SOME TRANSFORMATIONS OF ALKYL α-FURFURYL SULFOXIDES

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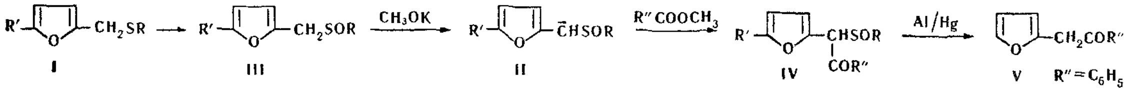
Under the influence of sodium or potassium methoxide, alkyl α-furfuryl sulfoxides are converted, through removal of a proton from the methylene group of the furfuryl residue, to the corresponding carbanions which, by reacting with methyl benzoate, form β-keto sulfoxides. The latter are cleaved to phenyl α-furfuryl ketone by the action of amalgamated aluminum. In the case of α-furfuryl α-thienyl sulfoxide, nucleophilic attack is directed nonselectively to one of the methylene groups. This method opens up the possibility for the synthesis of hard-to-obtain, unsymmetrical ketones in which one of the radicals is an aryl (hetaryl) grouping, and the other is a benzyl group or its heterocyclic analog.

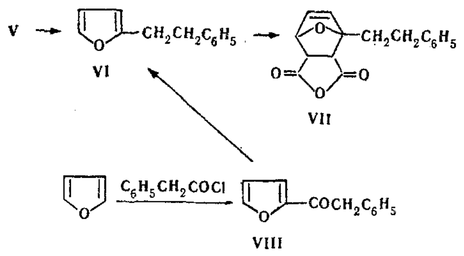
We have previously shown [1] that alkyl α-furfuryl sulfides (I) exchange an α-hydrogen atom of the furan ring with an aldehyde group under the conditions of the Vilsmeier reaction. In this connection, we note that under the same conditions, alkyl α-thienyl sulfides are cleaved to form thienyl chloride and aminomercaptals [2]. With the idea of finding a method for introducing a substituent into the methylene group, during which a new C−C bond would be formed, we studied the reactions of esters with carbanions (II) formed by the action of bases on alkyl α-furfuryl sulfoxides (III). Reactions of the methylsulfinyl carbanion (formed by the action of hydrides [3,4], alkoxides [5,6], and n-butyllithium [4] on dimethyl sulfoxide) with esters are currently well known. The products of these reactions are the extremely reactive β-keto sulfoxides [4,7]. Analogous transformations of other sulfoxides are completely unknown.

Our experiments showed that the formation of alkylsulfinyl-α-furfuryl carbanions proceeds under the influence of potassium or sodium methoxides. The structures of the keto sulfoxides (IV), which are products of the reaction of carbanions II with esters, were proved by reductive cleavage of four of them to phenyl α-furfuryl ketone (V) by the action of amalgamated aluminum, as in [4]:



The structure of ketone V was confirmed by its reduction to 1-α-furyl-2-phenylethane (VI), which was identified by its adduct (VII) with maleic anhydride [8].

It seemed of interest to study the direction of the reaction with alkoxides in the case of α-furfuryl benzyl sulfoxide (IIIe) and α-furfuryl α-thienyl sulfoxide (IIId):



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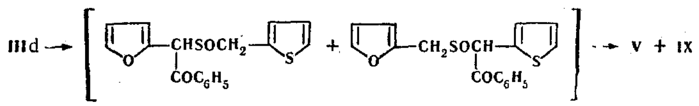
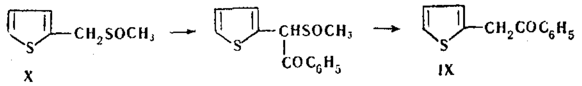
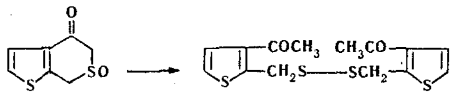
As became clear during reductive cleavage of the corresponding products of condensation with methyl benzoate, the first of the sulfoxides reacts with base only by means of its furfuryl residue – only phenyl α-furfuryl ketone (V) was isolated – while in the second case, both possible ketones – V and phenyl α-thienyl ketone (IX) – are obtained. (The yield of IX is somewhat lower.)



