SYNTHESIS AND REACTIONS OF BENZO[b]FURO[2,3-c]PYRYLIUM SALTS

V. I. Dulenko and S. V. Tolkunov

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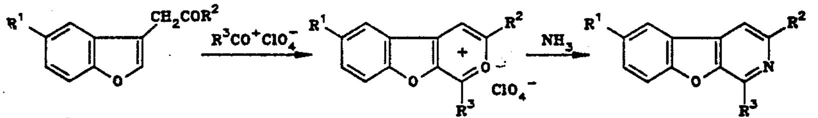
A method has been developed for the synthesis of 3-acetonyl- and 3-phenacylbenzo[b]furans by cyclization of 1-arloxy-2,4-pentanediones and 1-phenyl-4-aryloxy-1,3-butanediones in polyphosphoric acid. Acylation of 3-acetonyl(phenyl-benzo-[b]furans with aliphatic acid anhydrides in the presence of perchloric acid gives the benzo[b]furo[2,3-c]pyrylium perchlorates. The recyclization of the pyrylium salts with ammonia, aqueous alkali, and morpholine has been examined.

The synthesis of biologically active compounds from pyrylium salts holds promise. In this connection, the acid-catalyzed cyclization reaction is of interest [1], this having previously provided a number of condensed pyrylium and pyridine salts [2, 7].

We here describe the synthesis of some benzo[b]furo[2,3-c]pyrylium salts (III-V) by acid catalyzed cyclization

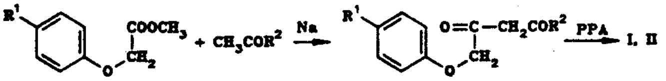


Ia,b; IIa,b IIIa-c–Va-c VIa-c; VIIa,b; VIIIa,b

I, II a $R^1=H$, b $R^1=CH_3$; Ia,b $R^2=CH_3$; IIa,b $R^2=C_6H_5$; IIIa $R^1=H$, $R^2=CH_3$, $R^3=C_2H_5$; b $R^1=R^2=R^3=CH_3$; c $R^1=R^2=CH_3$, $R^3=C_2H_5$; IV $R^1=H$, $R^2=C_6H_5$; V $R^1=CH_3$, $R^2=C_6H_5$; IV, Va $R^3=CH_3$, b $R^3=C_2H_5$, c $R^3=C_3H_7$; VIa $R^1=H$, $R^2=CH_3$, $R^3=C_2H_5$; b $R^1=R^2=R^3=CH_3$; c $R^1=R^2=CH_3$, $R^3=C_2H_5$; VII $R^1=H$, $R^2=C_6H_5$; VIII $R^1=CH_3$, $R^2=C_6H_5$; VII, VIIIa $R^3=CH_3$, b $R^3=C_2H_5$

The starting materials used were 3-acetonyl- and 3-phenacylbenzo[b]furans (I, II). Benzo[b]furans containing acetonyl or phenacyl groups in the 3-position are difficult to obtain. There are only two examples of the synthesis of the 3-acetonylbenzo[b]furan (Ia) from the 3-formyl derivative and an excess of diazomethane [8], and from coumaran-3-one by the Wittig reaction [9]. The principal drawback of these methods is the use of difficultly accessible starting materials.

We have found that the β-diketones (IXa-d), obtained by the Claisen reaction from the aryloxyacetate esters and methyl ketones (acetone and acetophenone) in the presence of metallic sodium, are convenient compounds for the synthesis of 3-acetonyl(phenacyl)benzo[b]furans.



IX a-d

IX a $R^1=H$, $R^2=CH_3$; b $R^1=CH_3$, $R^2=CH_3$; c $R^1=H$, $R^2=C_6H_5$; d $R^1=CH_3$, $R^2=C_6H_5$

The cyclizationof 1-aryloxypentane-2,4-diones (IXa, b) takes place in polyphosphoric acid under mild conditions (35-40°C) to give (Ia, b) in yields of up to 20%. The cyclization of 1-phenyl-4-aryloxybutane-1,3-diones (IXc, d) requires much more severe conditions (100-110°C), compounds (IIa) and (IIb) being obtained in yields up to 50%. The lower yields of ketones (Ia) and (Ib) may be due to their instability in acid media.

