Chemistry of Benzo[*b*]furan IV. (1). Chemical Behaviour of Furo[3,4-*b*]benzofuran and Synthesis of 4-Arylbenzofuro[2,3-*d*]pyridazines.

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Furo[3,2-*b*]benzofuran was demonstrated to be an intermediate for the synthesis of dibenzofuran and 1,4-epoxy-1,4-dihydrodibenzofuran ring systems. Starting from the readily available aryl 3-bromomethyl-2-benzo[*b*]furyl ketones, a method was developed for the synthesis of 4-arylbenzofuro[2,3-*d*]pyridazines.

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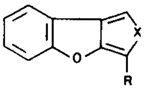
As a part of a program designed to expand the chemistry of benzo[*b*]furan (2,3) recently we reported the synthesis of substituted thieno[3,4-*b*]benzofuran (I, X = S) and substituted seleno[3,4-*b*]benzofuran (I, X = Se) (4). It was of interest to prepare the oxa-analog of this ring, namely substituted furo[3,4-*b*]benzofuran (I, X = O).



I

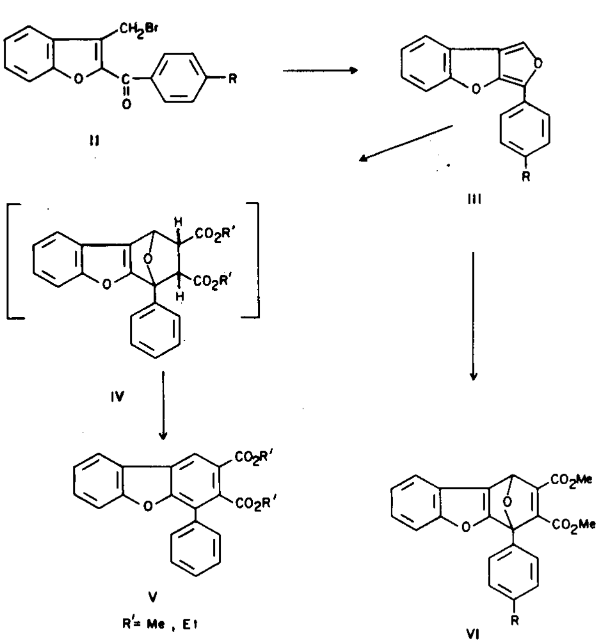
As the neighbouring carbonyl group in aryl 3-bromomethy-2-benzo[*b*]furyl ketones (II) (4) is well placed to interact with the bromomethyl group, it seemed likly that the desired compound, 3-arylfuro[3,4-*b*]benzofurans (III), could be prepared from II. Examples of the neighbouring group participation of this type were reported previously (5-8). Heating compound II under different experimental conditions did not give the desired compound III. In fact, in all cases either the starting material or an untractable mixture was obtained. However, an equilibrium between compounds II and III could not be ruled out. In fact, in a similar case, such an equilibrium was reported previously (9). The existence of this equilibrium was established by capturing the intermediate III through a Diels-Alder reaction with dienophiles (9,10).

Reaction of dimethyl maleate and diethyl fumarate with compound II (R = H) afforded dimethyl 4-phenyldibenzofuran-2,3-dicarboxylate (V, R′ = Me), and diethyl 4-phenyldibenzofuran-2,3-dicarboxylate (V, R′ = Et), respectively, in good yields. The mechanism suggested for the formation of these dibenzofurans is shown in Scheme I.

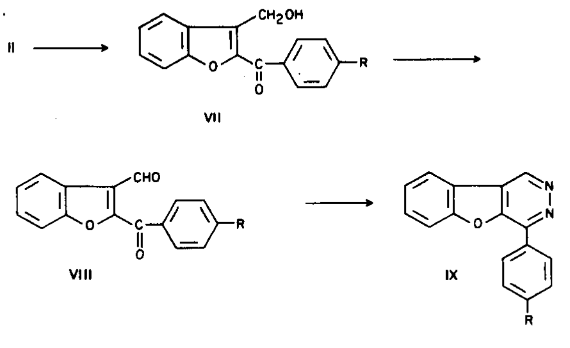
As it could be seen from this mechanism, the Diels-Alder reaction of compound III (R = H) with dimethyl maleate or diethyl fumarate would give the intermediate IV. This intermediate was unstable under the reaction conditions and aromatized by dehydration to compound V. The reaction of compound II with dimethyl acetylenedicarboxylate gave compound VI which was quite stable and could be isolated in high yield (See Scheme I).