Ketone IX was also obtained from methyl α-thienyl sulfoxide (X):

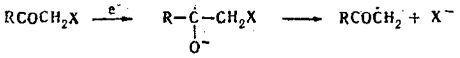


In addition to phenyl α-furfuryl ketone, a second reaction product – dibenzyl disulfide – was isolated by reductive cleavage of keto sulfoxide IVd, obtained from benzyl α-furfuryl sulfoxide and methyl benzoate. Correspondingly, bis(3-acetyl-2-thienyl) disulfide (XII) was obtained from cyclic keto sulfoxide XI:



XI XII

The formation of these disulfides indirectly confirms the mechanism of the reductive cleavage of compounds of the type under consideration proposed in [7]:



$$\mathrm{RCOCH_2X} \xrightarrow{e^-} \mathrm{R{-}\underset{\displaystyle O^-}{\underset{|}{\dot{C}}}{-}CH_2X} \longrightarrow \mathrm{RCO\dot{C}H_2 + X^-}$$

X= halogenCH_3S, CH_3SO, CH_3SO_2

In particular, a sulfenic acid anion should be formed when X = RSO. It is known [9] that sulfenic acids readily disproportionate to form disulfides and sulfinic acids, and the latter, in turn, are capable of being converted to disulfides under the conditions of metal reduction (Zn or Al).

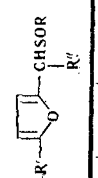
The molecules of the keto sulfoxides (IV) that we obtained contained two asymmetric atoms – the carbon and the sulfoxide sulfur – and can consequently exist as two diastereoisomers. The melting point ranges of these compounds and the PMR spectra serve as a confirmation of the fact that we were actually dealing with mixtures of diastereoisomers. In this connection, it should be noted that the purity of the β-keto sulfoxides is of no significance for definite purposes, in particular, for the production of the difficult-to-obtain ketones containing α-furfuryl radicals on the basis of alkyl α-furfuryl sulfoxides, since the same ketone is obtained from both diastereoisomers during reductive cleavage.

EXPERIMENTAL

The alkyl α-furfuryl sulfoxides (III) used in this research were obtained by oxidation of the corresponding sulfides (I), which were synthesized in part by known methods and in part from α-furfurylamine methiodides [10]. Methyl α-furfuryl sulfide (Ia) [11] and isopropyl α-furfuryl sulfide (Ib) [12] were obtained from furfuryl mercaptan and, respectively, methyl iodide and isopropyl bromide. We have previously described [1] the preparation of tert-butyl α-furfuryl sulfide (Ic) from tert-butylmercaptan and furfuryl chloride. α-Furfuryl α-thienyl sulfide (Id) was obtained in 80% yield from α-furfurylmercaptan and α-thienyl chloride and had bp 114-117° (0.7 mm), n_D^{20} 1.5972, and d_4^{20} 1.2188. Found %: C 57.0, 56.9; H 4.6, 4.7; S 30.3, 30.1. $C_{10}H_{10}OS_2$. Calculated %: C 57.1; H 4.8; S 30.5. We described the similar synthesis of benzyl α-furfuryl sulfide (Ie) in [1].

Methyl 5-Methyl-2-furfuryl Sulfide (If). This was obtained by the method in [10], as follows. A mixture of 19 g (0.25 mole) of thiourea, 34 g (0.24 mole) of methyl iodide, and 10 ml of water was refluxed with stirring until the thiourea dissolved (about 8 h). A solution of alkoxide obtained from 200 ml of isobutanol and 11.5 g (0.5 g-atom) of Na was then added, after which the mixture was refluxed for 9 h. A 28.1 g (0.1

