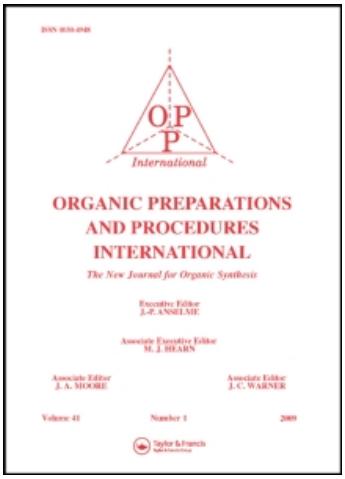

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SELECTIVE N-SUBSTITUTION OF 2,6-DIMETHYLPIPERAZINE

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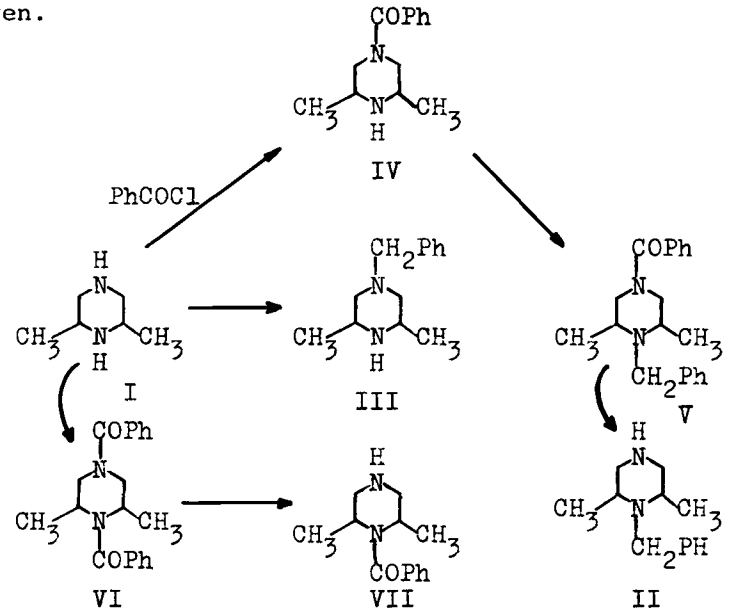
The monoalkylation of cis-2,6-dimethylpiperazine (I) at nitrogen to form 1-alkyl-cis-2,6-dimethylpiperazine (II) or 1-alkyl-cis-3,5-dimethylpiperazine (III) has been described for the preparation of intermediates.[1,2] Quantities of these compounds were required in our laboratory for the preparation of N-nitrosamines[3] so an improved, more convenient synthetic route was explored. The steric interference for reaction at the nitrogen flanked by the methyl groups should permit selective substitution or elimination reactions at the unhindered nitrogen.



This approach proved possible, for reaction of cis-2,6-dimethylpiperazine (I) with benzoyl chloride gave 1-benzoyl-cis-3,5-dimethylpiperazine (IV). The benzylation of IV gave 1-benzyl-4-benzoyl-cis-2,6-dimethylpiperazine (V), which on hydrolysis gave 1-benzyl-cis-2,6-dimethylpiperazine (II). The isomeric 1-benzyl-cis-3,5-dimethylpiperazine (III) was formed by the direct benzylation of I.

Combinations of the steps of direct alkylation or protection by acylation of the 2,6-disubstituted piperazine provide convenient procedures for selective substitution at either of the nitrogens. The 1,4-dibenzoyl-cis-2,6-dimethylpiperazine (VI) can be selectively hydrolyzed at the less hindered amide group to give 1-benzoyl-cis-2,6-dimethylpiperazine (VII).

EXPERIMENTAL

1-Benzoyl-cis-3,5-dimethylpiperazine (IV). - To a 0.25 M solution of 8.7 g (0.078 mmol) of cis-2,6-dimethylpiperazine (I)[4] in acetone was added 11.04 g (0.080 mmol) of anhydrous potassium carbonate. The mixture was cooled to 5° and 10.9 g (0.078 mmol) of benzoyl chloride was added dropwise. The mixture was allowed to stir at room temperature for 3 hr. The solvent was removed under reduced pressure and the residue was dissolved in distilled water. The organic materials were extracted into ether and washed with 1N HCl. Sodium hydroxide (3N) was added to the aqueous layer to pH = 8. The product was extracted with ether and filtered through magnesium sulfate and the solvent was removed by evaporation on a rotary evaporator. The crude product was recrystallized

from acetone to give 15.64 g (92% yield) of IV, mp. 118-119°, lit.[1] mp. 117-119°; nmr ($CDCl_3$): δ 7.7 (s, 5H), 2.6-3.7 (m, 6H), 1.62 (s, 1H), 1.14 (d, 6H); ir: 3500, 1640 cm^{-1}.

