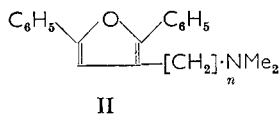
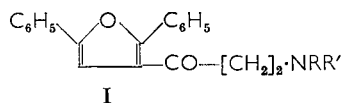


Note on derivatives of 2,5-diphenylfuran

P. M. G. BAVIN

Aminoalkyl derivatives of 2,5-diphenylfuran have been prepared and shown to be general central nervous system depressants.

SEVERAL derivatives of 2,5-diphenylfuran have been prepared and examined for tranquillising action on the central nervous system. Both groups of compounds, (I) and (II), summarised in the Table, were general central nervous system depressants and did not warrant further examination.



The obvious route to *NN*-dimethyl[3-(2,5-diphenylfur-3-yl)propyl]-amine (IIc) was thwarted by extensive decomposition which accompanied attempted reduction of the Mannich bases (I) by a variety of reagents (sodium borohydride, aluminium lithium hydride, catalytic hydrogenation, hydrazine) (cf. Williams & Day, 1952). For the preparation of the tertiary amines (II), 3-bromo-2,5-diphenylfuran was a suitable intermediate. Of several brominating agents examined, only *N*-bromosuccinimide gave, with 2,5-diphenylfuran, a product free from substitution in the phenyl groups. The bromide was converted via the nitrile to 2,5-diphenylfur-3-oic acid, identical with the product of a Kröhnke degradation (Arnold, Murai & Dodson, 1950) of the acetyl compound, 3-acetyl-2,5-diphenylfuran. The dimethylaminomethyl compound (IIa) was readily obtained by reduction of the corresponding dimethylamide. The homologues (IIb) and (IIc) were very conveniently prepared by reaction between 2,5-diphenylfur-3-ylmagnesium bromide and the appropriate ω -dimethylaminoalkyl chloride. Although the yields were low, the products were easily isolated in a high state of purity. This method has been used extensively in these laboratories (Ganellin & Ridley, 1964) and appears to be widely applicable.

Experimental

3-Bromo-2,5-diphenylfuran. 2,5-Diphenylfuran (44 g, 0.2 mol) and *N*-bromosuccinimide (39.2 g, 0.22 mol) were boiled under reflux for 2 hr with carbon tetrachloride (200 ml) and concentrated hydrobromic acid (4 drops). The mixture was chilled to complete crystallisation of the succinimide and filtered. The filtrate was washed with sodium bicarbonate solution, dried (MgSO_4), and evaporated to leave a yellow solid, crystallisation of which from ethanol gave pale yellow needles (49.8 g, 83%), m.p. 65–66°. Found: C, 64.4; H, 3.6. Calc. for $\text{C}_{16}\text{H}_{11}\text{BrO}$: C,



From Smith, Kline & French Laboratories, Welwyn Garden City, Hertfordshire.

DERIVATIVES OF 2,5-DIPHENYLFURAN

64.2; H, 3.7%. Although this material ran as a single spot on thin-layer chromatograms and was suitable for the preparation of the Grignard reagent, chromatography from hexane on alumina gave colourless needles, m.p. 79–80° (Lutz & Reese, 1959, record m.p. 77–78° but other authors have noted the range observed by us).

3-Cyano-2,5-diphenylfuran. A mixture of the bromodiphenylfuran (180 g) and cuprous cyanide (60 g) was boiled under reflux for 2 hr with dimethylformamide (180 ml) and pyridine (4 drops). The mixture was cooled, poured into excess aqueous ammonia (d 0.88) and extracted with carbon tetrachloride. Evaporation of the dried (K_2CO_3) extract left a yellow solid which crystallized as white needles (88.3 g) from acetone, m.p. 115–116°. Found: C, 83.1; H, 4.5; N, 6.0. Calc. for $C_{17}H_{11}NO$: C, 83.2; H, 4.5; N, 5.7%.