TABLE 1



Comp.	R	R′	R″	bp (mm)	mp	n_D^{20}	d_{20}^4	Empirical formula	Found %			Calc. %			Yield, %
									C	H	S	C	H	S	
IIIa	CH_3	H	H	81—82 (0,3)	—	1,5465	1,2336	$C_6H_8O_2S$	50,1; 50,2	5,5; 5,6	21,9; 22,1	49,9	5,6	22,2	88
IIIb	i-C_3H_7	H	H	102—103 (0,7)	—	1,5298	1,1407	$C_8H_{12}O_2S$	55,4; 55,3	6,9; 7,0	18,4; 18,7	55,8	7,0	18,6	94
IIIc	t-C_4H_9	H	H	94—95 (0,16)	46,5—47,5	—	—	$C_9H_{14}O_2S$	57,8; 57,6	7,7; 7,6	—	58,1	7,6	—	87
IIId	2-Thienyl	H	H	—	75—76	—	—	$C_{10}H_{10}O_2S_2$	53,2; 53,3	4,8; 4,7	27,9; 28,1	53,1	4,5	28,4	89
IIIe	Benzyl	H	H	—	82—83	—	—	$C_{12}H_{12}O_2S$	65,8; 65,7	5,6; 5,7	14,5; 14,5	65,4	5,5	14,5	86
IIIf	CH_3	CH_3	H	85—87 (0,15)	45—46	—	—	$C_7H_{10}O_2S$	52,8; 52,7	6,9; 6,7	20,3; 20,1	53,1	6,4	20,3	89
IVa	CH_3	H	Benzoyl	—	101—103	—	—	$C_{13}H_{12}O_3S$	62,6; 62,4	4,8; 4,8	12,8; 12,7	62,9	4,9	12,9	72
IVb	i-C_3H_7	H	Benzoyl	—	80—97	—	—	$C_{15}H_{16}O_3S$	64,7; 64,7	5,8; 5,9	11,6; 11,7	65,2	5,8	11,6	61
IVc	CH_3	H	2-Furoyl	—	104—107	—	—	$C_{11}H_{10}H_4S$	55,2; 55,7	4,1; 4,2	13,2; 13,4	55,5	4,2	13,5	82
IVd	Benzyl	H	Benzoyl	—	75—110	—	—	$C_{19}H_{16}O_3S$	70,5; 70,4	5,0; 5,0	10,1; 9,8	70,3	5,0	9,9	54

mole) sample of 5-dimethylaminomethyl-2-methylfuran methiodide [13] was added to the resulting mercaptide, and the reaction mass was refluxed for 24 h. The isobutanol was removed by vacuum distillation, and the residue was dissolved in 250 ml of water and extracted with ether. The extract was washed with water, dried over $MgSO_4$, and the ether was removed by distillation. The residue was fractionated to give 8.4 g (42%) of If with bp 72-78° (2 mm), n_D^{20} 1.5185, and d_4^{20} 1.0514. Found %: C 58.9, 59.2; H 7.0, 7.0; S 22.1, 22.4. $C_7H_{10}OS$. Calculated %: C 59.1; H 7.1; S 22.6.

tert-Butyl 5-Methyl-2-furfuryl Sulfide (Ig). A 9.9 g (0.11 mole) sample of tert-butyl mercaptan and 28.1 g (0.1 mole) of 5-dimethylaminomethyl-2-methylfuran methiodide [13] were added successively to alkoxide prepared from 150 ml of isobutanol and 2.3 g (0.1 g-atom) of Na, after which the reaction mass was refluxed for 24 h and treated as described in the previous experiment to give 10.3 g (56%) of Ig with bp 109-110° (18 mm), n_D^{20} 1.5004, and d_4^{20} 0.9800. Found %: C 65.2, 65.0; H 8.8, 8.7; S 17.4, 17.5. $C_{10}H_{16}OS$. Calculated %: C 65.2; H 8.7; S 17.4. Sulfide Ig was also obtained in 82% yield by Kishner reduction of 26.3 g (0.13 mole) of 5-tert-butylmercaptomethyl-2-formylfuran [1] by the action of 28 ml of 72% hydrazine hydrate and 24 g of KOH in 160 ml of diethylene glycol at 130-150° for 5 h; the product boiled at 99-100° (12 mm) and had n_D^{20} 1.5004.

