New Synthesis of Octahydro-2-methyl-2*H*-pyrazino[1,2-*a*]pyrazine

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A new method has been developed for the synthesis of octahydro-2-methyl-2*H*-pyrazino-[1,2-*a*]pyrazine. 2-Benzylaminoethanol was the starting material.

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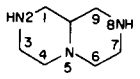
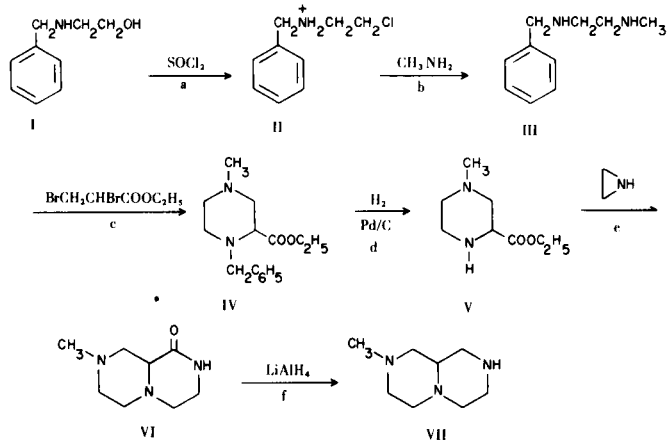
This paper reports results on our continued interest in nitrogen bridgehead compounds. Our initial work in this field dealt with the synthesis of 2*H*-octahydropyrido-[1,2-*a*]pyrazine and its derivatives (1). In this work we were particularly interested in the structure containing a bridgehead nitrogen with a secondary amine nitrogen four atoms away. Octahydro-2*H*-pyrazino[1,2-*a*]pyrazine contains two secondary amine nitrogens each of which is four atoms away from the bridgehead nitrogen atom and it was to this interesting system that we turned our attention.



The synthesis of this ring system was first reported in 1962 by Rink and Feiden (2). Their procedure, in our hands did not prove efficient. Consequently we developed a new procedure for synthesizing this ring system which is shown in Scheme I.

Scheme I



Theoretically two isomeric products could be formed in step C. Jucker and Rissi (3) carried out this particular step in 1962 and obtained only one product. They proved conclusively that the ethoxycarbonyl group in compound IV is attached to the carbon atom which is adjacent to the benzylamino nitrogen atom. Further evidence for this structure is the reaction of compound V with ethyleneimine to form compound VI which is clearly the result of an ortho condensation. The infrared spectra of compounds VII and VIII showed a group of bands in the 2700-2800 cm^{-1} region. It is believed that these bands indicate a trans ring structure (4).

Alkylation of the N-H group at position 8, in compound VII, occurred readily as shown by the easy introduction of the benzhydryl group to form octahydro-2-methyl-8-(diphenylmethyl)-2*H*-pyrazino[1,2-*a*]pyrazine (compound VIII).

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 521 double beam spectrophotometer. Nmr spectra were measured on a Varian Associates A-60A spectrometer and chemical shifts are expressed in parts per million downfield from tetramethylsilane.

The following compounds were obtained *via* the reference indicated.

N-Benzyl-2-chloroethylamine Hydrochloride (II) (5).

N-Benzyl-*N'*-methylethylenediamine (III) (3).

Ethyl 1-Benzyl-4-methyl-2-piperazinecarboxylate (IV) (3).

Ethyl 4-Methyl-2-piperazinecarboxylate (V) (3).

Octahydro-2-methyl-2*H*-pyrazino[1,2-*a*]pyrazin-1-(5*H*)one (VI).

Ethyl 4-methyl-2-piperazinecarboxylate (14 g., 0.0814 mole) was dissolved in 50 ml. of absolute ethanol and 0.1 ml. of a 7.54 *M* solution of ethanolic hydrogen chloride was added to the solution. Ethyleneimine (3.49 g., 0.0811 mole) dissolved in 25

ml. of absolute ethanol was then added dropwise to the refluxing solution. The solution was refluxed for 48 hours and then concentrated under reduced pressure. The solid which separated was recrystallized from ethylacetate, yield 40%, m.p. 177.5-179°; ir (cm^{-1}): 1600 amide carbonyl, 2700 and 2850 trans ring (4), 3400 amide NH; nmr (deuteriochloroform): singlet at δ 2.33 (CH_3), the "a" proton gave a multiplet centered at δ 3.68 (1H), the N-H gave a poorly defined absorbance centered at δ 7.29.

Anal. Calcd. for $C_8H_{15}N_3O$: C, 56.78; H, 8.93; N, 24.83. Found: C, 56.83; H, 8.72; N, 24.70.

Octahydro-2-methyl-2*H*-pyrazino[1,2-*a*]pyrazine (VII).

Octahydro-2-methyl-2*H*-pyrazino[1,2-*a*]pyrazin-1(5*H*)one (2 g., 0.0118 mole), suspended in 60 ml. of dry tetrahydrofuran, was added dropwise with stirring to 0.721 g. (0.0190 mole) of lithium aluminum hydride in 25 ml. of dry tetrahydrofuran. The mixture was refluxed for 18 hours. The mixture was cooled to 0-5° and 3 ml. of water added dropwise with stirring. After stirring for 2 hours, the mixture was filtered and the collected salts washed with hot ethanol-2-propanol (50/50). All of the filtrates were combined and dried (sodium sulfate). The solvents were removed *in vacuo* at room temperature and the residual oil was fractionally distilled, yield 65%, b.p. 96-100° at 0.75 mm.; the ir spectrum showed no carbonyl peak indicating complete reduction of the lactam; nmr (carbon tetrachloride): singlet at δ 1.22 (1H, NH proton), singlet at 2.15 (3H, CH_3), complex multiplet centered at 2.18 (13 H, ring protons).

Anal. Calcd. for $C_8H_{17}N_3$: C, 61.89; H, 11.04; N, 27.07. Found: C, 61.95; H, 11.18; N, 26.95.

Octahydro-2-methyl-8-(diphenylmethyl)-2*H*-pyrazino[1,2-*a*]-pyrazine (VIII).

Triethylamine (1.39 g., 1.1 equivalents) was added to a solution of 1.94 g. (0.0125 mole) of 2-methyloctahydro-2*H*-pyrazino[1,2-*a*]pyrazine in 16 ml. of acetone. Benzhydryl bromide (3.088 g., 0.0125 mole) was added and the solution was stirred for 2 hours and allowed to stand overnight. The precipitated triethylamine hydrobromide was removed and the filtrate was concentrated to an oil. Ether was added to the oil to precipitate the remaining triethylamine hydrobromide and the filtrate was evaporated to dryness. The resulting solid was recrystallized from acetone, yield 75%, m.p. 118.5-119.5°; nmr (carbon tetrachloride): singlet at δ 2.08 (3H, CH_3); singlet at 4.13 (1H, benzhydryl C-H); multiplet centered at 7.23 (10H, aromatic); the rest of the spectrum integrated correctly for 13 protons).

Anal. Calcd. for $C_{21}H_{27}N_3$: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.28; H, 8.40; N, 13.05.

REFERENCES AND NOTES

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