TABLE 1. DERIVATIVES OF 2,5-DIPHENYLFURAN

	LD50 ^a	M.p. of hydrochloride ^b	Formula of hydrochloride	Calculated				Found				
				C	H	N	Cl'	C	H	N	Cl'	
Ia, R = R' = Me	375	189–190° ^c										
Ib, R, R' =  NMe	450	210–212°	$C_{24}H_{28}Cl_2N_2O_2$				15.85					15.52 15.46
Ic, R, R' =  O	1000	191–192° ^d	$C_{28}H_{24}ClNO_3$	69.42	6.08	3.52	8.91	69.15	6.01	3.46		8.80
IIa, n = 1	180	225–225.5°	$C_{19}H_{10}ClNO$	72.71	6.42	4.46	11.30	72.41	6.27	4.29		11.34
IIb, n = 2	50	212–213°	$C_{20}H_{12}ClNO$	73.27	6.77			72.84 72.81	6.77 6.94			
IIc, n = 3	500	135–136°	$C_{21}H_{14}ClNO$	73.80	7.08	4.09	10.29	73.28 73.19	7.23 7.40	3.82		10.29

a mg/kg, i.p. in male albino mice, mortalities being recorded for 7 days.

b corrected.

c Lutz & Rowlett (1948).

d Free base, m.p. 101.5°, Lutz & Rowlett (1948).

2,5-Diphenylfur-3-oic acid. Hydrolysis of the nitrile with potassium hydroxide in boiling diethylene glycol gave 2,5-diphenylfur-3-oic acid, m.p. 223–224° after crystallisation from ethanol, identical with the Kröhnke degradation product of 3-acetyl-2,5-diphenylfuran (Lutz & Rowlett (1948) record m.p. 217°).

NN-Dimethyl-2,5-diphenylfur-3-amide. The dimethylamide, prepared from the foregoing acid via the acid chloride in the usual way, crystallised from benzene-hexane as pale yellow needles, m.p. 88.5–89.0°. Found: C, 78.15; H, 5.9; N, 4.7. Calc. for $C_{19}H_{17}NO_2$: C, 78.3; H, 5.9; N, 4.8%.

NN-Dimethyl[2-(2,5-diphenylfur-3-ylmethyl)amine]. Reduction of the dimethylamide by extraction from a Soxhlet thimble with ethereal aluminium lithium hydride gave the dimethylaminomethyl compound (IIa).

NN-Dimethyl[2-(2,5-diphenylfur-3-yl)ethyl]amine hydrochloride. The bromodiphenylfuran (30 g) was converted to the Grignard reagent by warming and stirring with magnesium (3 g) in anhydrous benzene-ether

(1:1, 150 ml), the reaction being complete in approximately 15 min. A solution of 2-dimethylaminoethyl chloride (from 30 g of the hydrochloride) in toluene was added and the mixture stirred and warmed on the steam-bath for 3 hr. The mixture was poured onto ice and excess hydrochloric acid and extracted with benzene-hexane. The aqueous layer was chilled, basified with 40% aqueous sodium hydroxide solution and extracted several times with ether. The dried (MgSO_4) extracts were evaporated to leave an oil (Iib), the hydrochloride of which crystallised from isopropanol-ether as white needles (6.9 g), m.p. 212–213°. The dimethylaminopropyl compound was prepared similarly.

3-(2,5-Diphenylfur-3-oyl)propionitrile. The methiodide from (Ia) (m.p. 189–190° decomp., 12.2 g) was stirred and heated on a steam-bath for 3 hr with potassium cyanide (12.2 g) and dimethyl sulphoxide (150 ml). The mixture was cooled, diluted with water and extracted several times with ether. Evaporation of the extracts left an oil which was purified by chromatography (hexane-alumina). The pure cyano-ketone crystallised as pale yellow needles from methanol (4.1 g.) m.p. 98–99°. Found: C, 79.6; H, 5.3; N, 4.65. Calc. for $\text{C}_{20}\text{H}_{15}\text{NO}_2$; C, 79.7; H, 5.0; N, 4.65%.

The cyano-ketone decomposed during attempted reduction with ethereal aluminium lithium hydride.

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