The perchloric acid-catalyzed acylation of ketones (I) and (II) takes place at the free α-position of the furan ring to give the benzo[b]furo[2,3-c]pyrylium perchlorates (III-V), obtained in yields of 85-96% (Table 1).

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TABLE 1. Properties of Compounds (III-V)

Compound	mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	Cl		C	H	Cl	
IIIa	187—188	53,4	3,7	11,6	$C_{14}H_{13}ClO_6$	53,8	4,2	11,3	85
IIIb	212—213	53,6	3,8	11,1	$C_{14}H_{13}ClO_6$	53,8	4,2	11,3	89
IIIc	162—163	55,8	4,1	11,3	$C_{15}H_{15}ClO_5$	55,2	4,6	10,9	84
IVa	269—270	60,5	3,9	9,5	$C_{18}H_{13}ClO_6$	59,9	3,6	9,8	94
IVb	237—238	60,4	4,4	9,2	$C_{19}H_{15}ClO_6$	60,9	4,0	9,5	91
IVc	230—231	61,3	4,7	9,4	$C_{20}H_{17}ClO_6$	61,8	4,4	9,1	87
Va	265—266	60,6	4,3	9,4	$C_{19}H_{15}ClO_6$	60,9	4,0	9,5	96
Vb	241—242	61,4	4,8	9,3	$C_{20}H_{17}ClO_6$	61,8	4,4	9,1	90
Vc	234—235	62,9	4,3	9,3	$C_{21}H_{19}ClO_6$	62,6	4,7	8,8	88

TABLE 2. PMR Spectra of Benzo[b]furo[2,3-c]pyrylium Perchlorates (III-V) and Benzo[b]furo[2,3-c]pyridines (VI-VIII)

Compound*	Chemical shifts, ppm			
	R^1	R^2	R^3	H_{arom}
IIIa	—	2,83	1,47 t; 3,43 q	7,40—8,20
IIIb	2,40	2,83	3,04	7,80—8,20
IIIc	2,40	2,83	1,40 t; 3,40 q	7,80—8,20
IVa	—	—	3,04	7,35—8,10
IVb	—	—	1,53 t; 3,44 q	7,40—8,20
Va	2,40	—	3,03	7,40—8,20
Vb	2,40	—	1,53 t; 3,44 q	7,45—8,10
VIa	—	2,40	1,03 t; 17 q	7,56—7,86
VIb	2,57	2,90	3,02	7,73—8,10
VIc	2,57	2,90	1,43 t; 44 q	7,80—8,10
VIIa	—	—	2,50	7,10—8,00
VIIb	—	—	1,50 t; 3,10 q	7,10—8,00
VIIIa	2,44	—	2,50	7,10—8,00
VIIIb	2,44	—	1,50 t; 3,10 q	7,10—8,00

*Solvent for (IIIa-c), (IVa, b), (Va, b), and (VIb, c), CF_3COOH; for (VIa) CD_3CN, and for (VIIa, b) and (VIIIa, b), $CDCl_3$. In the case of (VIb, c), the spectra of the hydrochlorides are given.

The IR spectra of salts (III-V) show absorption at 1645-1640 and 1550 cm^{-1} for the symmetrical and antisymmetrical stretching vibrations of the pyrylium ring. The absorption at 1505, 1035, 890, and 770 cm^{-1} is due to stretching vibrations of the C=C bonds in benzo[b]furan. Absorption of the ClO_4^- anion is seen at 1105-1085 cm^{-1}. The PMR spectra of the salts (III-V) correspond to their structures (Table 2).

Examination of the reactions of (III-V) with ammonia showed that they give the corresponding pyridine bases (VI-VIII) (Tables 2 and 3). The ease of formation of (VI-VIII) is dictated by the substituents in the pyrylium ring. For instance, the perchlorates (IIIa-c), which have alkyl substituents, exchange the oxygen atom for nitrogen on boiling in alcoholic ammonia, but (IV) and (V) require more severe conditions (boiling with an excess of ammonium acetate in acetic acid) to give the pyridine bases (VII) and (VIII).

