AMINOALKYLATION OF SULFAZONE

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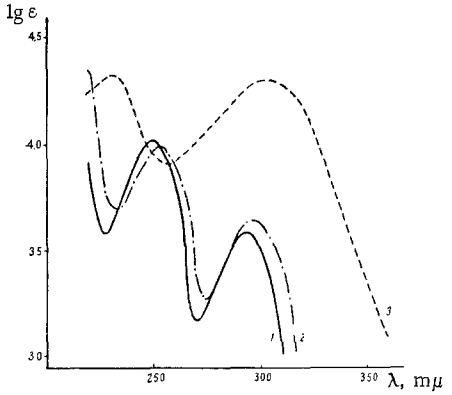
2-(α-Acetamidobenzil)sulfazone and 2-benzalsulfazone were obtained by reacting 3-ketothiamorpholine dioxide (sulfazone) with benzylidenebisacetamide in boiling acetic acid. The double bond in 2-benzalsulfazone can add alcohols (methanol, ethanol) to give correspondingly 2-(α-methoxybenzil)- and 2-(α-ethoxybenzil) sulfazone. Reaction of sulfazone with benzylidenebisurea in boiling acetic acid gave 2-(α-ureidobenzyl)sulfazone.

We previously showed that when 3-ketothiamorpholine dioxide (sulfazone, I) was aminoalkylated, aminoalkylation products could not be obtained, the main products of the reactions being disulfazonylmethane and its derivatives [1].



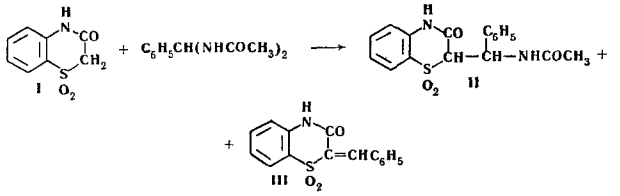
UV absorption spectra (in dioxane): 1) Sulfazone; 2) benzalsulfazone; 3) 2-(α-ethoxybenzyl)-sulfazone.

It is known that these amino compounds can be obtained, not only by direct aminoalkylation, but also by amidoalkylation with subsequent removal of the acyl group by hydrolysis [2]. In this connection we carried out work on amidoalkylation of sulfazone with various reagents.

Reaction of N-(dimethylaminomethyl)phthalimide methiodide [3] with I gave a product which could not be purified. Even simple solution in ethanol led to decomposition of this product to give disulfazonylmethane. A similar kind of conversion is known for the reactive phthalimidomethyl derivatives [4].

Amidoalkylation of I with benzylidenebisacetamide [5] led to our isolating two products, 2-(α-acetamidobenzyl)sulfazone (II) and 2-benzalsulfazone (III). The reaction was run in glacial acetic acid; increase in the reaction time from 2 to 6 hours cut the yield of II from 41.5 to 24%, while the yield of III rose from 27 to 36.6%.

When the reaction was run in acetic anhydride, only III was obtained, the yield being up to 69%.

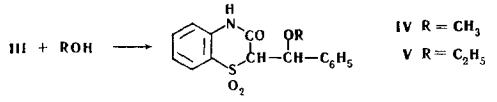


A confirmation of the structure of II is its IR spectrum containing an absorption band at 1680 cm^{-1}, characteristic of the CO group in amides [6], along with a band at 1720 cm^{-1} (CO group in I).

Hydrolysis of II with 20% hydrochloric acid did not give the expected 2-(α-aminobenzyl)sulfazone. Only I (70%) was isolated from the reaction products, while the filtrate was found to contain, in addition to I, unchanged II and benzaldehyde.

The structure of III is confirmed by its synthesis from I and benzaldehyde by a modified Perkin reaction [7] (see experimental). The III obtained had a melting point which was not sharp, possibly due to formation of III in the form of a mixture of cis and trans forms, not separated on recrystallizing.