As it could be seen from the Scheme I, the accessibility of furo[3,4-*b*]benzofuran as a reactive intermediate had important consequences. Thus, substituted dibenzofurans and 1,4-epoxy-1,4-dihydro-4-aryldibenzofurans could be obtained in high yields (See Experimental and Table I).

Scheme I



a) R = H; b) R = Br; c) R = Cl; d) R = CH_3; e) R = CH_3O-; f) R = CH_3S-

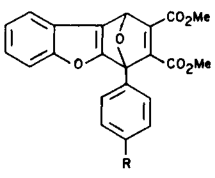


a) R = H; b) R = Br; c) R = Cl; d) R = CH_3; e) R = CH_3O-; f) R = CH_3S-

Finally, in view of the potent pharmacological activity of the pyridazine ring system, it was also of interest to incorporate the pyridazine moiety into the benzo[*b*]furan. Therefore, 4-substituted benzofuro[2,3-*d*]pyridazines (IX) were prepared as it is shown in Scheme I.

Hydrolysis of compound II through chromatography on activated alumina (11) followed by oxidation of com-

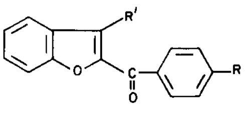
Table I



Compound	R	Yield (%)	M.p. °C (a)	Formula	Calcd.	Found	Calcd.	Found
					C%		H%	
VIa	H	70	208-210	$C_{22}H_{16}O_6$	70.21	70.03	4.26	4.44
VIb	Br	68	224-226	$C_{22}H_{15}BrO_6$	58.02	58.20	3.30	3.18
VIc	Cl	75	213-215	$C_{22}H_{15}ClO_6$	64.31	64.50	3.65	3.83
VId	CH_3	65	200-202	$C_{23}H_{18}O_6$	70.77	70.59	4.62	4.46
VIe	CH_3O-	75	227-228	$C_{23}H_{18}O_7$	67.98	67.79	4.43	4.25
VIf	CH_3S-	73	232-233	$C_{23}H_{18}O_6S$	65.40	65.26	4.27	4.09

(a) All compounds were crystallized from ether.

Table II



Compound	R	R′	Yield (%)	M.P. °C (a)	Formula	Calcd.	Found	Calcd.	Found
						C%		H%	
VIIa	H	CH_2OH	60	64-65	$C_{16}H_{12}O_3$	76.19	76.38	4.76	4.94
VIIb	Br	CH_2OH	60	137-139	$C_{16}H_{11}BrO_3$	58.00	58.15	3.32	3.05
VIIc	Cl	CH_2OH	58	138-140	$C_{16}H_{11}ClO_3$	67.02	72.15	4.96	4.77
VIId	CH_3	CH_2OH	65	78-80	$C_{17}H_{14}O_3$	76.69	76.49	5.26	5.07
VIIe	CH_3O-	CH_2OH	70	102-103	$C_{17}H_{14}O_4$	72.34	72.15	4.96	4.77
VIIf	CH_3S-	CH_2OH	70	97-98	$C_{17}H_{14}O_3S$	68.46	68.65	4.70	4.85
FIIIa	H	CHO	90	97-98	$C_{16}H_{10}O_3$	76.80	76.99	4.00	4.15
VIIIb	Br	CHO	87	129-131	$C_{16}H_9BrO_3$	58.36	58.17	2.74	2.58
VIIIc	Cl	CHO	92	110-111	$C_{16}H_9ClO_3$	67.49	67.31	3.16	3.02
VIIId	CH_3	CHO	90	94-95	$C_{17}H_{12}O_3$	77.27	77.35	4.54	4.71
VIIIe	CH_3O-	CHO	85	102-103	$C_{17}H_{12}O_4$	72.86	72.67	4.29	4.37
VIIIf	CH_3S-	CHO	95	104-105	$C_{17}H_{12}O_3S$	68.92	68.75	4.05	4.17

(a) All compounds were crystallized from petroleum ether.

pound VII with manganese dioxide afforded 3-formyl-2-benzo[*b*]furyl ketones VIII. Treatment of compound VIII with hydrazine in ethanol gave 4-arylbenzofuro-[2,3-*d*]pyridazines (IX) in high yields.