Alkyl α-Furfuryl Sulfoxides (III) (see Table 1). A solution of 56 g of 22% hydrogen peroxide in 50 ml of acetic acid was added dropwise at 20° to a solution of 0.35 mole of alkyl α-furfuryl sulfide (I) in 300 ml of glacial acetic acid, purified by distillation over CrO_3,* and the resulting solution was allowed to stand at about 20° for 18 h. The acetic acid was then removed by vacuum distillation, and the residue was poured into 200 ml of 10% KOH. This mixture was extracted with chloroform, and the extract was washed with water and dried with $MgSO_4$. The solvent was removed by distillation, and the residue was vacuum distilled over calcium hydride or recrystallized from heptane.

β-Keto Sulfoxide (IV) (see Table 1). A mixture of 2.35 g of methyl α-furfuryl sulfoxide and 2.22 g of methyl benzoate (0.016 mole of each) in 30 ml of absolute dimethylformamide was added at 20° to a solution of potassium methoxide obtained from 0.7 g (0.018 g-atom) of potassium and 20 ml of absolute methanol, after which the solvent was removed by vacuum distillation at ~10 mm for 3 h (bath temperature 30-35°) and at ~2 mm to dryness. All of the operations, beginning with the preparation of the potassium methoxide, were carried out under argon. The yellowish, solid residue was dissolved in 100 ml of water and 70 ml of ether, and the aqueous solution was separated and thoroughly extracted, first with chloroform to remove neutral impurities, and then with ether. It was then acidified to pH 4-5, and the resulting precipitate was filtered, washed on the filter, and dried to give 1.8 g of IVa with mp 96-103°. Extraction of the filtrate with chloroform yielded another 1.4 g of IVa to give a total yield of

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*Partial resinification occurs during acidification in impure acetic acid, and the yield of sulfoxide decreases.

3.2 g (72%). A sample for analysis was recrystallized from ethyl acetate–ether (1 : 4). The other β-keto sulfoxides (IV) were similarly obtained.

Phenyl α-Furfuryl Ketone (V). A total of 150 ml of a 10% aqueous solution of mercuric chloride was added to 1.8 g (0.2 g-atom) of aluminum foil cut up into small pieces (about 1 cm^2). After 40 sec, the mercuric chloride solution was decanted, and the amalgamated aluminum was washed with 100 ml of absolute alcohol and then with ether, after which a solution of 5 g (0.02 mole) of ω-(methylsulfinyl)-ω-(2-furyl)acetophenone (IVa) (mp 96-103°) in 300 ml of 10% aqueous tetrahydrofuran, cooled to 0°, was added to it, and the reaction mass was stirred at −2 to 0° for 15 min. The resulting precipitate was filtered and washed on the filter with 50 ml of tetrahydrofuran. The combined filtrates were evaporated in vacuum, and the residual oil was extracted with ether. The ether solution was washed with water and dried with $MgSO_4$. The ether was removed by distillation, and the residue was distilled to give 2.77 g (75%) of V with bp 110-111° (0.6 mm) and mp 30° (from petroleum ether). Found %: C 77.3, 77.4; H 5.5, 5.3. $C_{12}H_{10}O_2$. Calculated %: C 77.4; H 5.4. The semicarbazone had mp 158.5-159.5° (from alcohol). Found %: C 64.3, 64.1; H 5.3, 5.2. $C_{13}H_{13}N_3O_2$. Calculated %: C 64.2; H 5.4.

Under similar conditions, 1.95 g (70%) of V with mp 30° was obtained by the reduction of 4.15 g of ω-(isopropylsulfinyl)-ω-(2-furyl) acetophenone (IVb).

1-α-Furyl-2-phenylethane (VI). A. Under the conditions described for the preparation of Ig, 6.5 g (78%) of VI with bp 78-79° (1.5 mm), n_D^{20} 1.5390, and d_4^{20} 1.0281 was obtained by Kishner reduction of 9 g of phenyl α-furfuryl ketone. According to [8], this compound has bp 241-243° (760 mm). Compound VI gave 3-(β-phenylethyl)-3,6-endoxo-Δ^4-tetrahydrophthalic anhydride (VII) with mp 73-75° (from $CHCl_3$–petroleum ether) by reaction with maleic anhydride in absolute ether; it did not depress the melting point of an authentic sample (for the synthesis of which, see below).