1-Benzyl-4-benzoyl-cis-2,6-dimethylpiperazine (V). - Sodium hydride 999 mg (57% oil dispersion; 23 mmol) was washed three times with dry hexane, suspended in 1 ml of dry THF and cooled to 5°. A 0.5 M solution of 2.58 g (11.87 mmol) of 1-benzoyl-cis-3,5-dimethylpiperazine (IV) in THF containing 0.100 ml of dry N,N-dimethylformamide was added to the hydride. The cooling bath was removed and the mixture was stirred at room temperature for 0.5 hr. Freshly distilled benzyl bromide (2.721 ml; 22.9 mmol) was added dropwise to the reaction mixture and the mixture was heated under reflux for 10 hr in inert atmosphere. The mixture was allowed to cool to room temperature and ice-water was added. The organic materials were extracted with ether and the etheral solution was washed twice with 1N HCl. The aqueous layer was made basic (pH 8) with 3N NaOH and the product was extracted into ether. The organic layer was filtered through $MgSO_4$ and evaporation of the solvent gave an orange oil which was distilled under reduced pressure to give 3.08 g (84% yield) of V; bp. 199-200°/1 mm, lit.[1] bp. 200°/1 mm; nmr ($CDCl_3$): δ 7.6 (s, 10H), 4 (s, 2H), 1.05 (b, 6H); ir (neat): 3010, 1640 cm^{-1}.

1-Benzyl-cis-2,6-dimethylpiperazine (II). - To 3.08 g (0.01 mol) of 1-benzyl-4-benzoyl-cis-2,6-dimethylpiperazine (V) was added 50 ml 6M ethanolic KOH and 10 ml water. The solution was heated under reflux with vigorous stirring for 3 hr.

The product was extracted into ether, and the solution was filtered through magnesium sulfate. Evaporation of the solvent followed by distillation of the residue under reduced pressure gave 1.73 g (86%) of II as a clear liquid; bp. 91-92°/0.2 mm (lit.[1] bp. 97-98°/0.6 mm); nmr ($CDCl_3$): δ 7.65 (m, 5H), 2.7-3.1 (m, 6H), 1.75 (s, 1H), 1.1 (d, 6H); ir (neat): 3400, 3010, 1601 cm^{-1}.

1,4-Dibenzoyl-cis-2,6-dimethylpiperazine (VI). - To a 0.25 M solution of 1.45 g (13 mmol) of cis-2,6-dimethylpiperazine (I) was added 3.75 ml (28 mmol) of triethyl amine. The solution was cooled in a ice-water bath, then 3.1 ml (27 mmol) of benzoyl chloride was added dropwise. The ice bath was removed, and the reaction mixture was stirred at room temperature for 2 hr. The triethyl amine hydrochloride which was formed was removed by suction filtration and washed with ether. The organic layer was subsequently washed with 1N HCl and 5% aqueous sodium bicarbonate. The solution was filtered through magnesium sulfate, and the solvent was removed on a rotary evaporator. The product was recrystallized from ethanol and water to furnish 4.18 g (100%) of VI; mp. 149-150° (lit.[2] mp. 147-148°); nmr ($CDCl_3$): δ 7.56 (s, 10H), 4.55 (m, 2H), 3.3-4.1 (m, 4H), 1.35 (d, 6H); ir ($CHCl_3$) 1660, 3100 cm^{-1}.

1-Benzoyl-cis-2,6-dimethylpiperazine (VII). - A mixture of 50 ml of 6M KOH in ethanol and 10 ml of water was added to 3.20 g (0.0099 mmol) of 1,4-dibenzoyl-cis-2,6-dimethylpiperazine (VI). The solution was heated under reflux for 3 hr and the product was extracted into ether. The ether solution was washed with 1N HCl. Sodium hydroxide solution was added to

the aqueous layer to pH = 8, and the basic product was extracted into ether. The extract was washed with 5% aqueous sodium bicarbonate and filtered through $MgSO_4$, and the solvent was evaporated. Recrystallization of the residual solid from acetone gave 1.91 g (89%) of VII, mp. 109-110° (lit.[1] mp. 110-112°); nmr ($CDCl_3$): δ 7.7 (s, 5H), 4.4 (m, 2H), 2.97 (g, 4H), 1.76 (s, 1H), 1.4 (d, 6H); ir ($CHCl_3$) 3400, 1670 cm^{-1}.

1-Benzyl-cis-3,5-dimethylpiperazine (III). - A mixture of 3 g (0.026 mmol) of cis-2,6-dimethylpiperazine (I) and 50 ml anhydrous acetone was heated to 50°. The amine dissolved at this temperature. Anhydrous K_2CO_3 (3.6 g, 0.026 mmol) and 3.3 g (0.026 mmol) of benzyl chloride were added over a 5 min period. The reaction mixture was stirred at 50° for 2 hr during which time a solid precipitated. The reaction mixture was dissolved in water and extracted three times with $CHCl_3$. The solvent was removed on a rotary evaporator leaving an orange oil. The oil was distilled under reduced pressure to give 3.5 g (67.3%) of III; bp. 70°/0.4 mm (lit.[1] bp. 85-86°/0.6 mm); nmr ($CDCl_3$): δ 7.10 (s, 5H), 3.34 (s, 2H), 1.48 (t, 4H), 2.52-2.88 (m, 2H), 1.20 (s, 1H), 0.92 (d, 6H); ir (neat) 3240, 736, 639 cm^{-1}.

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4. This compound was obtained from Aldrich Chemical Co., Milwaukee. Analysis by nmr showed it to be primarily the cis-isomer.

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