The physical constants of the compounds prepared are summarized in Tables II and III.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage and are uncorrected. The ir spectra were obtained using a Perkin-Elmer model 267 spectrograph (potassium bromide discs). The nmr spectra were recorded on a Varian T-60 spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were run on a Varian Model MAT MS-311 spectrometer at 70 eV.

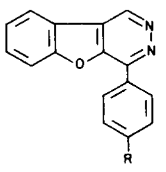
Reaction of Phenyl 3-Bromomethyl-2-brnzo[*b*]furyl Ketone with Dimethyl Maleate.

A mixture of phenyl 3-bromomethyl-2-benzo[*b*]furyl ketone (IIa, 315 mg., 1 mmole) (4) and dimethyl fumarate (576 mg., 4 mmoles) were heated at 170° for six hours. After cooling, the residue was purified by tlc (silica gel, chloroform), and the desired compound was crystallized from ether to give 252 mg. (70%) of V (R′ = Me), m.p. 155°, mixed melting point with an authentic sample 155° (4).

Reaction of Phenyl 3-Bromomethyl-2-benzo[*b*]furyl Ketone with Diethyl Fumarate.

A mixture of IIa (315 mg., 1 mmole) and diethyl fumarate (516 mg., 3 mmoles) were heated at 170° for 6 hours and worked up as above. The desired compound was crystallized from ether

Table III



Compound	R	Yield (%)	M.p. °C (a)	Formula	Calcd.	Found	Calcd.	Found	Calcd.	Found
					C%		H%		N%	
IXa	H	80	161-162	$C_{16}H_{10}N_2O$	78.05	78.23	4.06	4.24	11.38	11.56
IXb	Br	65	209-210	$C_{16}H_9BrN_2O$	59.26	59.26	2.77	2.58	8.62	8.43
IXc	Cl	70	177-178	$C_{16}H_9BlN_2O$	68.45	68.27	3.21	3.03	9.98	9.79
IXd	CH_3-	68	173-175	$C_{17}H_{12}N_2O$	78.46	78.64	4.62	4.51	10.77	10.92
IXe	CH_3O-	75	203-204	$C_{17}H_{12}N_2O_2$	73.91	73.75	4.35	4.54	10.15	10.32
IXf	CH_3S-	78	183-184	$C_{17}H_{12}N_2OS$	69.86	69.71	4.11	4.03	9.59	9.41

(A) All compounds were crystallized from ethanol.

to give 252 mg. (60%) of V (R′ = Et), m.p. 89-90°; nmr deuteriochloroform): 8.70 (s, 1H, aromatic), 8.15-7.80 (m, 2H, aromatic), 7.63-7.33 (m, 7H, aromatic), 4.70-4.0 (2q, 4H, CH_2), and 1.53-0.90 ppm (2t, 6H, CH_3).

Anal. Calcd. for $C_{24}H_{20}O_5$: C, 74.23; H, 5.15. Found: C, 74.42; H, 5.34.

Dimethyl 1,4-Epoxy-1,4-dihydro-4-phenyldibenzo[*b*]furan-2,3-dicarboxylate (VIa).

A mixture of IIa (315 mg., 1 mmole) and dimethyl acetylenedicarboxylate (710 mg., 5 mmoles) were heated at 170° for 6 hours and worked up as above to give 263 mg. (70%) of VIa, m.p. 208-210° (ether); ir: 1720 (ester), 1660 cm^{-1} (C=C); nmr (deuteriochloroform): 3.50-3.13 (m, 1H, aromatic), 7.66-7.33 (m, 9H, H_1 and aromatic), 3.96 (s, 3H, CH_3O), and 3.62 ppm (s, 3H, CH_3O); ms m/e (relative intensity): 376 (M$^+$, 55), 345 (32), 344 (100), 286 (44), 258 (33), 200 (17), and 100 (14).