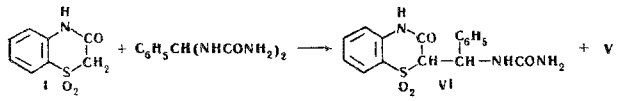
In purifying III it was found that its double bond can undergo nucleophilic addition of alcohols [8,9]. Methanol and ethanol were added to the double bond of III to give 2-(α-methoxybenzyl)sulfazone (IV) and 2-(α-ethoxybenzyl)sulfazone (V).



The structures of IV and V are assumed from analogies in the literature [10]. Confirmation of the structures of IV and V is found in their UV spectra coinciding with that of I, and differing markedly from that of III (see figure).

Since we established that I undergoes amidoalkylation when treated with benzylindenebisacetamide, it was of interest to effect the analogous reaction of I with the unusual aminoalkylating reagent benzylidenebisurea. The usual products of this kind of reaction are ureido derivatives [11] which are intermediates for synthesizing heterocyclic compounds, among them a number of pyrimidines.

When this reaction was run in dry ethanol in the presence of HC, or in glacial acetic acid at the boiling point of the solvent, 2-(α-ureidobenzyl)sulfazone (VI) was obtained in 22 and 41.5% yields respectively. The structure of VI is confirmed by its IR spectrum showing an absorption band at 1670 cm^{-1}, characteristic of the CO group in ureides [6], and by a positive reaction with dimethylaminobenzaldehyde [12].



When the reaction was run in ethanol, V was isolated in up to 18% yield along with VI. Obviously V is obtained through addition of the ethanol to the III formed in the reaction mixture. To settle the question as to whether III is formed by scission of VI, or by side reactions, the stabilities of III and VI were investigated under the conditions used in synthesizing VI. It was shown that VI breaks down into I, benzaldehyde, and a small amount of V, while III under the same conditions gives mainly V and only a small amount of I and benzaldehyde. Hydrolysis of VI with 20% HCl also takes place with formation of I, benzaldehyde, and an insignificant amount of III. At the same time the hydrolysis of III under the same conditions shows that the latter is more stable than VI. From these results it can be concluded that in the reaction of I with benzylidenebisurea, III is obviously not formed directly from VI.

EXPERIMENTAL

2-(α-Acetamidobenzyl)sulfazone (II). 2 g (10.2 mmole) I was dissolved in a minimum amount of glacial AcOH at 120°, and 2.12 g (10.2 mmole) benzylidenebisacetamide added to the resultant solution. The whole was heated for 2 hr at 120°, the AcOH vacuum-distilled off, and the residue diluted with dry ether. The precipitate was separated off, treated with $CHCl_3$, and the $CHCl_3$-insoluble II filtered off. Yield 1.45 g (41.5%), mp 161–163° (ex dioxane). Found: N 8.05; 7.93; CH_3CO 11.8; 12.0%. Calculated for $C_{17}H_{16}N_2O_4S$: N 8.14; CH_3CO 12.4%. The reaction product was insoluble in water, ether, and $CHCl_3$, slightly soluble in dioxane, and readily soluble in EtOH, AcOH, acetone, and dimethylformamide.

The $CHCl_3$ filtrate was treated with petrol ether (bp 40–60°), and the precipitate filtered off. Yield of III 0.78 g (27%). III was purified by reprecipitation from a $CHCl_3$ solution, and recrystallizing from glacial AcOH. The reaction product melted at about 180°. Found: C 63.1; 63.2; H 3.82; 3.95; N 4.89; 4.75; S 11.4; 11.4%. Calculated for $C_{15}H_{11}NO_3S$: C 63.2; H 3.89; N 4.91; S 11.2%.

Benzalsulfazone (III). a) A mixture of 4 g (20.6 mmole) I, 4.25 g (20.6 mmole) benzylidenebisacetamide, and 21 m*l* Ac_2O was heated for 6 hr at 140°. The Ac_2O was vacuum-distilled off, the residue treated with dry ether, and the resultant solid filtered off. Yield 4 g (69%). Its IR spectrum was identical with that of the III prepared in the previous experiment.

b) 10.82 g (102 mmole) benzaldehyde and 5.2 g mmole) Et_3N were added to 10 g (51 mmole) I dissolved in a minimum amount of glacial AcOH. The mixture was heated for 6 hr at 125°, the acetic acid being slowly distilled off. The residual AcOH was vacuum-distilled off, the crystallized product filtered off and vacuum-dried. Yield of III 7.87 g (54.3%). IR spectrum of the reaction product isolated was identical with that of III previously prepared. III was readily soluble in water, ether, and benzene, moderately soluble in $CHCl_3$.

