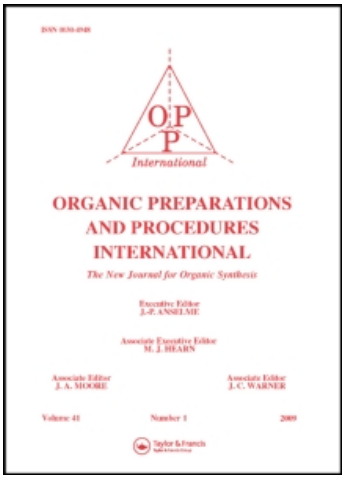

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A NEW SYNTHESIS OF SYMMETRIC PIPERAZINES DERIVATIVES

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A NEW SYNTHESIS OF SYMMETRIC PIPERAZINES DERIVATIVES

Submitted by (01/13/93)

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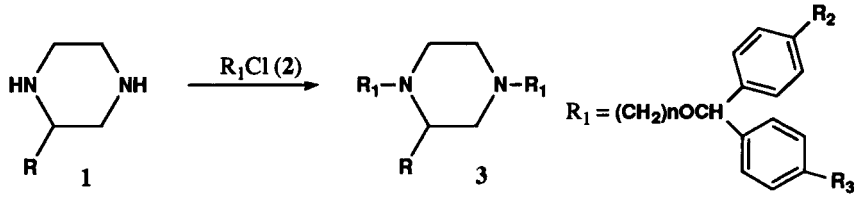
Cinnarizine and the GBR 12783[1] derivative were recently found to be specific inhibitors of *dopamine* uptake. The present paper describes the synthesis of new piperazine salts. These symmetric derivatives **3a-j** were obtained directly from variously substituted benzhydrylchloroalkanes **2**[2] in dimethylformamide at 160° in presence of potassium carbonate. From the oily bases, dihydrochloride salts **3a-d** were generated with hydrochloric acid while the dioxalate salts **3e-j** were obtained with oxalic acid. The structures of these symmetric piperazines were confirmed by NMR.



a) $R = R_2 = R_3 = H$, n = 2, X = Cl
b) $R = R_2 = R_3 = H$, n = 3, X = Cl
c) $R = R_2 = R_3 = H$, n = 4, X = Cl
d) $R = R_2 = R_3 = H$, n = 6, X = Cl
e) $R = R_3 = H$, $R_2 = CH_3$, n = 2, $X = C_2O_4H$
f) $R = CH_3$, $R_2 = R_3 = H$, n = 2, $X = C_2O_4H$
g) $R = R_2 = CH_3$, $R_3 = H$, n = 2, $X = C_2O_4H$
h) $R = R_3 = H$, $R_2 = Cl$, n = 2, $X = C_2O_4H$
i) $R = H$, $R_2 = R_3 = Cl$, n = 2, $X = C_2O_4H$
j) $R = H$, $R_2 = R_3 = F$, n = 2, $X = C_2O_4H$

EXPERIMENTAL SECTION

Melting points were determined on a Kofler WME type apparatus and were uncorrected. IR spectra were recorded as KBr pellets on a Philips PU spectrometer. ^1H NMR spectra were obtained on a Varian EM 390 spectrometer at 90 MHz in DMSO-d_6 with TMS as an internal reference and chemical shifts are expressed as δ (ppm). The benzhydrylchloroalkanes were prepared according to the literature method.[2]

1,4-(Benzhydryloxyethyl)piperazine Dihydrochlorides (3a). General Procedure.- A mixture of 5 g (0.058 mol) of piperazine **1**, 28.66 g (0.116 mol) of benzhydrylchloroalkane **2**, 16.01 g (0.116 mol) powdered potassium carbonate and 70 mL of dimethylformamide was refluxed for 3 hrs, cooled, poured into an ice-water mixture and extracted with ethyl acetate. The filtrate was dried and concentrated. The residue was dissolved in isopropanol and etheral hydrogen chloride was added to bring the pH to 2.5. The dihydrochloride was collected and recrystallized from acetonitrile to give 20 g (60%) of **3a**. The dioxalate **3e** was obtained by treatment of the corresponding base in presence of oxalic acid in isopropanol, (62%) of **3e**. The data for products **3b-3j** are summarized in the Table 1.

TABLE 1. 1,4-Disubstituted Piperazine Derivatives.