Anal. Calcd. for $C_{22}H_{16}O_6$: C, 70.21; H, 4.26. Found: C, 70.03; H, 4.44.

Other dimethyl 1,4-epoxy-1,4-dihydro-4-aryldibenzo[*b*]furan-2,3-dicarboxylates were prepared similarly (See Table I).

Phenyl 3-Hydroxymethyl-2-benzo[*b*]furyl Ketone (VIIa).

A solution of IIa (3.15 g., 0.01 mole) in chloroform (7 ml.) was placed on a chromatographic column (3 cm diameter) with 200 g. of alumina (neutral, activity II, Merck) as the absorbent. The column was eluted consecutively with 10% chloroform-petroleum ether, 20% chloroform-petroleum ether and chloroform. The desired compound was eluted with chloroform and crystallized from petroleum ether to give 1.51 g. (60%) of VIIa, m.p. 64-65°; ir: 3440 (OH), 1642 cm^{-1} (C=O); nmr (deuteriochloroform): 8.30-8.0 (m, 2H, aromatic), 7.90-7.16 (m, 7H, aromatic), 5.03 (s, 2H, CH_2), and 4.63 ppm (s, 1H, OH); ms m/e (relative intensity): 252 (M$^+$, 20), 250 (100), 233 (40), 232 (19), 204 (20), 104 (41), 77 (67) and 51 (21).

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.19; H, 4.76. Found: C, 76.38; H, 4.94.

Other aryl 3-hydroxymethyl-2-benzo[*b*]furyl ketones were prepared similaryl (See Table II).

Phenyl 3-Formyl-2-benzo[*b*]furyl Ketone (VIIIa).

A mixture of VIIa (2.52 g., 0.01 mole) and manganese dioxide (25 g.) in 150 ml. of chloroform was stirred overnight. The reaction mixture was filtered and evaporated. The residue was crystallized from petroleum ether to give 2.25 g. (90%) of VIIIa, m.p. 97-98°; ir: 1673 (C=O aldehyde), 1640 cm^{-1} (C=O, ketone); nmr (deuteriochloroform): 9.66 (s, 1H, HCO), 8.36-8.03 (m, 3H, aromatic), and 7.76-7.30 ppm (m, 6H, aromatic); ms m/e (relative intensity): 250 (M$^+$, 55), 249 (100), 220 (74), 204 (37), 193 (39), 165 (47), 145 (28), 105 (49), and 77 (65).

Anal. Calcd. for $C_{16}H_{10}O_3$: C, 76.80; H, 4.00. Found: C, 76.99; H, 4.15.

Other aryl 3-formyl-2-benzo[*b*]furyl ketones were prepared similarly (See Table II).

4-Phenylbenzofuro[2,3-*d*]pyridazine (IXa).

A solution of VIIIa (250 mg., 1 mmole) and hydrazine hydrate (100 mg., 2 mmoles) in 20 ml. of ethanol was refluxed for 4 hours. The solvent was evaporated and the residue was crystallized from ethanol to give 197 mg. (80%) of IXa, m.p. 161-162°; nmr (deuteriochloroform): 9.68 (s, 1H, H_1), 8.60-8.20 (m, 2H, aromatic), and 8.10-7.23 ppm (m, 7H, aromatic); ms m/e (relative intensity): 246 (M$^+$, 100), 218 (24), 189 (74), 95 (50), 94 (22), and 57 (16).

Anal. Calcd. for $C_{16}H_{10}N_2O$: C, 78.05; H, 4.06; N, 11.38. Found: C, 78.23; H, 4.24; N, 11.56.

Other 4-arylbenzofuro[2,3-*d*]pyridazines were prepared similarly (See Table III).

Acknowledgement.

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