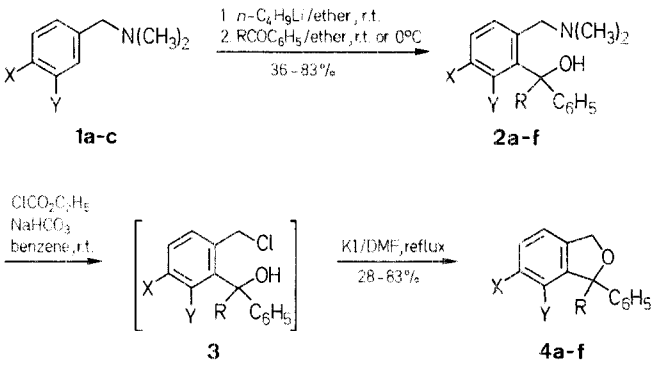

1	X	Y	2-4	X	Y	R
a	OCH_3	H	a	OCH_3	H	C_6H_5
b	OCH_3	OCH_3	b	OCH_3	OCH_3	C_6H_5
c	$-OCH_2O-$		c	$-OCH_2O-$		C_6H_5
			d	OCH_3	H	H
			e	OCH_3	OCH_3	H
			f	$-OCH_2O-$		H

A Useful Synthesis of Alkoxyphthalans (1,3-Dihydro-2-benzofurans)

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A convenient, general synthesis of alkoxy- and dialkoxyphthalans having phenyl substituents at the 1-position from substituted *N,N*-dimethylbenzylamines is described.

The phthalan (1,3-dihydro-2-benzofuran) ring system is of interest not only because it is present in some natural products[1] but also because it is a novel synthon for the synthesis of complex molecules.[2-4] A few phthalan derivatives are known to possess biological activities[5] and some of them have found industrial application.[6]

Two different approaches have been reported[7,9] for the synthesis of phthalans. The first method utilises[7,8] 2-hydroxymethylbenzylalcohol derivatives while the second one makes use of 2-hydroxymethylbenzylamines.[9] In the former method, the benzylalcohols are cyclised[7,8] using an acid catalyst while in the latter the quaternary methiodides are obtained first, and then thermally cyclised[9] to give phthalans. We report here a simple method (Scheme) for the synthesis of phthalans **4** from 2-hydroxymethyl-N,N-dimethylbenzylamines **2**. In our method the carbinolamines **2** give phthalans **4** by reaction with ethyl carbonochloridate and sodium hydrogen carbonate, presumably via the intermediacy of **3**. In two cases (**2a** and **2c**), the chloroalcohols (**3a** and **3c**) were isolated in pure form and converted into the phthalans (**4a** and **4c**) by reaction with potassium iodide in dimethylformamide. The advantage of the present method is that the carbinol amines **2** can be directly converted into the phthalans **4**. The carbinol amines **2** have been synthesized by making use of the heteroatomdirected lithiation reaction,[10,11] which provides a substitution pattern which is not easily available by direct acid-catalysed methods. Except for **4a**, all products reported here are new. The structures of all products were determined on the basis of their analytical and spectral data. The protons 1-H and 3-H in compounds **4d–f** exhibited an ABX pattern in the ^{1}H-NMR spectrum.

All m.p.s and b.p.s are uncorrected. IR spectra were recorded on a Beckmann IR-20 Infrared spectrophotometer and the ^{1}H-NMR spectra on a Perkin-Elmer R-32 (90 MHz) instrument.

2-(Dimethylaminomethyl)phenyl Carbinols 2:
The carbinolamines **2a,c,e,f** are prepared as reported.[9,12] Compounds **2b** and **2d** are prepared from amines **1b** and **1a**, respectively, by lithiation of these amines with butyllithium, followed by reaction with benzaldehyde or benzophenone.

5,6-Dimethoxy-2-(dimethylaminomethyl)phenyl Diphenyl Carbinol (2b):
A solution of *N,N*-dimethyl-3,4-dimethoxybenzylamine (**1b**; 1.95 g, 0.01 mol) in ether (30 ml) is treated with butyllithium [0.045 mol; prepared from lithium (0.6 g) and 1-bromobutane (4.5 ml) in ether (100 ml)]. The metallation mixture is stirred at room temperature for 2 h and then treated with a solution of benzophenone (8.2 g, 0.045 mol) in ether (20 ml). The mixture is stirred at room temperature for 2 h and then decomposed with water (70 ml). The ether layer is separated and the aqueous layer extracted with ether (2 × 30 ml). The combined ether layer is extracted with 4 normal hydrochloric acid (2 × 30 ml) and the ether layer is discarded. The acid layer is neutralised with 10 normal sodium hydroxide, the solid obtained is filtered off, washed with water, and recrystallised from hexane to give **2b**; yield: 2.52 g (77%); m.p. 122–123°C.