The recyclization of the salts with aqueous alkalies and secondary amines has been studied in the case of the perchlorate (IIIa). With aqueous alkali, ring opening occurs followed by intramolecular crotonic condensation to give the hydroxydibenzofuran (X), confirming the rule [6, 7] that the carbonyl group of the opened pyrylium ring not conjugated with the aromatic ring participates in crotonic condensation.

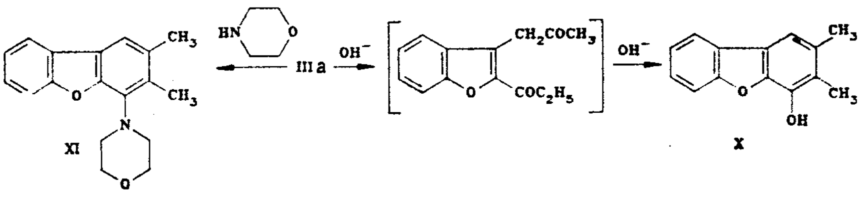

TABLE 3. Properties of Compounds (VI-VIII)

Compound	mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
VIa	54—55	80,0	6,4	6,5	$C_{14}H_{13}NO$	79,6	6,2	6,6	84
VIb	243—244*	79,2	6,6	6,4	$C_{14}H_{13}NO$	79,6	6,2	6,6	86
VIc	223—224*	79,8	6,3	6,4	$C_{15}H_{15}NO$	80,0	6,7	6,2	80
VIIa	110—111	83,4	5,4	5,2	$C_{18}H_{13}NO$	83,7	5,0	5,4	89
VIIb	68—69	83,3	5,2	5,4	$C_{19}H_{15}NO$	83,5	5,5	5,1	83
VIIIa	100—101	83,2	5,4	5,3	$C_{19}H_{15}NO$	83,5	5,5	5,1	84
VIIIb	81—82	83,4	6,3	5,2	$C_{20}H_{17}NO$	83,6	6,0	4,9	83

*Melting point of the picrate.

TABLE 4. Properties of Compounds (I), (II), and (IX)

Compound*	bp, °C (mm) [mp, °C]	IR spectrum, cm^{-1} (C=O)	Found, %		Empirical formula	Calculated, %		Yield, %
			C	H		C	H	
Ia	129—131 (2)	1705	76,2	5,4	$C_{11}H_{10}O_2$	75,9	5,8	19
Ib	132—135 (2)	1705	76,2	6,8	$C_{12}H_{12}O_2$	76,6	6,5	21
IIa*	199—205 (2) [73—74]	1690	81,0	5,4	$C_{16}H_{12}O_2$	81,3	5,1	46
IIb	185—190 (1)	1690	81,2	5,4	$C_{17}H_{14}O_2$	81,6	5,6	52
IXa	138—140 (2) [230—231]**	1605	68,1	6,4	$C_{11}H_{12}O_3$	68,6	6,5	63
IXb	142—145 (2) [230—231]**	1605	69,6	7,1	$C_{12}H_{14}O_3$	69,9	6,8	61
IXc*	[80—81]	1610	75,2	5,8	$C_{16}H_{14}O_3$	75,6	5,5	70
IXd*	[53—54]	1610	75,8	6,4	$C_{17}H_{16}O_3$	76,1	6,0	72

*Compounds (IIa), (IXc, d) were crystallized from heptane.
**Melting points of the copper derivatives.

The perchlorate (IIIa) reacts with morpholine to give 1-N-morpholino-2,3-dimethylbenzofuran (XI), the structure of which was established by its PMR spectrum.

EXPERIMENTAL

IR spectra were obtained on a UR-20 instrument in vaseline oil, and PMR spectra on a Tesla BS-467 (60 MHz), internal standard TMS. The spectra of the pyrylium salts were obtained in CF_3COOH.

General Method of Preparation of (IXa-d). To a suspension of sodium prepared from 0.11 g of sodium in 80 ml of toluene was added at 20°C 0.1 mole of the methyl aryloxyacetate, followed by the dropwise addition at the same temperature with stirring of 0.1 mole of the methyl ketone (acetone or acetophenone). The mixture was kept for 6 h, then heated to 80°C for 2 h. It was then cooled, 150 ml of dry ether added, and the sodium salt which separated was filtered off and washed well with ether. To a suspension of the sodium salt in 250 ml of ether was added a 10% solution of hydrochloric acid, until the salt dissolved completely. The ether layer was separated, dried over Na_2SO_4, and the ether removed. The residue was distilled in vacuo or crystallized (Table 4).