Cmpd.	Yield (%)	mp.[a] (°C)	Time (hrs)	Salts	^{1}H NMR/TMS (δ) ppm
3a	60	198	3	2HCl	4.50 (2NH), 7.30 (Ar, 4 C_6H_5), 5.53 (2H, 2CH), 3.90, 3.43 (16H, CH_2).
3b	72	192	3	2HCl	4.10 (2NH), 7.23 (Ar, 4 C_6H_5), 5.40 (2H, 2CH), 3.56, 3.23 (20H, CH_2).
3c	60	194	3	2HCl	4.60 (2NH), 7.25 (Ar, 4 C_6H_5), 5.50 (2H, 2CH), 3.80, 3.40, 2.10 (24H, CH_2).
3d	40	178	4	2HCl	3.73 (2NH), 7.30 (Ar, 4 C_6H_5), 5.53 (2H, 2CH), 3.40, 3.10, 1.56 (16H, CH_2).
3e	62	212	4	$2(CO_2H)_2$	8.56 (2NH), 7.33, 7.10 (Ar, 2 C_6H_5, 2 C_6H_4), 5.43 (2H, 2CH), 3.40, 3.00 (16H, CH_2), 2.26 (6H, $2CH_3$).
3f	35	189[b]	4	$2(CO_2H)_2$	6.83 (2NH), 7.26 (Ar, 4 C6H5), 5.43 (2H, 2CH), 3.50, 3.00 (14H, CH_2), 2.63 (1H, C<u>H</u>-CH_3), 1.13 (3H, CH-C<u>H</u>$_3$).
3g	30	118[b]	4	$2(CO_2H)_2$	6.73 (2NH), 7.26, 7.10(Ar, 2 C_6H_5, 2 C_6H_4), 5.40 (2H, 2CH), 3.56, 3.03 (14H, CH_2), 2.43 (1H, C<u>H</u>-CH_3), 1.13 (3H, CH-C<u>H</u>$_3$), 2.26 (6H, $2CH_3$).
3h	40	204	4	$2(CO_2H)_2$	7.90 (2NH), 7.33 (Ar, 2 C_6H_5, 2 C_6H_4), 5.50 (2H, 2CH), 3.60, 3.00 (16H, CH_2).
3i	50	199	4	$2(CO_2H)_2$	9.00 (2NH), 7.30 (Ar, 4 C_6H_4), 5.30 (2H, 2CH), 3.36, 2.80 (16H, CH_2).
3j	80	222[b]	4	$2(CO_2H)_2$	7.80 (2NH), 7.28, 7.00 (Ar, 4 C_6H_4), 5.40 (2H, 2CH), 3.60, 3.15 (16H, CH_2).

a) Crystallized from acetonitrile unless otherwise noted. b) Ethanol.

TABLE 2. Elemental Analysis Data of Compounds 3.

Cmpd	Elemental Analysis Data (Found)			
	C	H	N	Cl
3a	70.47 (70.50)	6.93 (6.70)	4.83 (4.92)	12.23 (12.30)
3b	71.16 (71.20)	7.30 (7.28)	4.61 (4.62)	11.67 (11.70)
3c	71.79 (71.80)	7.61 (7.65)	4.40 (4.46)	11.15 (11.22)
3d	72.91 (72.95)	8.16 (8.22)	4.05 (4.10)	10.25 (10.28)
3e	67.21 (67.18)	6.49 (6.43)	3.92 (4.00)	– –
3f	66.84 (66.90)	6.33 (6.40)	4.00 (4.05)	– –
3g	67.56 (67.58)	6.64 (6.70)	3.85 (3.81)	– –
3h	60.40 (59.99)	5.34 (5.34)	3.71 (3.67)	– –
3i	55.35 (55.46)	4.65 (4.70)	3.40 (3.58)	– –
3j	60.15 (60.20)	5.04 (5.10)	3.69 (3.72)	– –

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SAMARIUM TRIIODIDE CATALYZED DITHIOACETAL AND DITHIOKETAL FORMATION

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Recently, lanthanide compounds, in particular samarium (II) diiodide, have gained increasing popularity as versatile reagents in organic synthesis.[1] However as far as we know, little attention has been devoted to the application of samarium (III) compounds. Very recently, we have found that samarium triiodide promoted the efficient formation of the carbon-carbon double bond between α-haloketones and carbonyl compounds, and the opening of the tetrahydrofuran ring accompanied by the coupling with acyl chloride.[2] We now report the dithioacetalization or dithioketalization of carbonyl compounds in the presence of samarium triiodide.

At room temperature, most carbonyl compounds are satisfactorily dithioacetalized or dithioketalized by 1,2-dithioethane or 1,3-dithiopropane in anhydrous acetonitrile in the presence of two equivalents of samarium triiodide (Method A). Furthermore, satisfactory results were also obtained with catalytic amount of samarium triiodide (0.1 equiv.) with longer reaction time (Method B). Samarium triiodide is conveniently prepared from samarium powder and iodine either stepwise prior to the reaction or *in situ* in a one-pot reaction. In the case of sterically hindered ketones, such as benzophenone or α-bromocamphor, the desired dithioketals were not obtained probably because of