Registry No.—Ia, 874-14-6; Ib, 4401-71-2; Ic, 13509-52-9; Id, 3013-92-1; Ie, 15018-59-4; IIa, 674-97-5; IIb, 15981-91-6; IIc, 3977-29-5; IId, 1683-86-9; IIe, 6307-35-3; III, 22404-50-8; IV, 2080-17-3; V, 66-22-8; VIa, 141-90-2; VIb, 615-78-1; VIc, 64985-69-5; VIc (3-Bu isomer), 64975-70-8; VId, 1194-71-4; VII, 51741-99-2; VIII, 64272-68-0; IXa, 57100-18-2; IXa HCl, 59464-15-2; IXb HCl, 64975-71-9; IXb α isomer, 64999-53-7; X, 59464-18-5; guanidine hydrochloride, 14317-32-9; methylguanidine sulfate, 1866-88-2; urea, 57-13-6; butylurea, 592-31-4; 3-butyluracil, 28289-95-4; 1-butyluracil, 705-06-6; thiourea, 62-56-6; *N*-methylthiourea, 598-52-7; *N*-butylthiourea, 1516-32-1; 1,3-dimethylthiourea, 534-13-4; 2-thiothymine, 636-26-0; *S*-ethylthiuronium bromide, 1071-37-0; cyanoguanidine, 461-58-5; pseudouridine, 1445-07-4; dimethylformamide dimethyl acetal, 4637-24-5.

References and Notes

(1) This investigation was supported by funds from the National Cancer Institute, National Institutes of Health, and U.S. Public Health Service Grants No. CA-08748, 18601, and 18856.
(2) Presented in part at the Division of Medicinal Chemistry, 174th National Meeting of the American Chemical Society, Chicago, Ill., 1977, Abstract No. 54.
(3) L. Szabo, T. I. Kalman, and T. J. Bardos, *J. Org. Chem.*, **35**, 1434 (1970).
(4) H. Hayatsu, *Prog. Nucleic Acid Res. Mol. Biol.*, **16**, 75 (1976).
(5) I. H. Pitman, M. J. Cho, and G. S. Rork, *J. Am. Chem. Soc.*, **96**, 1840 (1974).
(6) B. Bannister and F. Kagan, *J. Am. Chem. Soc.*, **82**, 3363 (1960); R. W. Chambers and V. Kurkov, *ibid.*, **85**, 2160 (1963); E. J. Reist, A. Benitez, and L. Goodman, *J. Org. Chem.*, **29**, 554 (1964).
(7) B. A. Otter, E. A. Falco, and J. J. Fox, *Tetrahedron Lett.*, 2967 (1968); B. A. Otter, E. A. Falco, and J. J. Fox, *J. Org. Chem.*, **33**, 3593 (1968); D. Lipkin, C. Cori, and M. Sano, *Tetrahedron Lett.*, 5593 (1968).
(8) K. Isono and T. Azuma, *Chem. Pharm. Bull.*, **20**, 193 (1972); O. Mitsunobu, S. Takizawa, and H. Morimoto, *J. Am. Chem. Soc.*, **98**, 7858 (1976).
(9) H. Inoue and T. Ueda, *Chem. Pharm. Bull.*, **19**, 1743 (1971); S. Senda, K. Hirota, and T. Asao, *J. Org. Chem.*, **40**, 353 (1975); S. Senda, K. Hirota, T. Asao, and Y. Yamada, *Heterocycles*, **4**, 1765 (1976); P. F. Torrence, B. Bhooshan, J. Descamps, and E. D. Clercq, *J. Med. Chem.*, **20**, 974 (1977).
(10) H. U. Blank, I. Wempen, and J. J. Fox, *J. Org. Chem.*, **35**, 1131 (1970).
(11) D. J. Brown, "Mechanisms of Molecular Migrations", Vol. 1, B. S. Thyagatajan, Ed., Interscience, New York, N.Y., 1968, p 209.
(12) D. J. Brown and M. N. Paddon-Row, *J. Chem. Soc. C*, 164 (1966).