$C_{24}H_{27}NO_3$ (377.5) calc. C 76.36 H 7.21
found 76.10 7.09

IR (Nujol): $\nu = 3450\ cm^{-1}$ (br., OH)

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 2.08$ [s, 6H, $N(CH_3)_2$]; 2.78 (s, 3H, OCH_3); 3.39 [s, 2H, CH_2-$N(CH_3)_2$]; 3.80 (s, 3H, OCH_3); 6.75 (d, 1H, $J = 8$ Hz, Ar-H); 6.88 (d, 1H, $J = 8$ Hz, Ar-H); 7.1–7.4 ppm (m, 10 H_{arom}).

2-(Dimethylaminomethyl)-5,6-methylenedioxybenzyl Alcohol (2d):
A solution of *N,N*-dimethyl-3,4-methylenedioxybenzylamine (**1a**; 1.65 g, 0.01 mol) in ether (30 ml) is treated with butyllithium [0.03 mol; prepared from lithium (0.45 g) and 1-bromobutane (3.0 ml) in ether (100 ml)]. The metallation mixture is stirred at room temperature for 24 h and then cooled to 0°C. A solution of benzaldehyde (5.3 g, 0,03 mol) in ether (20 ml) is added at 0°C and stirring is continued for 1 h. The mixture is then decomposed with water (70 ml) and worked up as described for **2b** to give an oily product. This is chromatographed over silicagel using hexane/ethyl acetate (9:1) as eluent to give **2d**; yield: 1.7 g (63%); m.p. 71–72°C (chloroform/hexane).

$C_{17}H_{21}NO_2$ (271.3) calc. C 75.24 H 7.80
found 75.47 7.90

IR (Nujol): $\nu = 3350\ cm^{-1}$ (br., OH).

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 2.18$ [s, 6H, $N(CH_3)_2$]; 3.08, 3.21 [*d*, 1H each, $J = 13$ Hz, CH_2-$N(CH_3)_2$]; 3.78 (s, 3H, OCH_3); 5.79 (s, 1H, -CHOH); 6.68–7.50 ppm (m, 8H, 3 H_{arom} + 5 H_{arom}).

Table. Phthalans **4** and 2-Chloromethylphenyl Diphenyl Carbinols **3a** and **3c** Prepared