B. A solution of 17.5 ml of stannous chloride in 100 ml of dry benzene was added with stirring at 4° in the course of 40 min to 10.1 g of furan and 23 g of phenylacetyl chloride in 400 ml of dry benzene. The mixture was stirred at 20° for 3 h and was then poured into 500 ml of ice water. The resulting mixture was acidified with 20 ml of concentrated hydrochloric acid. The benzene layer was separated, washed with water and saturated $NaHCO_3$ solution, and dried with $MgSO_4$. After removal of the solvent by distillation, the residue was repeatedly extracted with petroleum ether, the extracts were evaporated, and the residual yellow oil was fractionated to give 1.8 g of benzyl α-furyl ketone (VIII) with bp 120-124° (0.7 mm) {bp 161-163° (10 mm) [14]}. Kishner reduction of 1.7 g of VIII gave 1 g of VI with bp 104-105° (8 mm) and n_D^{20} 1.5370; this gave an adduct (VII) with maleic anhydride with mp 73-75° (mp 73-74° [8]).

Reduction of ω-(Benzylsulfinyl)-ω-(2-furyl)acetophenone (IVd) with Amalgamated Aluminum. Under the conditions described for the reduction of IVa, 6.5 g of IVd gave a mixture of substances, from which, by fractionation of 0.7 mm [the first fraction (2.2 g) had bp 111-118°, the second fraction (0.7 g) had bp 118-140°, and the third fraction (1.3 g) had bp 140-170°] and fractional crystallization, 2.2 g (50%) of phenyl α-furfuryl ketone with mp 30° and 1.2 g of dibenzyl disulfide with mp 67-68.5° were isolated; the latter did not depress the melting point of an authentic sample.

Reduction of the Product of the Reaction of α-Furfuryl α-Thienyl Sulfoxide with Methyl Benzoate by Amalgamated Aluminum. Under the conditions described for the reduction of IVa, 5.3 g of a mixture of keto sulfoxides obtained from IIId and methyl benzoate gave a mixture of reaction products, from which, by fractionation at 0.7 mm [the first fraction (0.1 g) had bp 105-108°, the second fraction (1.8 g) had bp 108-140°, and the third fraction (0.7 g) had bp 140-158°] and fractional crystallization, 0.8 g of phenyl α-furfuryl ketone (V) with mp 30° (this sample did not depress the melting point of an authentic sample) and 0.5 g of phenyl α-thienyl ketone (IX) with mp 56-57° (from alcohol) were isolated. Found %: C 71.4, 71.6; H 5.1, 5.1; S 15.5, 15.4. $C_{12}H_{10}OS$. Calculated %: C 71.3; H 5.0; S 15.8. The latter did not depress the melting point of a sample of phenyl α-thienyl ketone that was obtained in our laboratory by I. B. Karmanova by reduction with amalgamated aluminum, under conditions similar to those described above, of ω-(methylsulfinyl)-ω-(2-thienyl)acetophenone – the product of the reaction of methyl α-thienyl sulfoxide (X) with methyl benzoate.

4-Keto-4,5,6,7-tetrahydro-6-thiathionaphthene 6-Oxide (XI). This was obtained in 60% yield by hydrogen peroxide oxidation in acetic acid of 4-keto-4,5,6,7-tetrahydro-6-thiathionaphthene [15] and had mp 169-173° (decomp., from alcohol). Found %: C 45.2, 45.3; H 3.3, 3.3; S 34.3, 34.4. $C_7H_6O_2S_2$. Calculated %: C 45.1; H 3.2; S 34.4. Under the conditions described for the reduction of IVa, 2.5 g of keto sulfoxide XI gave 1 g of disulfide XII with mp 88.5-89.5° (from alcohol). Found %: C 49.3, 48.9; H 4.0, 4.0; S 37.0, 37.1. $C_{14}H_{14}O_2S_4$. Calculated %: C 49.1; H 4.1; S 37.4.

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