Researches on Pyridodiazepines. Behavior of 7,8,9,10-Tetrahydro-5-methylcyclopenta[*e*]pyrido[3,2-*b*][1,4]-diazepin-6(5*H*)-one with Chloroacetyl Chloride

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Following a previous experiment, an original heteropolycyclic structure **4** was obtained by a reaction of chloroacetyl chloride with compound **3** bearing a conjugated double bond system. The condensation develops with an initial NH-chloroacetylation and ring closure by quaternarization of the pyridine nitrogen. This is achieved through an 1,4-cycloaddition of chloroketene to make a pyranone ring.

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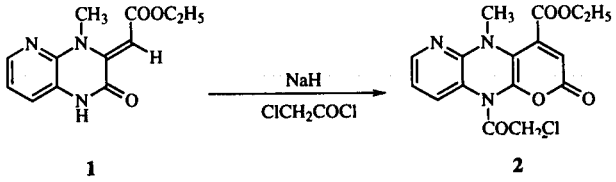
When ethyl [2(1*H*)-oxo-5-azaquinoxalin-3(4*H*)-ylidene]carboxylate (**1**) was refluxed, in dry tetrahydrofuran/toluene with chloroacetyl chloride after being treated with sodium hydride, 4-carbethoxy-10-(chloroacetyl)-5,10-dihydro-5-methyl-2*H*-pyrano[3,2-*b*]pyrido[2,3-*e*]-pyrazin-2-one (**2**) was obtained by a two-step synthesis [1] (Scheme I).

Scheme I

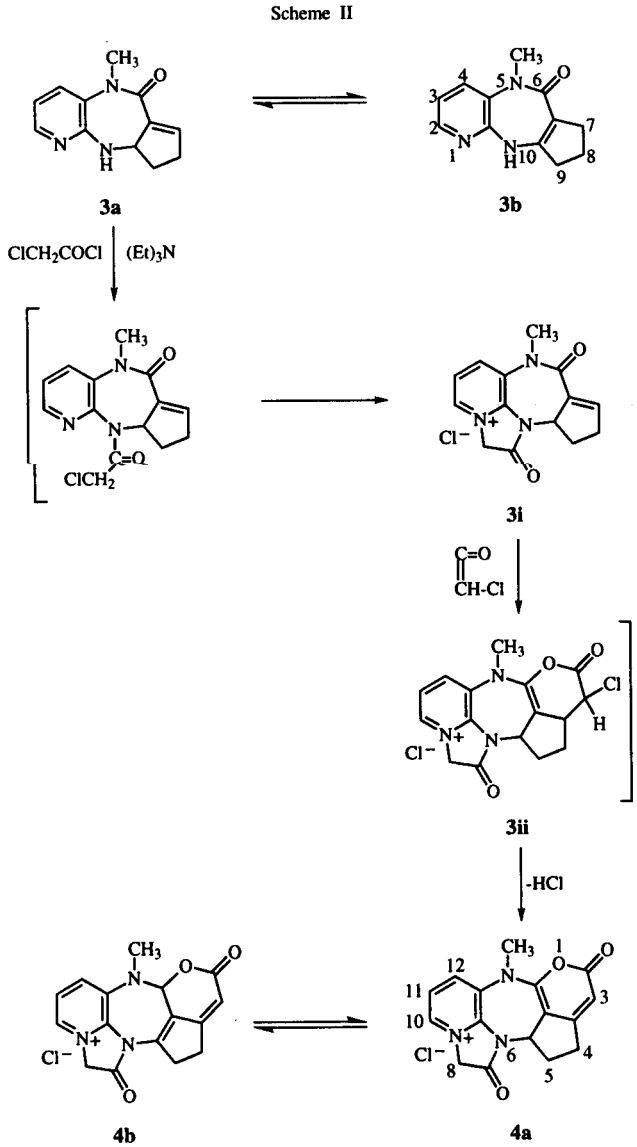


1 **2**

Developing our researches on pyrido[2,3-*b*][1,4]diazepinone derivatives [2,5] and with regard to the pharmacological importance of the pyran nucleus, we applied the above reaction to 7,8,9,10-tetrahydro-5-methylcyclopenta[*e*]pyrido[2,3-*b*][1,4]diazepin-6(5*H*)-one (**3a**) [2] that contains an analogous conjugated double bond system to **1**. The reaction of **3a** with chloroacetyl chloride and triethylamine in boiling dioxane provided compound **4** with a molecular formula of $C_{16}H_{14}ClN_3O_3$. The structural identification of the compound obtained was not easy owing to the tautomeric forms **4a** <=> **4b** which in deuteriochloroform are in rapid equilibrium (ratio, 4:1).

