudo t, 1H, 6-H), 7.33 (pseudo t, 1H, 7-H), 7.54 (d, 1H, 8-H), 8.25 (d, 1H, 5-H) ; ^{13}C-NMR (methanol-d_4), δ: 22.41 (CH_3), 36.97 (CH_2), 112.85 (6-C), 117.01 (8-C), 123.54 (5-C), 124.36 (7-C), 127.86 (2-C or 3-C), 128.36 (3-C or 2-C), 141.15 (8a-C), 173.41(C=O) ; ms (m/z) = 204 (M^+).

2-Methylpyrido[1,2-e]purine 9 and *4-chloro-2-methylpyrido[1,2-e]purine* 10: A solution of the amine 8 (160 mg, 0.78 mmol) in chloroform (free of stabilizant) was treated with thionyl chloride (4.8 ml) and pyridine (4.8 ml). The mixture was stirred at room temperature overnight, treated with sodium hydroxyde (4N, 50 ml), and extracted with dichloromethane. After usual work up, chromatography of the residue gave 9 (100 mg, 68%) as white plates; mp 99- 101°C; ^{1}H-NMR ($CDCl_3$), δ: 2.52 (s, 3H, CH_3), 7.46 (pseudo t, 1H, 8-H), 7.49 (pseudo t, 1H, 7-H), 7.69 (s, 1H, 4-H), 7.98 (d, 1H, 6-H), 8.67 (d, 1H, 9-H) ; ^{13}C-NMR ($CDCl_3$), δ_{CH}: 14.50 (CH_3), 111.24 (8-C), 119.85 (6-C), 124.39 (9-C), 139.13 (7-C), 149.78 (4-C); ms (m/z) = 184 (M^+), 169 (M^+-CH_3), 157 (M^+-HCN), 143 (M^+-CH_3CN). Further elution gave 1.5 mg (1%) of 10 as an oil which could not crystalize; ^{1}H-NMR ($CDCl_3$), δ: 2.89 (s, 3H, CH_3), 6.98 (pseudo t, 1H, 8-H), 7.58 (m, 1H, 7-H), 7.74 (d, 1H, 6-H), 8.67 (d, 1H, 9-H); ms (m/z) = 220 (M^++2, 33), 218 (M^++1, 100), 183 (M^+-Cl, 80),78 (47).

3-Aminoimidazo[1,2-a]pyridine-3-carboxamide 11: To bromhydric acid (40 ml) previously cooled to -10°C was added portionwise tin (5 g, 42 mmol) then 3-nitroimidazo[1,2-a]pyridine-2-carboxamide (6) (4.38 g, 21 mmol) without the temperature rose above 0°C. The mixture was stirred for further 1 hour, then allowed to stand at room temperature and stirred overnight. The precipitate was collected, dissolved in water, made alkaline with

sodium carbonate and evaporated to dryness. The residue was chromatographed on neutral alumina (eluent dichloromethane-methanol 95:5 v/v) to give 3.5 g of 11 (93%) as pale yellow plates; mp 249-251°C, ^{1}H-NMR (dimethylsulfoxyde-d_6), δ: 6,00 (br. s, 2H, NH_2), 6.70 (pseudo t, 1H, 6-H), 7.05 (m, 2H, 7,8-H), 8.01 (dd, 1H, 5-H).

