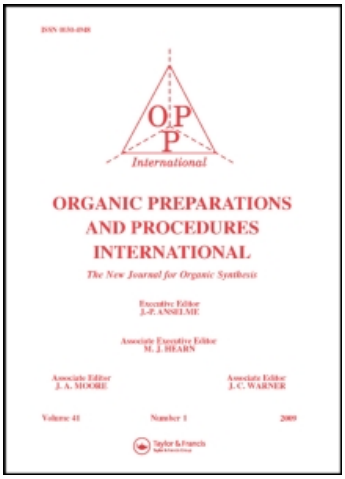

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SYNTHESIS OF N-DESMETHYL MESORIDAZINE

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Abs., 26, 3232 (1932).

11. P. Bruylants, Bull. Soc. Chim. Belg., 41, 309 (1932).

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SYNTHESIS OF N-DESMETHYL MESORIDAZINE

Submitted by (02/07/89) T. Mohammad †, E. M. Hawes* and K. K. Midha

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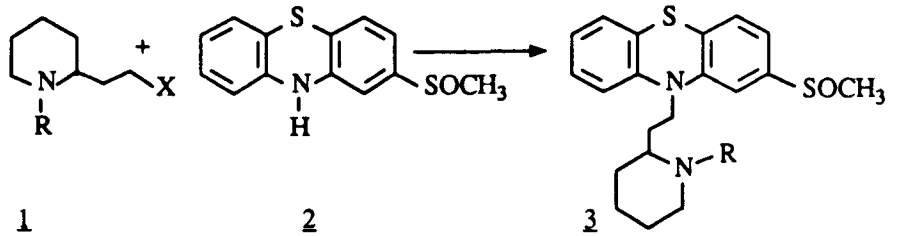
10-[2-(2-Pipridinyl)ethyl]-2-methylsulfinyl-10H-phenothiazine (N-desmethyl mesoridazine, 3b), a metabolite of mesoridazine (3c) is a piperidine-type phenothiazine antipsychotic agent which was needed for studies of the metabolism and disposition of mesoridazine as an internal standard for its quantitation in the body fluids and for the preparation of hapten to conjugate with proteins. We found only one report[1] of the synthesis of 3b by direct condensation of 1b with 2 using sodium amide in refluxing toluene. However, under similar reaction conditions (sodium hydroxide in refluxing toluene), we either failed to obtain 3b or it was isolated in only very poor yield (~ 5%). The N-10 alkylation of 2 with 1b did not succeed most likely because the latter is known to undergo intramolecular cyclodehydrohalogenation under basic conditions to form conidine.[2]



1 2 3

a) R = H, X = OH c) R = CHO, X = OH
b) R = H, X = Cl d) R = CHO, X = Cl

a) R = CHO
b) R = H
c) R = CH_3

Although mesoridazine (3c) is available in large quantities, its N-demethylation is plagued by two problems:[3] (i) competing N-dealkylation at the 10-position of the phenothiazine ring, and (ii) lability of the sulfoxide group under the acidic conditions[4] employed for demethylation. The difficulties were overcome by the preparation of 1d from 1a followed by condensation of 1d with 2 (sodium hydroxide in refluxing toluene) to form 3a (not isolated);[5] alkaline hydrolysis of 3a in ethanol provided N-desmethyl mesoridazine (3b). The overall yield from 1a was 29%.

EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes on a Gallenkamp melting point apparatus and are uncorrected. ^1H NMR spectra in deuteriochloroform were recorded on a Varian T-60 spectrometer with TMS as an internal standard. Low resolution electron impact mass spectra (EIMS) of probe samples were recorded on a Vg Micromass 7070HE instrument at 70 eV coupled to a Vg 2035 data system. Elemental analyses for samples dried over phosphorus pentoxide at 60° under reduced pressure were performed by Guelph Chemical Laboratories, Ltd., Guelph, Ontario.

1-Formyl-2-(2-hydroxyethyl)piperidine (1c).- A stirred mixture of carbinolamine 1a (10.32 g, 0.08 mol) and ethyl formate (22.20 g, 0.30 mol) was refluxed on a steam bath for 2 hrs. The solution was concentrated under reduced pressure and the residual liquid was distilled in vacuo to yield formamide 1c as a light yellow oil (11.80 g, 94%), bp. 142-144°/0.5 mmHg; IR (neat): 3430 (O-H), 1720 (w) 1660 (s) (C = O) cm^{-1}; ^1H NMR: δ 1.33-2.13 (m, 8H, C_3-H_2, C_4-H_2, C_5-H_2, piperidinyl CH_2), 2.60-3.93 (m, 5H, addition of D_2O causes the multiplet to collapse to a multiplet of 4H, C_6-H_2, CH_2OH, OH), 4.23-4.90 (m, 1H, C_2-H), 8.10 (distorted s, 1H, CHO); EIMS: m/z (rel. int.) 157 (8, $M^{+\cdot}$), 112 (100).