General Method of Preparation of (I) and (II). To 200 g of polyphosphoric acid was added with vigorous stirring a solution of 0.1 mole of (IX) in 100 ml of dry toluene. In the preparation of (Ia) and (Ic), the reaction mixture was kept at 35°C for 1.5 h, and in the preparation of (IIa) and (IIb), at 110°C for 3 h. The mixture was cooled and poured into 0.8 kg of ice. The toluene layer was separated, and the aqueous layer extracted with 150 ml of toluene. The toluene extract was washed with 100 ml of 5% NaOH solution, dried over $CaCl_2$, the toluene removed, and the residue distilled in vacuo (Table 4).

Benzo[b]furo[2,3-c]pyrylium Perchlorates (III-V). To a solution of 0.01 mole of (I) or (II) in 5 ml of the appropriate anhydride was added at 20°C with stirring an acylating mixture of 0.05 mole of the anhydride and 0.01 mole of 70% perchloric acid. The mixture became warm, and after a time it solidified. After 20 min the mixture was diluted with 20 ml of ether, and the solid filtered off, washed with cold alcohol and ether, and dried. It was crystallized from acetic acid (Table 1).

Benzo[b]furo[2,3-c]pyridines (VIa-c). Gaseous ammonia was passed into a suspension of 0.01 mole of (IIIa-c) in 30 ml of alcohol for 20 min. The solution was then boiled for 20 min, and poured into a mixture of ice and water. The product was extracted with ether and dried over potassium carbonate. After removal of the ether, the residue was crystallized from hexane (Table 3).

Benzo[b]furo[2,3-c]pyridines (VII-VIIIa, b). A mixture of 0.01 mole of (IV-Va, b) and 0.03 mole of ammonium acetate in 40 ml of glacial acetic acid was boiled for 1.5 h. The mixture was then poured on to ice and water, and the product filtered off and dried. It was crystallized from aqueous alcohol (Table 3).

1-Hydroxy-2,3-dimethyldibenzofuran (X). To a mixture of 3.13 g (0.01 mole) of the perchlorate (IIIa) in 50 ml of alcohol was added a solution of 2.8 g of potassium hydroxide in 5 ml of water. The mixture was boiled for 5 h, cooled, poured into 50 ml of 10% potassium hydroxide, and extracted with ether. The aqueous layer was separated and acidified with hydrochloric acid until it gave an acid reaction. The solid was filtered off. Yield 0.75 g (37%), mp 128-129°C (from carbon tetrachloride). IR spectrum: 3260, 1520, 1325, 1345, 1220, 1180, 1165, 1080, 1020, 935, 870, 860, 770, 750, 735 cm^{-1}. PMR spectrum (in Cd_3CN): 2.23 (3H, s, 2-CH_3), 2.33 (3H, s, 3-CH_3), 7.10-8.00 ppm (5H, arom.). Calculated: C 785, H 6.8%. $C_{14}H_{11}O_2$. Found: C 78.3, H 5.5%.

1-Morpholino-2,3-dimethyldibenzofuran (XI). A mixture of 3.13 g (0.01 mole) of the perchlorate (IIIa) and 15 ml of morpholine was boiled for 3 h. The excess secondary amine was distilled off under reduced pressure, and the residue dissolved in ether and washed well with 10% caustic alkali to remove the hydroxy-compound (X). The ether layer was dried over potassium carbonate, the ether removed, and the residue crystallized. Yield 1.6 g (57%), mp 119-120°C (from alcohol). IR spectrum: 1575, 1345, 1300, 1260, 1230, 1180, 1120, 1045, 1020, 955, 930, 875, 860, 775, 750 cm^{-1}. PMR spectrum (in $CDCl_3$): 2.60 (6H, s, 2,3-CH_3), 3.5 and 4.13 (8H, m, CH_2), 7.40-8.00 ppm (5H, H_{arom}). Calculated: C 76.6, H 6.8, N 5.0%. $C_{18}H_{19}NO_2$. Found: C 76.9, H 6.8, N 5.0%.

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