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CONSECUTIVE MENSCHUTKIN REACTION OF CYCLIC AMINES WITH DICHLOROMETHANE UNDER HIGH PRESSURE: SYNTHESIS OF METHYLENEBISAMINES

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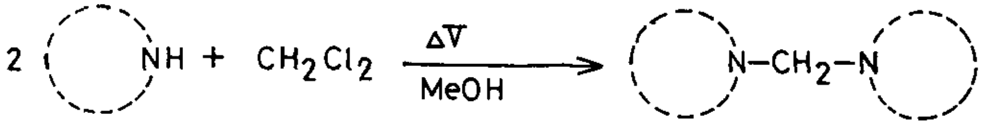
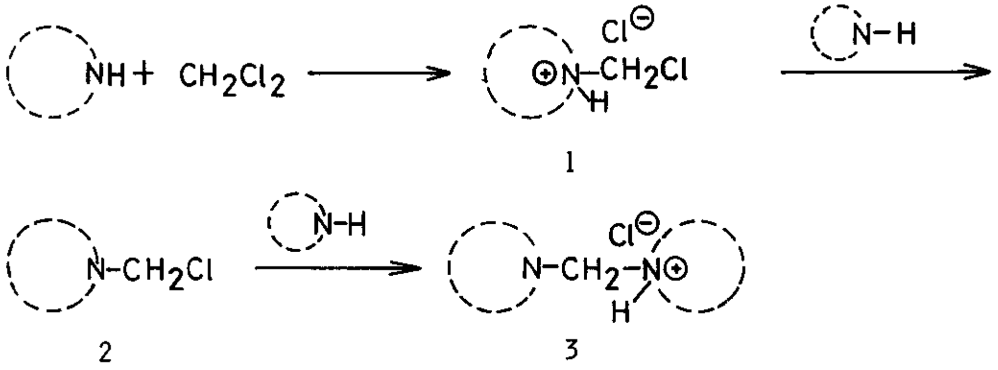
Abstract--- The reaction of heterocyclic amines such as pyrrolidine, piperidines, and morpholines with dichloromethane in methanol in the kiro bar region affording the corresponding methylenebisamines is described.

Methylene compounds linking two heteroatoms are of considerable importance in organic synthesis as exemplified in an application for the modified Mannich reaction.[1] Recent publication on the synthesis of methylenebisamines by reaction of 1,3-benzodioxole and 1,3-benzoxathiole with sodium dialkyl and alkyl aryl amides prompted us to report our own findings.[2] The Menschutkin reaction has a large negative volume of activation, e.g. -20∼ -60 cm^3/mol.[3] Indeed, even dichloromethane has proved to undergo the Menschutkin reaction with triethylamine to produce $Et_3N^+CH_2Cl\ Cl^-$ at high pressures.[4,5] This implies that in the presence of an appropriate secondary amine dichloromethane can serve as a C_1 unit for the high pressure reactions. Thus, we have now developed synthesis of some heterocyclic methylenebisamines by reaction of heterocyclic amines with dichloromethane using a high pressure technique.[6]



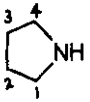
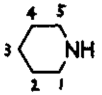
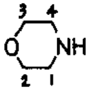
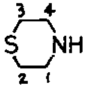
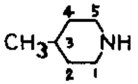
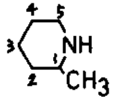
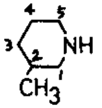
A typical experimental procedure is as follows: a mixture of amine (20 mmol) and dichloromethane (30 mmol) is diluted with methanol in a 10 ml poly(tetrafluoroethylene) capsule which is stored for 4-5 days at 6-9 kbar [1 MPa=10 bar≒10 atm] and ca. 30 °C/or at room temperature.[7] After releasing the pressure to atomosphere to remove the sample from the high pressure vessel, the reaction mixture is poured into saturated NaCl solution (100 ml) and is made basic with NaOH. The mixture is extracted with ether (25 ml x 3), and the combined extract is washed with saturated Na_2CO_3 solution and brine, and then dried over $MgSO_4$. Evaporation of the solvent and the unchanged amine under reduced pressure usually gives a pure methylenebisamine as revealed by ^{13}C NMR and elemental analysis.

The results are summarized in the Table.[8] The yields are apparently moderate, but virtually excellent when taking into consideration that one mole of amine is required for the liberation of the tertiary amine (**2**) from the initially formed ammonium salt (**1**). If this is indeed the case, the yields may be less than 67 %. A possible rationale for the yield of 71 % in the Table is that both/either **2** and/or **3** can serve as a base eliminating HCl. Interestingly, a pair of ^{13}C NMR signals are observed in the case of sterically hindered methylenebis(2-methylpiperidine) presumably due to the presence of the isomers.



As a matter of course, this reaction is amenable to the synthesis of acyclic methylenebisdialkyl or alkylarylamines. For example, reaction of N-methylaniline and diethylamine with dichloromethane at 9 kbar and 30 °C for 4 days gave 48 % and 53 % yield of the corresponding methylenebisamines respectively.

Table Heterocyclic Methylenebisamines from Dichloromethane and Amines[a]

Starting[b] material	Pressure (kbar)	Temp (°C)	Time (days)	Yield[c] (%)	^{13}C-N.M.R. ($CDCl_3$/TMS) δ [ppm]
	9	room temp	2	50[9]	23.0 (t, C-2,3): 52.2 (t, C-1,4): 77.0 (t, CH_2)
	8	room temp	2	54[10]	24.9 (t, C-3): 25.9 (t, C-2,4): 53.0 (t, C-1,5): 82.7 (t, CH_2)
	9	~30	4	54[11]	51.8 (t, C-1,4): 66.7 (t, C-2,3): 81.4 (t, CH_2)
	6	~30	4	51[d]	27.9 (t, C-2,3): 53.3 (t, C-1,4): 82.0 (t, CH_2)
	6	~30	3	62	22.0 (q, CH_3): 31.3 (d, C-3): 34.3 (t, C-2,4): 52.4 (t, C-1,5): 82.1 (t, CH_2)
	6	~30	4	56[e]	16.9, 18.0 (q, CH_3): 22.8, 23.5 (t, C-3): 25.9, 26.0 (t, C-4): 33.9, 34.5 (t, C-2): 49.7, 50.6 (t, C-5): 54.0, 54.3 (d, C-1): 73.6, 74.6 (t, CH_2)
	6	~30	5	71	19.5 (q, CH_3): 25.3 (t, C-3): 30.8 (d, C-2): 33.4 (t, C-4): 52.3 (t, C-5): 60.3 (t, C-1): 82.1 (t, CH_2)

[a] Satisfactory elemental analyses were obtained for all methylenebisamines. Unless otherwise noted, distillation or recrystallization for purification was unnecessary. [b] Numbering is only for C-13 NMR of the methylenebisamines in this Table. [c] Based upon the starting secondary amine. [d] mp 48-49 °C (from n-pentane) [e] Distillation was necessary for purification: bp 59-60 °C/2 mmHg.

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