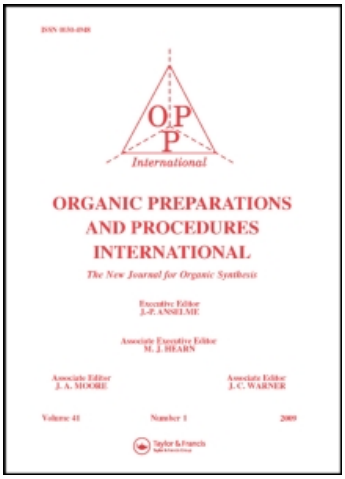

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1-ACYL-4-SUBSTITUTED PIPERAZINES

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OPPI BRIEFS

(By James A. Moore, Associate Editor)

1-ACYL-4-SUBSTITUTED PIPERAZINES

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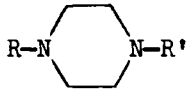
1-Acyl-4-substituted piperazines were prepared by the Schotten-Baumann reaction.

EXPERIMENTAL[2,3]

Intermediates. - The following piperazine derivatives were made by published procedures: 1-(2-hydroxyethyl),[4] 1-carbethoxy,[5] 1-diethylcarbamyl,[6] and 1-(4-isopropylbenzyl),[7] and 1-(3-hydroxypropyl)-4-methyl.[8-10]

1-(2-Methylmercaptoethyl)piperazine. - A solution of 65.5 g (0.76 mole) anhydrous piperazine in 150 ml ethanol was stirred at 75° when the addition of 62.0 g (0.4 mole) β-bromoethyl methyl sulfide[11] was begun. The heat of reaction maintained the temperature at 75-80° during the addition (40 min.). At the end of this time the mixture was refluxed for 10 hrs. There was then added 30.5 g of potassium carbonate, sufficient water to dissolve the solids and the solution was refluxed

TABLE I. - 1-Acyl-4-Substituted Piperazines



R	R'	Salt[a]	Appearance	Mp.°[b] [bp.° (mm)]	Solvent[c] [n_D^{25}]	Yield, %[d]
$-COCHCl_2$	$-CH_2CH_2OH$	Ci	Fine needles	164.5-165.5i	M	59.5
	$-CH_2CH_2SCH_3$	C	Needles	178-179[d]	iPr-Pe	76
	$-COOC_2H_5$	B	Viscous oil	[126-127(0.1)]	[1.5164]	73.5
	$-CON(C_2H_5)_2$	B	Needles	67-69 [ca. 150(9μ)]		91
	$-CH_2C_6H_4$-p-iPr	C	Prisms	232-233	iPr	82.5
$-COCH=CHCH_3$	$-CH_2CH_2OH$	B	Viscous oil	[115-117(0.66)]	[1.5290]	84.5
$-COCH=C(CH_3)2$	$-CH_2CH_2OH$	Ci	Microcryst	133-134	iPr	90.5
$-CO(DCC)$[e]	$-CH_2CH_2OH$	Ci	Warty cryptocryst	183-184i	A-E	92[f]

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[a] B, base; Ci, dihydrogen citrate; C, hydrochloride.

[b] d signifies decomposition; i, decomposition with intumescence.

[c] Legend: A, ethanol; E, ether; iPr, propanol-2; M, methanol; Pe, pentane.

[d] Represents yield a form of base or salt, as tabulated.

[e] 3,4-dichlorocinnamyl. [f] Crude base melted 143-144.5°.

3 hrs. It was concentrated *in vacuo*, and water was removed azeotropically. Thorough extraction of the residue with benzene, followed by fractional distillation, led to removal of excess piperazine as a sublimate, and then the mono- and bis-(2-methylmercaptoethyl)piperazines. The former (31.9 g, 49.8% yield) was a colorless liquid, bp. 125-128°/15 mm; n_D^{25} 1.5182.

1,4-bis(2-Methylmercaptoethyl)piperazine. - (15.7 g, 33.6% yield based upon the halide salt) was a viscous yellowish oil, bp. 120-125°/0.5 mm; n_D^{25} 1.5279. It was characterized as the dihydrochloride, white plates (ethanol), mp. 262° (dec.).