Ethyl orthoformate cyclization:
Method A: A solution of the aminoamide 11 (2.68 g, 15.2 mmol) in ethyl orthoformate (32 ml) and glacial acetic acid (10 ml) was refluxed for 48 hours under nitrogen in the presence of molecular sieves 4Å. After cooling the 3*H*-pyrido[1,2-*e*]purin-4-one 12 (1.4 g, 50%) was collected by filtration as pale yellow plates; mp>260°C ; ir (KBr) 1690 cm^{-1} (C=O) ; ^{1}H-NMR (dimethylsulfoxyde-d_6), δ: 7.09 (t, 1H, 8-H), 7.52 (t, 1H, 7-H), 7.69 (d, 1H, 6-H), 8.14 (s, 1H, 2-H), 8.64 (d, 1H, 9-H) ; ms (m/z) = 186 (M^+, 100), 158 (11), 104 (30), 79 (26). The filtrate was evaporated to dryness and the residue chromatographed on neutral alumina. Elution with dichloromethane:methanol (98:2 v/v) gave the ethoxymethyleneimine 13 (200 mg, 6%) as white plates; mp 169-171°C ; ir (KBr) 3480 (NH_2), 1695 (C=O), 1230 cm^{-1} (COC); ^{1}H-NMR ($CDCl_3$), δ: 1.46 (t, 3H, CH_3), 4.50 (q, 2H, CH_2), 6.83 (dd, 1H, 6-H), 7.26 (dd, 1H, 7-H), 7.51 (d, 1H, 8-H), 8.23 (d, 1H, 5-H), 9.30 (s, 1H, H_{imine}) ; ms (m/z) = 232 (M^+, 95), 203 (33),186 (100), 159 (44), 131 (47), 104 (34), 78 (62). Further elution gave the 4-ethoxypyrido[1,2-*e*]purine 14 (50 mg, 2%) as white plates; mp 224-226°C; ^{1}H-NMR ($CDCl_3$), δ 1.46 (t, 3H, CH_3), 4.22 (q, 2H, CH_2), 6.98 (dd, 1H, 8-H), 7.42 (dd, 1H, 7-H), 7.74 (d, 1H, 6-H), 8.06 (s, 1H, 2-H), 8.49 (d, 1H, 9-H); ^{13}C-NMR ($CDCl_3$), δ_{CH}: 15.35 (CH_3), 42.20 (CH_2), 112.82 (8-C), 119.20 (6-C), 123.78 (7-C), 128.64 (9-C), 144.38 (2-C) ; ms (m/z) = 214 (M^+, 89), 186 (100), 158 (28), 104 (18), 78 (48).

Method B: A solution of the aminoamide 11 (0.7 g, 3.8 mmol) in ethyl orthoformate (10 ml) and glacial acetic acid (3 ml) was refluxed for 17 h. After cooling, the solution was evaporated to dryness and the residue suspended in dichloromethane. The precipitate was collected and washed with hot ethanol to give 12 in 81% yield.

Ethyl orthoacetate cyclization: A solution of aminoamide 11 (2.68 g, 15.2 mmol) in ethyl orthoacetate was refluxed for 15 hours in the presence of molecular sieves 4Å. After cooling the solution was evaporated to dryness. The residue was chromatographed on neutral alumina eluting with dichloromethane:methanol 98:2 (v/v) to afford the imine 15 (500 mg, 14%) as white plates; mp 111-113°C; ^{1}H-NMR ($CDCl_3$), δ: 1.36 (t, 3H, CH_3), 2.01 (s, 3H, CH_3), 4.43 (q, 2H, CH_2), 6.75 (dd, 1H, 6-H), 7.15 (dd, 1H, 7-H), 7.48 (d, 1H, 8-H), 7.65 (br.s, 2H, NH_2), 7.90 (d, 1H, 5-H); ms (m/z): 246 (M^+, 20), 218 (10), 176 (82), 104 (62), 78 (100). Further elution using 5% of methanol in dichloromethane gave recovered starting compound 11 (1 g).

The imine 15 (500 mg, 2 mmol) in acetic anhydride (20 ml) was heated at 80°C for 5 hours under stirring. After addition of ethanol (20 ml) the solvent was evaporated *in vacuo*. The residue, after usual work up, was chromatographed on neutral alumina (eluent dichloromethane) to give the acetamide 16 as white plates; mp 134-136°C; ^{1}H-NMR ($CDCl_3$), δ: 1.40 (t, 3H, CH_3), 2.01 (s, 3H, CH_3), 2.53 (s, 3H, $COCH_3$), 4.43 (q, 2H, CH_2), 6.77 (dd, 1H, 6-H), 7.17 (dd, 1H, 7-H), 7.40 (d, 1H, 8-H), 7.87 (d, 1H, 5-H), 9.90 (br.s, 1H, NH) ; ms (m/z) = 288 (M^+, 31), 200 (21), 158 (36), 105 (19), 78 (50).

