The Reaction of Several o-Methoxy Aromatic Aldehydes with Ethylthioxide. Novel Substitution and Condensation

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Synopsis.   The reaction of o- and p-anisaldehyde with potassium ethylthioxide in diglyme at 90—120 °C gave the corresponding demethylated products, while 2,6-dimethoxy-benzaldehyde and 9-(2-p-cymenyl)-2-methoxy-1-anthralde-hyde afforded two novel condensation and substitution products, VII and VI respectively.

Although many demethylation methods of methyl aryl ethers have been reported, few have referred to the direct demethylation of o-methoxy aromatic aldehydes except when Lewis acids have been used. For the establishment of "asymmetric inversion catalysts,"[1] the demethylation of a key intermediate, 9-(2-p-cymenyl)-2-methoxy-1-anthraldehyde (IV), was required. IV was not satisfactorily demethylated by Lewis acids, e.g., $AlCl_3$, BBr_3, or BCl_3. Therefore, we attempted the indirect demethylation of methoxy-aromatic aldehydes with the ethylthioxide anion,[2] where the aldehyde group may be first blocked by ethylthioxide to form thioacetal and then regenerated by the use of cupric chloride and cupric oxide.[3] The treatment of o- or p-anisaldehyde, I or II, by this process gave a satisfactory product; however, the application of the method to some other methoxyaldehydes afforded novel results. The present paper will describe these reactions of ethylthioxide with methoxy-aromatic aldehydes.

For the treatment of methoxy-aromatic aldehydes with ethylthioxide (Process A), potassium ethylthioxide, prepared in situ by the reaction of potassium metal with ethanethiol in diglyme, was stirred with the compounds from I to V at 95—120 °C. During the reaction, the anisaldehydes, I and II, were changed to the corresponding 2- and 4-bis(ethylthio)methylphenols, which were detected on tlc spots. However, the corresponding bis(ethylthio)methyl-derivatives of 2,6-dimethoxybenz-aldehyde (III) or 9-(2-p-cymenyl)-2-methoxy-3-an-thraldehyde (V) did not give rise to any further de-methylation. On the other hand, IV gave only a novel substitution product in which the methoxy group was replaced by the ethylthio group, while the aldehyde group remained. On the basis of the spectral analyses, this was shown to be 9-(2-p-cymenyl)-2-ethylthio-1-anthraldehyde (VI).

After the reaction had been accomplished, the mix-ture was acidified with 6M HCl and extracted with ethyl acetate. The organic layer was dried, and the solvents were evaporated under reduced pressure. The residue was then used in the next reaction.

To regenerate the aldehyde group, (Process B), the ethylthio compound described above was refluxed in aqueous acetone in the presence of cupric chloride and cupric oxide.[3] By this process, the bis(ethylthio)-methyl group was converted quantitatively to the aldehyde group in the cases of I, II, and V. However,

the bis(ethylthio)methyl derivative of III was con-densed with acetone to form (E)-2,6-dimethoxybenzal-acetone (VII). VI was stable under Process B. The results obtained after Processes A and B are collected in Table 1.
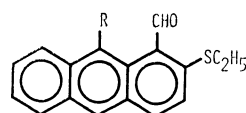
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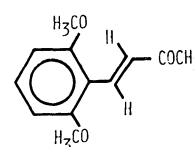
VI   **VII**

TABLE 1. RESULTS OF THE REACTION OF METHOXY-AROMATIC ALDEHYDES WITH ETHYLTHIOXIDE FOLLOWED BY THEIR TREATMENTS WITH CUPRIC CHLORIDE AND CUPRIC OXIDE IN ACETONE

Starting material	Product	Fate of methoxy[a]	Yield (%)
I	Salicylaldehyde	A	52[b]
II	4-Hydroxybenzaldehyde	A	43[b]
III	(VII)	B	32[b]
IV	(VI)	C	71[b]
V	9-(2-p-Cymenyl)-2-methoxy-3-bis(ethyl-thio)methylanthracene	B	81[c]

a) A. demethylation B. survival C. substitution b) total yield after the processes A and B. c) yield after the pro-cess A. The product was converted to the starting mate-rial by the process B.

In order to establish which, the formation of thio-acetal or its demethylation, is first, several methoxy-aromatics were treated with the same reagents as in Process A. None of the substances, anisole, m-di-methoxybenzene, and 9-(2-p-cymenyl)-2-methoxyan-thracene, was demethylated or substituted by the ethylthio group, and the starting materials were re-covered. Therefore, it may be deduced that the for-mation of thioacetal precedes demethylation in I, II, III, and V. The abnormal reactivity of the thio-acetals of III and V can be explained by the steric requirement and by the potential reactivity of the anthracene derivative to ethylthioxide, respectively. Since VII was prepared directly by the reaction of III with acetone in the presence of cupric chloride, VII is assumed to be formed after the regeneration of the aldehyde group from the bis(ethylthio)methyl group. As regards the condensation mechanism and the general reaction, subsequent works are undertaken.

The novel direct substitution of a methoxy group by

an ethylthio group in IV may be caused by the non-coplanarity between the aldehyde group and the aromatic ring;[1] it is supported by the concept of symbiosis. According to the HSAB principle,[4] the ethylthioxide anion is a soft base and the aryl cation is a soft acid. Therefore, the formation of VI is symbiotically more favored than the demethylation of IV. The problem remained to discover why demethylation occurs with the aid of ethylthioxide, as may be seen in the cases of I, II, and the compounds cited in Ref. 2.

