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INTERESTING ERRORS IN SULFUR CHEMISTRY, 12

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I. IN THE LEUCKART SYNTHESIS OF THIOPHENOLS

In a study of the Leuckart synthesis, along with the expected aryl ethylxanthates **1**, which could be hydrolyzed as usual to the arenethiols, aryl dithiolcarbonates **2** were

$$\underset{}{ArN_2^+} + EtOC(S)S^- \rightarrow \underset{\mathbf{1}}{ArSC(S)OEt} + \underset{\mathbf{2}}{(ArS)_2CO} \qquad (1)$$

isolated in crude yields of up to 72% (Eq. 1).[1] All early indications were that our product ("XXIII" in ref. 1) from a *p*-nitrobenzenediazonium salt also was a dithiolcarbonate, just as had been found with five other diazonium salts. We assumed that the difference of our mp (183.5–184.5 °C) for the product ("XXIII" in ref. 1) from one reported for the nitro dithiolcarbonate (174.5 °C, no range given) merely reflected greater purity for our product. Later,[2] however, conversation with Dr. Terence C. Owen (then of England and now at the University of South Florida) led to concern that the infrared spectrum of "XXIII", which we had presumed to be bis-(*p*-nitrophenyl) dithiolcarbonate, lacked a carbonyl band closer to ca. 1700 cm^{-1} than ca. 1590 cm^{-1}. Since the other dithiolcarbonates showed bands close to 1700 cm^{-1}, probably the carbonyl frequency, although analyses for C, H, and S deviated less than 0.4% from expectation for the nitro dithiolcarbonate, we began to suspect that the S analysis reported to us for the product "XXIII" might be incorrect. Indeed, "XXIII" turned out to be bis-(*p*-nitrophenyl) disulfide **3** and not bis-(*p*-nitrophenyl) dithiolcarbonate **4**.[2] Compound "XXIII" had an infrared spectrum identical with that of commercial bis-(*p*-nitrophenyl) disulfide **3**, and

$$\underset{\mathbf{3}}{(p\text{-}O_2NC_6H_4S)_2} \qquad \underset{\mathbf{4}}{(p\text{-}O_2NC_6H_4S)_2CO}$$

the mp did not depress that of the commercial disulfide **3**; *new* analyses were consistent with the disulfide **3**. Anal. Calcd. for $C_{12}H_8N_2O_4S_2$ **3**: C, 46.74; H, 2.61; S, 20.80. Found: C, 47.06; H, 2.76; S, 20.91, 21.11 (previous S%, 19.00; calcd. for **4**, 19.07). Of the theoretical values for C, H, and S of the dithiolcarbonate **4** and disulfide **3** only the S% differs by more than 0.3, thus explaining why the incorrect analysis for sulfur led to the erroneous structural assignment.

Since no connection was proved between the disulfide **3** and the dithiolcarbonate **4**, the *p*-nitrobenzenediazonium salt could no longer be stated to be among the general group that yields dithiolcarbonates [although, of course, the dithiolcarbonate **4** *may* have formed first and then given the disulfide **3**].

II. IN THE CHEMISTRY OF POLYSULFIDE SULFINATES

Synthesis of agents that might protect animals against otherwise lethal effects of ionizing radiation, such as X-rays, led us to synthesize the disulfide bissulfinate **5**. The antiradiation agent **5** produced 73% survival of mice at an intraperitoneal dose of 200 mg/kg.[3,4] A particularly attractive feature of **5** as an antiradiation drug was the

$$\underset{\mathbf{5}}{NaO_2S(CH_2)_4SS(CH_2)_4SO_2Na} \qquad \underset{\mathbf{6}}{NaO_2S(CH_2)_4SSS(CH_2)_4SO_2Na}$$

atypical absence of a nitrogen-containing functionality.[3-5] The promise of **5** then led us to synthesize **6**. The trisulfide bissulfinate **6** proved not only to be more readily obtainable than **5** *but* was even more promising as an antiradiation drug. Thus an intraperitoneal dose of 300 mg/kg **6** produced 100% survival,[3,4] and even a dose as low as 37.5 mg/kg gave 73–93% survival;[3] **6** also was active when given orally.[4]