3-Aminoimidazo[1,2-a]pyridine-2-carbonitrile 17: To bromhydric acid (30 ml) previously cooled to -10°C was added portionwise tin (4 g, 33.6 mmol) then 3-nitroimidazo[1,2-*a*]pyridine-2-carbonitrile (6) (3.2 g, 17 mmol) without the temperature rose above 0°C. The mixture was stirred for further 1 hour, then allowed to stand at room temperature and stirred further for 2 hours. The precipitate was collected, dissolved in water, made alkaline with sodium carbonate and extracted with hot dichloromethane. After usual work up, the residue was chromatographed on neutral alumina (eluent dichloromethane-methanol 95:5 v/v) to give 2.7 g of 17 (96%) as white plates; mp 209-211°C, ^{1}H-NMR

(dimethylsulfoxyde-d_6), δ: 6,50 (br. s, 2H, NH_2), 7.00 (m, 2H, 6,7-H), 7.25 (d, 1H, 8-H), 8.10 (dd, 1H, 5-H).

4-Aminopyrido[1,2-e]purine 18: A solution of the aminonitrile 17 (916 mg, 5.78 mmol) and formamidine acetate (200 mg, 1.69 mmol) in ethoxyethanol (10 ml) was refluxed for 4 hours. After cooling, the solution was evaporated to dryness. After usual work up, the residue was chromatographed on neutral alumina eluting with dichloromethane:methanol (4%) to give 18 (300 mg, 84%) as pale yellow plates; mp >260°C ; ir (KBr) 3310 (NH_2), 1642 (CNC) 1330, 755 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ: 5.90 (s, 2H, NH_2), 6.96 (pseudo t, 1H, 8-H), 7.79 (pseudo t, 1H, 7-H), 7.66 (dt, 1H, 6-H), 8.49 (s, 1H, 2-H), 8.64 (dt, 1H, 9-H) ; ms (m/z) = 185 (M^+, 100), 158 (42), 104 (23), 78 (46).

4-Amino-2-methylpyrido[1,2-e]purine 19: this compound was obtained according to the above procedure using acetamidine acetate instead of formamidine acetate (74% yield) as white plates; mp 238-240°C; ir (KBr) 3290, 3260, 1643, 1330, 750 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ: 2.85 (s, 3H, CH_3), 5.25 (s, 2H, NH_2), 7.14 (t, 1H, 8-H), 7.64 (t, 1H, 7-H), 7.75 (d, 1H, 6-H), 8.62 (d, 1H, 9-H) ms (m/z): 199 (M^+, 100), 157 (25), 104 (12), 78 (45).

REFERENCES

(1) K.Takeda, K.Shudo, T.Okamoto, and T.Kosuge, Chem. Pharm. Bull., 26(9), 2924, (1978); K.Takeda, K. Shudo, T. Okamoto, M. Nagao, K. Wakabayashi, and T. Sugimura, Carcinogenesis, 1, 889, (1980); K.N'Goy, C. de Meester, D. Pairon, L. Fabry, B. Loukakou, C. N'Zouzi, G. Saint-Ruf, M. Mercier, and F. Poncelet, Mutation Res., 136. 23, (1984); K. N'Goy, G. Saint-Ruf, and C. de Meester, Mutation Res., 156. 53, (1985); S. Hayashi, M.E. Moller, and S.S. Thorgirsson, Jpn. J. Cancer Res. (Gann), 76, 835, (1985).

(2) Y. Hashimoto, K. Shudo, and T. Okamoto, Chem. Pharm. Bull., 27, 2352, (1979); Y. Hashimoto, K.Shudo, and T. Okamoto, Biochem. Biophys. Res. Commun., 92, 971, (1980); Y. Hashimoto, K. Shudo, and T. Okamoto, J. Am. Chem. Soc., 104. 7636, (1982); Y. Hashimoto, and K. Shudo, Biochem. Biophys. Res. Commun., 116, 1100, (1983); Y. Hashimoto, K. Shudo, and T. Okamoto, Acc. Chem. Res., 17, 403, 1984.

(3) S. Takeyama, Y. Hirakawa, T. Tanaka, T. Kawachi, and T. Saginura, Toxicol. Lett., 4, 281, (1979).

(4) C. Negishi, A. Umemoto, J.J. Rafter, S. Sato, and T. Saginura, Mutation Res., 175. 23, (1986).

(5) H.M. Geyer, L.L. Martin, C.A. Crichlow, F.W. Dekow, D.B. Ellis, H. Kruse, L.L. Setescak, H. Worm, J. Med. Chem., 25, 340 (1982).

(6) J.C. Teulade, G. Grassy, J.P. Girard, J.P. Chapat, and M. Simeon de Buochberg, Eur. J. Med. Chem., Chim. Ther., 13(3). 109, (1978).

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