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.14; H, 9.55; N, 8.92. Found: C, 60.66; H, 9.57; N, 8.52

1-Formyl-2-(2-chloroethyl)piperidine (1d).- Thionyl chloride (12.58 g, 0.105 mol) was added to a stirred solution of formamide 1c (11.0 g, 0.07 mol) in dry chloroform (30 ml) at ice-bath temperature. After the addition was over, the solution was slowly brought to ambient temperature and then refluxed for 2 hrs. The solution was concentrated under reduced pressure and the residual liquid distilled in vacuo to afford the chloride 1d (9.47 g, 77%), bp. 115-116°/0.35 mmHg; IR (neat): 1715(w) 1660 (s) (C = O) cm^{-1}; ^1H NMR: δ 1.40-2.23 (m, 8H, C_3-H_2, C_4-H_2, C_5-H_2, piperidinyl CH_2), 3.13-4.97 (m, 5H, C_2-H, C_6-H_2, CH_2Cl), 8.17 (distorted s, 1H, CHO); EIMS: m/z (rel. int.) 177/175 (1/3, $M^{+\cdot}$), 112 (100).

Anal. Calcd. for $C_8H_{14}ClNO$: C, 54.70; H, 7.98; N, 7.98. Found : C, 54.46; H, 7.87; N, 7.79

10-[2-(2-Piperidinyl)ethyl]-2-methylsulfinyl-10H-phenothiazine (3b).- A stirred mixture of 2-methylsulfinyl-10H-phenothiazine (2, 5.22 g, 0.02 mol) and sodium hydroxide (0.96 g, 0.024 mol) in dry toluene (110 ml) was refluxed under a nitrogen atmosphere in the absence of direct intense light using a water separator. After 1 hr reflux, the solution turned red and a solution of the chloride 1d (3.86 g, 0.022 mol) in toluene (20 ml) was added slowly while reflux was continued . After the addition was over, the solution was further heated at reflux for 4 hrs. The reaction mixture was cooled, washed with water and dried (Na_2SO_4). The solvent was removed under reduced pressure to yield 7.72 g of viscous oil presumed to be 3a. A stirred solution of 3a in 95% EtOH (100 ml) containing 1M NaOH (30 ml) was refluxed for 24 hrs. The solvents were removed under reduced pressure and the residual oil was dissolved in benzene, washed with water and extracted into 15% tartaric acid (3 x 50 ml). The combined tartaric acid extracts were washed with benzene and the separated aqueous layer was basified with NaOH. The liberated amine was extracted into CH_2Cl_2 (3 x 50 ml) and the combined organic extracts were washed with water and dried. The solvent was evaporated in vacuo and

the residual oil was purified by column chromatography over silica gel to give pure N-desmethyl mesoridazine (3b, 2.98 g, 40%) as an oil, ^{1}H NMR: δ 1.00-2.10 (m, 9H, addition of D_2O causes it to collapse to a multiplet of 8H, C_3-H_2, C_4-H_2, C_5-H_2, piperidinyl CH_2, NH), 2.30-3.27 (m containing S(O)CH_3 spike at 2.70, 6H, C_2-H, C_6-H_2, S(O)CH_3), 4.03 (app t, J = 7.0 Hz, 2H, phenothiazinyl CH_2), 6.77-7.50 (m, 7H, ArH); EIMS: m/z (rel. int.) 372 (3, $M^{+\cdot}$), 84 (100). A solution of the oil in dry ethanol was treated with benzenesulfonic acid in ethanol and the besylate salt crystallized as white solid, mp. 145-147°, lit.[1] mp. 142-144°.

Anal. Calcd. for $C_{26}H_{30}N_2O_4S_3$: C, 58.87; H, 5.66; N, 5.28; S, 18.11
Found: C, 58.57; H, 6.00; N, 4.94; S, 18.12

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REFERENCES

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1. Neth. Patent 6,600,184 (1966); Chem. Abstr., 66, 2580r (1967).
2. E. R. Lavagnino, R. R. Chauvette, W. N. Cannon and E. C. Kornfeld, J. Am. Chem. Soc., 82, 2609 (1960).
3. Unpublished results from these laboratories.
4. S. Oae in "Organic Chemistry of Sulfur", S. Oae, Ed., p. 383, Plenum, New York, NY, 1977; M. Madesclaire, Tetrahedron, 44, 6537 (1988).
5. See P. N. Craig, M. Gordon, J. J. Lafferty, B. M. Lester, A. M. Pavloff and C. L. Zirkle, J. Org. Chem., 25, 944 (1960) for a similar methodology.

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MONOMETHYLATION OF 3,4-DIHYDROXYBENZALDEHYDE AS AN ALTERNATE ROUTE TO ISOVANILLIN

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Numerous studies from our laboratory have dealt with alkylations under solid-liquid phase transfer catalysis (PTC) conditions without solvent.[1] The very selective monomethylation of