Product	Yield (%)	m.p. (°C)	Molecular Formula[a] or Lit. data	^{1}H-NMR ($CDCl_3$/TMS)/δ (ppm)
4a	64	91–92	91.5–92.5[9]	3.76 (s, 3H, OCH_3); 5.11 (s, 2H, $-CH_2O$); 6.7–6.9 (*m*, 2H$_{arom}$); 7.05–7.50 (*m*, 11H$_{arom}$)
4b	77	117–118	$C_{22}H_{20}O_3$ (332.4)	3.05 (s, 3H, OCH_3); 3.82 (s, 3H, OCH_3); 5.04 (s, 2H, $-CH_2-O$); 6.85 (s, 2H$_{arom}$); 7.15–7.60 (*m*, 10H$_{arom}$)
4c	83	168–169	$C_{21}H_{16}O_3$ (316.3)	5.16 (s, 2H, $-CH_2-O$); 5.90 (s, 2H, $-OCH_2O$); 6.67 (d, J = 8 Hz, 1H$_{arom}$); 6.80 (d, J = 8 Hz, 1H$_{arom}$); 7.2–7.6 (*m*, 10H$_{arom}$)
4d	28	oil	$C_{15}H_{14}O_2$ (226.3)	3.62 (s, 3H, OCH_3); 5.04 (dd, J = 12, 1.5 Hz, 1H, $-\underline{H}CH-O$); 5.24 (dd, J = 12, 2.5 Hz, 1H, $-HC\underline{H}-O$); 6.02 (*dd*, ill resolved, J = 2.5, 1.5 Hz, 1H, $-CH-O$); 6.45 (d, J = 2 Hz, 1H$_{arom}$); 6.73 (dd, J = 9, 2 Hz, 1H$_{arom}$); 7.06 (d, J = 9 Hz, 1H$_{arom}$); 7.23 (br.s, 5H$_{arom}$)
4e	30	oil	$C_{16}H_{16}O_3$ (256.3)	3.33 (s, 3H, OCH_3); 3.80 (s, 3H, OCH_3); 5.02 (dd, J = 12, 1.5 Hz, 1H, $-\underline{H}CH-O$); 5.27 (dd, J = 12, 2.5 Hz, 1H, $-HC\underline{H}-O$); 6.18 (dd, J = 2.5, 1.5 Hz, 1H, $-CH-O$); 6.8 (s, 2H$_{arom}$); 7.23 (br.s, 5H$_{arom}$)
4f	47	136	$C_{15}H_{12}O_3$ (240.3)	5.04 (dd, J = 12, 1.5 Hz, 1H, $-\underline{H}CH-O$); 5.24 (dd, J = 12, 2.5 Hz, 1H, $-HC\underline{H}-O$); 5.79 (s, 2H, $-OCH_2O-$); 6.17 (dd, ill resolved, J = 2.5, 1.5 Hz, 1H, $-C\underline{H}-O$); 6.59 (d, J = 9 Hz, 1H$_{arom}$); 6.72 (d, J = 9 Hz, 1H$_{arom}$); 7.3 (*m*, 5H$_{arom}$)
3a	98	117–118	$C_{21}H_{19}ClO_2$ (338.8)	3.35 (br.s, 1H, exchangeable with D_2O, OH); 3.59 (s, 3H, OCH_3); 4.49 (s, 2H, CH_2Cl); 6.21 (d, J = 2 Hz, 1H$_{arom}$); 6.79 (dd, J = 9, 2 Hz, 1H$_{arom}$); 7.23 (m, 10H$_{arom}$); 7.42 (d, J = 9 Hz, 1H$_{arom}$)
3c	86	132	$C_{21}H_{17}ClO_3$ (352.8)	3.9 (br.s, 1H, exchangeable with D_2O, OH); 4.3 (s, 2H, CH_2Cl); 5.7 (s, 2H, OCH_2O); 6.9 (d, J = 8 Hz, 1H$_{arom}$); 7.0 (d, J = 8 Hz, 1H$_{arom}$); 7.3 (s, 10H$_{arom}$)

[a] Satisfactory microanalysis obtained: C ±0.32, H ±0.28.

Phthalans 4b and 4f; General Procedure:
Sodium hydrogen carbonate (1.0 g, 12 mmol) is added to a stirred solution of carbinolamine **2b** or **2f** (1.5 mmol) in benzene (15 ml). A solution of ethyl carbonochloridate (1.04 g, 10 mmol) in benzene (5 ml) is added, the mixture is stirred at room temperature for 1 h, and then filtered. The solvent is removed under reduced pressure and the remaining solid is recrystallised from chloroform/hexane to afford **4b** or **4f**.

Chloroalcohols 3a and 3c:
The carbinolamines **2a** and **2c** are reacted with ethyl carbonochloridate in presence of sodium hydrogen carbonate in benzene solution as described above. The solid products obtained after work-up are recrystallised from chloroform/hexane to give **3a** or **3c** in 98 and 86% yield, respectively. In the case of **2a**, the reaction mixture is stirred for 8 h.

Conversion of 3a and 3c to Phahalans 4a and 4c:
Potassium iodide (0.05 g) is added to a solution of carbinol **3a** or **3c** (1 mmol) in dimethylformamide (3 ml) and the mixture is refluxed for 4 to 8 h (monitored by TLC). Water (15 ml) is added and the mixture is extracted with ether (2 × 20 ml). The ether layer is dried with sodium sulfate and evaporated and the remaining solid is recrystallised from chloroform/hexane to give phthalans **4a** or **4c**.

Phthalans 4d and 4e:
The carbinolamines **2d** and **2e** (1.5 mmol) are converted to the chloroalcohols **3d** or **3e**, respectively, as described for **3a** and **3c**. Benzylalcohols **3d** or **3e** are isolated as oily products. Without further purification they are converted into phthalans **4d** and **4e**, respectively as described for **4a** and **4c**. Evaporation of the dried ether layer gives viscous liquid which is purified by HPLC over silicagel using hexane/ethyl acetate (9:1) as eluent to give **4d** or **4e** as thick viscous oils.

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