To learn the effect of incorporating still more sulfur atoms in the chain, we used the synthesis of Eq. (2), which had been employed to make **6** [where m of Na_2S_m in Eq. (2) was 1 and n was 4], except with increasing values of m in the sodium polysulfide.[6] The largest number of sulfur atoms that could be obtained in the chain of **8** appeared to be about 5 (i.e. n = 4, m = ca. 3); such products in aqueous solution slowly lost sulfur,

$$\underset{\mathbf{7}}{\left[\begin{matrix}(CH_2)_n \\ SO_2\text{–}S\end{matrix}\right]} + Na_2S_m \rightarrow \underset{\mathbf{8}}{NaO_2S(CH_2)_nSS_mS(CH_2)_nSO_2Na} \qquad (2)$$

and the tetrasulfide **8** (n = 4, m = 2) seemed to be the maximum polysulfide bissulfinate that could persist for more than a few hours in water.[6] Incidentally, no significant improvement in antiradiation properties was apparent when m was ca. 3.[7]

Later, we sought the optimum value of n in Eq. (2) for the CH_2 groups.[8] To our astonishment, we found that when an aqueous solution of the trisulfide **6** was heated (in the dark) at 68 °C, in 80 min it rearranged completely to give **9** [Eq. (3)], where a sulfur atom in the trisulfide chain had been acquired by one of the SO_2Na functions.[8] A mechanism was suggested that started with an intramolecular attack of the terminal

$$\underset{\mathbf{6}}{NaO_2S(CH_2)_4SSS(CH_2)_4SO_2Na} \xrightarrow{H_2O,\,\Delta} \underset{\mathbf{9}}{NaO_2S(CH_2)_4SS(CH_2)_4SO_2SNa} \qquad (3)$$

SO_2Na on the trisulfide chain.[8] Consistent with this view of an intramolecular neighboring group effect, the trimethylene trisulfide (i.e. **8**, n = 3, m = 1) showed a similar intramolecular effect in rearranging completely in 40 min at 68 °C. In a consistent contrast, the pentamethylene trisulfide (i.e. **8**, n = 5, m = 1) required 18 h, as one might expect where the intramolecular effect was much smaller, if not absent.[8] The rearrangement at 68 °C evidently was predominantly heterolytic, since when predominant homolysis was induced under UV light at ca. 25 °C all three trisulfides rearranged in about the same times (140–280 min).[8]

These results with rearrangements indicated that the polysulfide bissulfinates first mentioned, i.e. **8** with n = 4 and m = 2–3,[6] probably contained some sulfide thiosulfonates, such as **9**, and a correction was, of course, published.[9]