The bis(methiodide) of the disubstituted piperazine was prepared in methanol and crystallized from methanol-pentane. It was a chalky white, microcrystalline solid which decomposed at 156° (if immersed in the bath at 150°).

Crotonyl chloride was made[12] from a commercial sample of the acid. Senecioyl chloride (β,β-dimethylacryloyl chloride) was prepared from mesityl oxide, *via* the acid.[13,14]

3,4-Dichlorocinnamoyl chloride. - The acid[15] (43.4 g, 0.2 mole) was suspended in boiling hexane (500ml) and treated with thionyl chloride (24.0 g, 0.21 mole) for one hour. After refluxing for 5 hrs. a trace of brownish solid was filtered, the solvent was removed, leaving a colorless oil. The acid chloride (44.8 g, 95.3% yield) solidified readily, and a sample twice crystallized from pentane formed white microcrystals, mp. 59.5-60°.

4-Acyl-1-substituted piperazines. - In general, the Schotten-Baumann reactions of the 1-substituted piperazines with the acid chlorides was carried out in dichloromethane at 0° to $+5^{\circ}$ with one equivalent of 1 N sodium hydroxide present. At the end of the reaction, after a day, the layers were separated and the organic layer was washed with saturated sodium chloride solution before drying. A number of the bases were converted directly to salts after removing the solvent.

3-(1-Methyl-4-piperazinyl)propyl 3,4-dichlorocinnamate dihydrochloride. - A solution of 9.5 g (0.04 mole) of 3,4-dichlorocinnamoyl chloride in 30 ml benzene was treated with 1-(3-hydroxypropyl)-4-methylpiperazine (6.45 g, 0.04 mole, of 98% pure basic alcohol) in 25 ml benzene. The mixture was refluxed for an hour before the solvent was removed, leaving a sticky white solid. The dihydrochloride was formed in ether solution yielding 16.4 g of a material of mp. 235-238° (dec.). Upon being crystallized twice from methanol-ether, microcrystals of mp. 251-252° (dec.) were obtained.

REFERENCES

1. To whom correspondence should be addressed at Division of Medicinal Chemistry, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, DC 20012.

2. Analyses were performed under the direction of Mr. M. E. Auerbach and Mr. K. D. Fleischer of this Institute. Mr. L. T. Fletcher rendered valuable technical assistance. All new compounds yielded satisfactory elemental analyses.

3. All melting points are corrected values, whereas boiling points are not.

4. S. M. McElvain and L. W. Bannister, J. Am. Chem. Soc., 76, 1129 (1954).

5. H. W. Stewart, R. J. Turner, J. J. Denton, S. Kushner, L. M. Brancone, W. L. McEwen, R. I. Hewett and Y. SubbaRow, J. Org. Chem., 13, 134 (1948).

6. S. Kushner, L. M. Brancone, R. I. Hewett, W. L. McEwen, Y. SubbaRow, H. W. Stewart, R. J. Turner and J. J. Denton, J. Org. Chem., 13, 144 (1948).

7. F. B. Zienty and G. W. Steahly, U. S. Patent 2 451 645.

8. Procedure similar to that of Zawisza, et al.[9,10] except that 1-(3-hydroxypropyl)piperazine was reductively methylated at 25° under 1500 p.s.i. hydrogen in methanol containing a slight excess of 37% formalin, using a 5% palladium-charcoal catalyst.

9. T. Zawisza, A. Machon and L. Kuczynski, Acta Polon. Pharm., 22, 477 (1965). [Chem. Abst., 64, 12 666d (1966)].

10. T. Zawisza, A. Machon and L. Kuczynski, Polish patent, 53 522 [Chem. Abst., 68, 114 651 (1968)].

11. E. Schneider, Chem. Ber., 84, 911 (1951).

12. H. Staudinger, J. Becker and H. Hirzel, Ber., 49, 1991 (1916).

13. L. I. Smith, W. W. Prichard and L. J. Spillane, Organic Syntheses, Coll. Vol., III, 302.

14. H. Staudinger and E. Ott, Ber., 44, 1636 (1911).

15. C. Walling and K. B. Wolfstirn, J. Am. Chem. Soc., 69, 854 (1947).