2-(α-Ethoxybenzyl)sulfazone (V). 0.14 g (0.49 mmole) III was dissolved in 2 m*l* EtOH with heating, 1–2 drops 10% NaOH added, and the reaction mixture left at room temperature for half an hour. The crystalline precipitate of V was filtered off, and vacuum-dried. Yield of V 0.11 g (64%), mp 161–163° (ex EtOH). Found: C 61.7; 61.6; H 4.96; 5.07; N 4.61. 4.37; S 9.60; 9.72; OC_2H_5 13.6; 13.6%. Calculated for $C_{17}H_{17}NO_4S$: C 61.6; H 5.17; N 4.23; S 9.67; OC_2H_5 13.6%.

2-(α-Methoxybenzyl)sulfazone (IV). Reaction was effected as in the previous experiment. Yield of IV 63%, mp 143–145° (ex MeOH). Found: C 60.7; 60.7; H 4.77; 4.68; S 10.1; 10.1; OCH_3 9.43; 9.44%. Calculated for $C_{16}H_{15}NO_4S$: C 60.6; H 4.77; S 10.1; OCH_3 9.76%.

IV and V were readily soluble in AcOH, dioxane, and acetone, slightly soluble in EtOH, and insoluble in water, benzene, $CHCl_3$, and ether.

2-(α-Ureidobenzyl)sulfazone (VI). a) in EtOH. 6 g (30.4 mmole) I and 6.35 g (30.4 mmole) benzylidenebisurea were refluxed for 1 hr in 40 m*l* EtOH containing 1.12 g (30.4 mmole) HCl gas. The reaction products were allowed to stand at room temperature, after a few days a precipitate of V separated, was filtered off, and the filtrate vacuum-evaporated to give a thick syrup. The VI which separated was filtered off and washed with EtOH. Yield of VI 2.28 g (21.8%), mp 153–154° (ex MeOH). Found: C 55.4; 55.7; H 4.43; 4.43; N 12.2; 12.4; S 9.48; 9.12%. Calculated for $C_{16}H_{15}N_3O_4S$: C 55.6; H 4.38; N 12.2; S 9.27%.

VI was readily soluble in AcOH, dioxane, dimethylformamide, and acetonitrile, slightly soluble in EtOH, insoluble in $CHCl_3$, benzene, and ether.

b) In AcOH. 5 g (26 mmole) I, 5.31 g (26 mmole) benzylidenebisurea, and 50 m*l* glacial AcOH, were heated together at 125°, to obtain a homogeneous solution (2 hr). The AcOH was vacuum-distilled off, and the residue diluted with MeOH, to give a syrupy solution. After some days a precipitate of VI separated of solution, it was filtered off, washed with EtOH, and vacuum-dried, yield 3.63 g (41.5%). The IR spectrum was identical with that of the VI obtained the the preceding experiment.

Hydrolysis of 2-(α-acetamidobenzyl)sulfazone (II). 0.3 g (0.87 mmole) II was heated with 3 m*l* 20% HCl for 1 hr. The precipitate of I formed on cooling was filtered off and vacuum-dried, yield 0.11 g (64%). The specimen obtained did not depress the mp of authentic I, and their IR spectra were identical. The filtrate contained I, unchanged II, and benzaldehyde.

The filtrate was analyzed by paper chromatography (paper: Leningrad Fast), the paper being fed with 20% formamide solution in MeOH, using 2 systems $CHCl_3$, saturated with formamide, and benzene, saturated with the formamide, the components being

subsequently detected with UV light, and by using the Zimmerman reaction [13].

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