Experimental

The melting points are uncorrected. The IR spectra were recorded on a Shimadzu IR-27 instrument. The NMR spectra were obtained using a Varian HA-100D spectrometer, with TMS as an internal standard. The mass spectra and the exact mass measurements were performed with a Model JMS-O1SG instrument (Japan Electron Optics Laboratory Co.). Merck Art. 7734 was used for the preparative separation of products on a silica gel column by elution chromatography, and Wakogel B-5 UA, for the thin-layer chromatography.

The starting materials, o- and p-anisaldehydes, (I) and (II), were commercially available. The compounds from III to V were prepared by a previously-reproted method.[1]

The Protection of the Aldehyde Group and Demethylation or Substitution (Process A). General Procedure. Potassium (0.03 mol) was added to a cooled solution of excess amounts of ethanethiol (10—15 ml) and 20 ml of diglyme to form, in situ, ethylthioxide. After the complete dissolution of the potassium metal, 0.01 mol of methoxy-aldehyde was added to the solution, after which the mixture was heated with gentle stirring at 95—110 °C for 20—24 hr. The mixture was then acidified with 50 ml of water containing a suitable amount of 6M HCl and extracted twice with 50 ml portions of ethyl acetate. The organic layer was then dried over anhydrous Na_2SO_4, and the solvents were evaporated under reduced pressure. The residue was used in the next reaction.

The Regeneration of the Aldehyde Group by the Deprotection of the Ethylthio Group (Process B). General Procedure. The crude residue was refluxed with cupric chloride (2 mol equiv.) and cupric oxide (4 mol equiv.) in 50 ml of aq. 99% acetone for 1—1.5 hr.[3] After the usual work-up, the residue was chromatographed on a silica gel column to give the products.

The products after the successive treatment of o- and p-anisaldehydes by Processes A and B were identified as salicyladehyde and 4-hydroxybenzaldehyde respectively; their structures were determined by a comparison of their spectral data, their behavior on tlc, and their melting points with those of authentic samples.

The successive treatments of 2,6-dimethoxybenzaldehyde (III) with Processes A and B resulted in the formation of

(E)-2,6-dimethoxybenzalacetone (VII).[5]   Mp 89—91 °C. NMR (CCl_4): δ 2.26 (3H, s, $-COCH_3$), 3.88 (6H, s, $-OCH_3$), 6.49 (2H, d, $J_{3,4}$=8.4 Hz, $C_{3,5}$-H), 6.97 (1H, d, $J_{\alpha,\beta}$= 16.6 Hz, C_α-H), 7.18 (1H, d, $J_{3,4}$=8.4 Hz, C_4-H), and 7.77 (1H, d, $J_{\alpha,\beta}$=16.6 Hz, C_β-H) ppm.

The successive treatments of 9-(2-p-cymenyl)-2-methoxy-1-anthraldehyde (IV) by Processes A and B gave 9-(2-p-cymenyl)-2-ethylthio-1-anthraldehyde (VI) in a 71% yield; it was a yellow viscous liquid. VI was unstable on exposure to air, and it was difficult to make the elemental analyses coincide. The exact mass measurement: Found (for a parent peak at m/e 398) 398.16724. Calcd for $C_{27}H_{26}OS$: 398.17048. IR (neat): $\nu_{C=O}$ 1668 cm^{-1}. NMR (CCl_4): δ 1.27 (6H, d, J=7.0 Hz, $-CH(CH_3)_2$), 1.28 (3H, t, J=7.0 Hz, $-CH_2-CH_3$), 1.89 (3H, s, Ar-CH_3), 2.88 (2H, quar, J=7.0 Hz, $-CH_2-CH_3$), 2.90 (1H, quin, J=7.0 Hz, $-CH(CH_3)_2$), 7.01 (1H, broad s, C_2'-H), 7.42 (1H, d, J=9.0 Hz, C_3-H), 7.93 (1H, d, J=9.0 Hz, C_4-H), 8.36 (1H, s, C_{10}-H), and 9.39 (1H, s, -CHO) ppm.

The treatment of 9-(2-p-cymenyl)-2-methoxy-3-anthraldehyde (V) by Process A produced 9-(2-p-cymenyl)-2-methoxy-3-bis(ethylthio)methylanthracene in an 81% yield; it was a fluorescent viscous pale green liquid. It was unstable on exposure to air and it was difficult to make the elemental analyses coincide. However, the structure was confirmed by spectral measurements of the crude sample. NMR (CCl_4): δ 1.24 (6H, t, J=6.6 Hz, $-CH_2-CH_3$), 1.30 (6H, d, J= 7.8 Hz, $-CH(CH_3)_2$), 1.85 (3H, s, Ar-CH_3), 3.68 (3H, s, $-OCH_3$), 5.44 (1H, s, S-CH-S), 6.58 (1H, s, C_1-H), 7.06 (1H, broad s, C_2'-H), 8.13 (1H, s, C_4-H), and 8.34 (1H, s, C_{10}-H) ppm. In addition, when this product was treated with the reagents of Process B, V was recovered in a quantitative yield.

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