Compound **4**, characterized as 4,5,5a,8-tetrahydro-13-methyl-2,7-dioxo-13*H*-cyclopenta[*e*]pyrano[3,2-*f*]pyrido [1,2,3-*ji*]-1,3a,7-triazaazulen-10-ium chloride was most likely accomplished through the reaction pattern suggested in Scheme II. It supposes the acylation of the amine group of tautomer **3a** with chloroacetyl chloride followed by a quaternarization reaction of the chloroace-

Scheme II



3a **3b** **3i** **3ii** **4b** **4a**

tyl chain on the pyridine nitrogen with ring closure to the imidazolone nucleus **3i** and the concomitant base catalyzed formation of chloroketene from chloroacetyl chloride. This intermediate produces a 1,4-cycloaddition to the diazepine conjugated system **3ii** and formation of **4** by hydrogen chloride elimination.

Compound **4** was identified on the basis of analytical data, mass (M^+, 331), ^1H and ^{13}C nmr spectra. In this connection the imidazole CH_2 singlet (δ, 4.80), the pyran H singlet (δ, 6.46) and the pyridine α-H double doublet (δ, 9.98) are particularly significant.

EXPERIMENTAL

All melting points were determined by the capillary method on a Büchi 510 apparatus and are uncorrected. The uv spectra was measured in 95% ethanol with a Perkin-Elmer Model 550S spectrophotometer. The ir spectrum was taken on a Perkin-Elmer Paragon 1000 PC spectrometer. The ^1H and ^{13}C nmr spectra were recorded on a Varian-Gemini 200 spectrometer with tetramethylsilane as the internal standard. The mass spectra were obtained on a Hewlett-Pakard 5989-A spectrometer at 70 eV coupled with a Hewlett-Pakard 5890 gaschromatograph. Elemental analysis for C, H, N was performed on the Carlo Erba Elemental Analyser Model 1106 at the Microanalytical Laboratory, Dipartimento di Scienze Farmaceutiche, Università di Genova.

7,8,9,10-Tetrahydro-5-methylcyclopenta[*e*]pyrido[2,3-*b*][1,4]-diazepin-6(5*H*)-one (**3b**).

The following procedure was preferred to that previously reported. To 4.5 g of 2-amino-3-methylaminopyridine [6] (30 mmoles) in 100 ml of xylene was refluxed with stirring while a solution of 2-oxocyclopentanecarboxylate (3.4 g, 22 mmoles) was added over a period of 90 minutes and refluxed for 2.5 hours. After cooling, a very small amount of an occasionally separated isomeric compound, 5,7,8,10-tetrahydro-5-methylcyclopenta[*e*]pyrido[2,3-*b*][1,4]diazepin-9(6*H*)-one (mp 230-232°) was removed by filtration and the xylene solution was extracted with 2*N* hydrochloric acid. The acid solution, made alkaline with sodium hydroxide, was extracted with methylene chloride and the organic solution, after drying over anhydrous sodium sulphate, was evaporated to dryness. By trituration with ethanol-ethyl ether, the oily residue obtained gave **3b** which was crystallized twice from ethanol (2.15 g, mp 172-173°; yield 33%). Compound **3b** in solution changes slowly to the tautomer 6a,7,8,9-tetrahydro-5-methylcyclopenta[*e*]pyrido[2,3-*b*][1,4]-diazepin-6(5*H*)-one (**3c**) (ratio 1:1.3 in deuteriochloroform).

Compound **3b** had ^1H nmr (deuteriochloroform): δ 1.82 (q, J = 8.0 Hz, 2H-8), 2.57 (t, J = 8.0 Hz, 2H-9), 2.68 (t, J = 8.0 Hz, 2H-7), 3.21 (s, N-CH_3), 6.97 (dd, J = 8.0 Hz, H-3), 7.25 (dd, J = 7.4 Hz, H-4), 7.43 (br s, H exchangeable), 7.86 (dd, J = 4.7 Hz, H-2); ^{13}C nmr (deuteriochloroform): δ 20.7 (t), 32.0 (t), 36.8 (q), 37.1 (t), 110.5 (s), 120.0 (d), 130.2 (s), 131.3 (d), 142.8 (d), 153.3 (s), 155.5 (s), 169.1 (s).