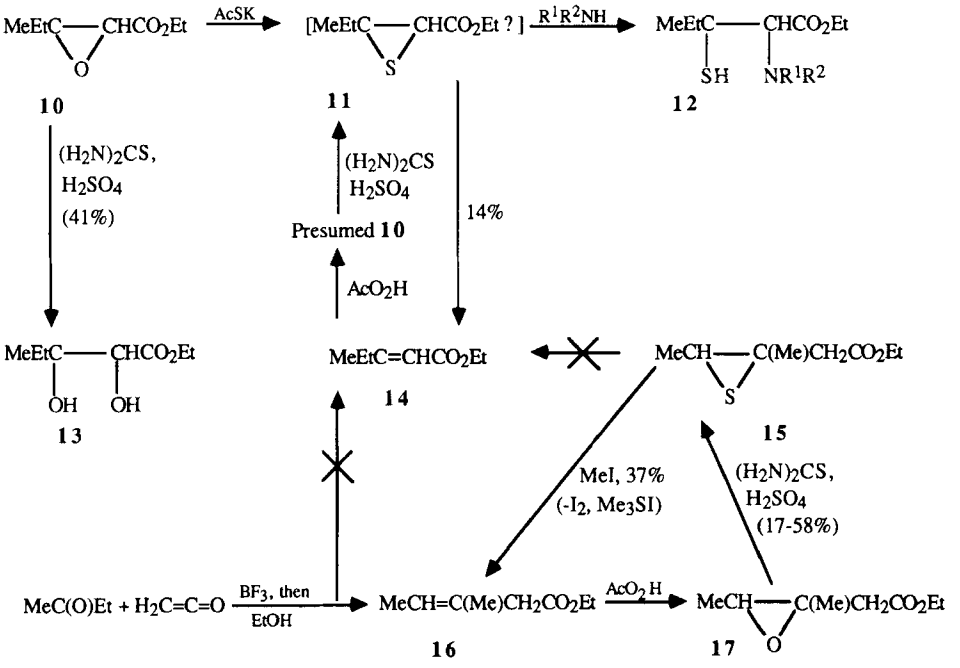
III. IN THE CHEMISTRY OF THIIRANES

Having confessed two of our own errors, perhaps it will not be amiss if we now describe an interesting slip from another laboratory, where we were able to help with a correction. We became interested in α,β-epithio esters, such as **11** of Scheme 1, in the hope that we could cleave them with amines to produce substituted cysteine derivatives such as **12**.[10]

Attempts first were made to convert a glycidate like **10** to an α,β-epithio esters like **11** (except without the 3-ethyl group).[10] When only other products resulted, we tried to convert **10** itself to **11** by a well known approach with a thioacetate.[10] Isolation of **14** indicated that the α,β-epithio ester **11** conceivably formed but, owing to instability, lost the sulfur atom.[10]

At this point, we encountered a report by Durden, Stansbury, and Catlette describing what they believed to be the first known α,β-epithio ester, **11**.[11] Their approach, shown in Scheme 1, proceeded from butanone to the presumed α,β-unsaturated ester **14** and thence to presumed **11**, by preparation of the presumed glycidate **10** and its conversion with thiourea.[11,12] When we used thiourea with **10** prepared by a Darzens reaction of butanone as previously reported by others, however, we obtained only the hydrolysis product **13** with no indication of **11** (Scheme 1).[10]

In mutual efforts to solve the riddle, Dr. Durden cooperated splendidly by supplying us with samples and information. His sample of the presumed glycidate **10** turned out



Scheme 1

to be subtly different from our **10** prepared by the Darzens method.[10] Our treatment of his glycidate as reported,[11] did indeed give an epithio ester, which proved to be identical with that of Durden *et al.*[10] However, reaction of this epithio ester (which turned out to be **15**) with methyl iodide, a means for desulfurizing episulfides specifically to the corresponding alkenes, gave an unsaturated ester that had spectra inconsistent with **14** but consistent with the known β,γ-unsaturated ester **16**; the refractive index and elemental analysis also agreed with those previously reported for **16**.[10] Hence the glycidate of Durden *et al.* was **17**, not **10**, and the epithio ester was the β,γ-epithio ester **15**, not the α,β-epithio ester **11**. It thus seems clear that the cause of the problem was that the reaction Durden *et al.* believed gave **14** actually gave **16**, and indeed we found that earlier workers had reported that **14** largely isomerizes to **16** during acid-catalyzed esterification.[10]

Later, Tung and Speziale obtained results like ours in numerous unsuccessful efforts to synthesize α,β-epithio amides, and they cited related failures by still others (it might be added that they felt that episulfides never formed but that intermediates lost sulfur directly).[13] However, still later, others reported α,β-epithio esters that were quite similar to those we and others had unsuccessfully sought.[14,15]

What lessons can be learned from our experiences? Episode I shows that one cannot have too much evidence for a conclusion, since any single piece may be misleading . . . just as the more nails one puts in a box, the stronger the box is likely to be. Episodes II and III show that one must always be on guard against unexpected rearrangements. And all three episodes show the value of encouraging sharp-eyed properly skeptical collaborators, since it was Dr. Terence C. Owen who caught the slips of Episodes I and III as a postdoctoral research associate and Dr. Jeffrey D. Macke who caught that of Episode II as a predoctoral student.

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