Compound **3c** had ^1H nmr (deuteriochloroform): δ 1.98 (m, 2H-8), 2.70 (m, 2H-9 and 2H-7), 2.91 (m, H-6a), 3.38 (s, N-CH_3), 7.22 (dd, J = 8.0 Hz, H-3), 7.64 (dd, J = 7.4 Hz, H-4), 8.40 (dd, J = 4.7 Hz, H-2); ^{13}C nmr (deuteriochloroform): δ 36.0 (q), 36.1 (t), 37.7 (t), 49.5 (d), 121.8 (d), 131.6 (s), 145.9 (d), 154.5 (s), 163.8 (s), 181.9 (s). The signals of a triplet and of doublet are overlapped with the corresponding signals of tautomer **3b**.

4,5,5a,8-Tetrahydro-13-methyl-2,7-dioxo-13*H*-cyclopenta[*e*]-imidazo[2,1-*c*]pyrano[3,2-*f*]pyrido[3,2-*b*][1,4]diazepin-9-ium Chloride.

To a mixture of **3** (2.15 g, 10 mmoles) in anhydrous dioxane (30 ml) chloroacetyl chloride (1.58 g, 14 mmoles) in anhydrous dioxane (3 ml) was added dropwise with stirring at room temperature and, subsequently, an anhydrous dioxane solution of triethylamine (1.5 g, 15 mmoles in 3 ml) was added. The reaction mixture was then refluxed for 8 hours, and, after cooling, was diluted with diethyl ether (5 ml) and the triethylamine hydrochloride which separated was removed by filtration. The organic solution, from filtration, was evaporated to dryness *in vacuo*. The oily residue from evaporation was dissolved in methylene chloride (20 ml) and the solution was subsequently washed with 0.5*N* hydrochloric acid, water, 0.5*N* sodium hydroxide and water, dried (sodium sulphate) and evaporated to dryness to give an oily residue (about 2 g). Upon trituration with ethanol (4 ml) of collected oil, 1.2 g (yield 36%) of **4**, as beige needles were obtained, mp 177-178° (ethanol); uv: λ max (log ε) 248 (4.28), 263 (4.29), 277 (4.31), 339 (4.19) nm; ir (potassium bromide): ν 1695, 1675 cm^{-1}; ms: m/z = 331.7 [M^+], 297 [M-Cl]$^+$.

Compound **4a** had ^1H nmr (deuteriochloroform): δ 2.20 (dq, J = 12.22 and 9.11 Hz, H-5), 2.6-3.0 (3m, 2H-4 and H-5), 3.49 (s, N-CH_3), 3.61 (d, J = 9.8 Hz, H-5a), 4.80 (s, 2H-8), 6.46 (br s, H-3), 7.31 (dd, J = 8.4 and 6.5 Hz, H-11), 7.51 (dd, J = 8.4 Hz, H-12), 9.97 (dd, J = 6.5 Hz, H-10); ^{13}C nmr (deuteriochloroform): δ 24.3 (m), 30.9 (t), 37.6 (q), 46.8 (t), 51.8 (d), 102.4 (s), 117.5 (d), 121.2 (d), 124.8 (d), 126.1 (d), 127.2 (s), 129.5 (s), 145.2 (s), 157.4 (s), 169.3 (s), 179.7 (s).

Compound **4b** had ^1H nmr (deuteriochloroform): δ 1.92 (m, H-5), 2.6-3.0 (m, 2H-4 and H-5), 3.35 (s, N-CH_3), 7.17-7.31 (m, H-11 and H-12), 9.86 (dd, H-10) (the signals of H-3, 2H-8 and H-13a are obscured by the signals of the mains tautomer); ^{13}C nmr (deuteriochloroform): δ 32.0 (t), 34.8 (t), 36.3 (q), 47.0 (t), 101.0 (s), 118.7 (s), 120.0 (d), 122.8 (d), 129.0 (s), 130.0 (s), 157.0 (s), 164.2 (s), 179.41 (s). Three pyridine doublets are obscured by the corresponding signals of the main tautomer.

Anal. Calcd. for $C_{16}H_{14}ClN_3O_3$ (331.74): C, 57.92; H, 4.25; Cl, 10.68; N, 12.66. Found: C, 57.86, H, 4.34; Cl, 10.97; N, 12.70.

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