(13) E. A. Oostveen, H. C. van der Plas, and H. Jongejan, *Recl. Trav. Chim. Pays-Bas*, **95**, 209 (1976).
(14) K. Hirota, K. A. Watanabe, and J. J. Fox, *J. Heterocycl. Chem.*, **14**, 537 (1977).
(15) H. Türler, "Procedures in Nucleic Acid Research", Vol. 2, G. L. Cantoni and D. R. Davies, Ed., Harper and Row, New York, N.Y., 1971, pp 680–699; N. K. Kochetkov and E. I. Budowsky, "Organic Chemistry of Nucleic Acids", Part B, Plenum Press, New York, N.Y., 1972, pp 381–423; D. M. Brown, "Basic Principles in Nucleic Acid Chemistry", Vol. 2, P. O. P Ts'o, Ed., Academic Press, New York, N.Y., 1974, pp 1–90; N. K. Kochetkov and E. I. Budowsky, *Prog. Nucleic Acid Res. Mol. Biol.*, **9**, 403 (1969); E. I. Budowsky, *ibid.*, **16**, 125 (1976).
(16) D. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, **9**, 199 (1952).
(17) D. V. Santi, C. F. Brewer, and D. Farber, *J. Heterocycl. Chem.*, **7**, 903 (1970).
(18) We have isolated crystalline 1,3-dimethylurea from the reaction mixture of **Ia** and 1 N sodium hydroxide.[14] Lovett and Lipkin [*J. Org. Chem.*, **42**, 2574 (1977)] also reported the isolation of 1,3-dimethylurea as well as formylacetic acid from the reaction of Ia and 1 N NaOH.
(19) (a) G. Shaw and R. N. Warrener, *J. Chem. Soc.*, 153 (1958); (b) R. N. Warrener and E. N. Cain, *Chem. Ind.*, 1989 (1964).
(20) E. Winterfeld and J. M. Nelke, *Chem. Ber.*, **100**, 3671 (1967); E. N. Cain and R. N. Warrener, *Aust. J. Chem.*, **23**, 51 (1970).
(21) D. Shugar and J. J. Fox, *Bull. Soc. Chim. Belg.*, **61**, 293 (1952); H. L. Wheeler and H. F. Merriam, *Am. Chem. J.*, **29**, 478 (1903).
(22) P. A. S. Smith "Open-Chain Nitrogen Compounds", Vol. 1, W. A. Benjamin, New York, N.Y., 1965, p 270.
(23) C. K. Chu, I. Wempen, K. A. Watanabe, and J. J. Fox, *J. Org. Chem.*, **41**, 2793 (1976).
(24) J. H. Burchenal, K. Ciovacco, K. Kalahar, T. O'Toole, R. Kiefner, M. D. Dowling, C. K. Chu, K. A. Watanabe, I. Wempen, and J. J. Fox, *Cancer Res.*, **36**, 1520 (1976).
(25) U. Reichman, K. Hirota, C. K. Chu, K. A. Watanabe, and J. J. Fox, *J. Antibiot.*, **30**, 129 (1977).
(26) 1,3-Dimethyl-5-fluorouracil (Id) was reported by Fikus et al. [*Biochem. Biophys. Res. Commun.*, **16**, 478 (1964)], who prepared Id by alkylation of 5-fluorouracil with diazomethane. We found, however, Id was prepared readily in quantitative yield by treatment of 5-fluorouracil with dimethyl sulfate in the presence of 2 equiv of NaOH.
(27) M. G. Biressi, M. Carissimi, and F. Ravenna, *Gazz. Chim. Ital.*, **93**, 1268 (1963).
(28) R. Hull, B. J. Lovell, H. T. Openshaw, and A. R. Todd, *J. Chem. Soc.*, 41 (1947).
(29) R. N. Lacey, *J. Chem. Soc.*, 839 (1954).
(30) D. J. Brown and N. W. Jacobsen, *J. Chem. Soc.*, 3172 (1962).
(31) W. Logemann, L. Caprio, and D. Artini, *Farmaco, Ed. Sci*, **12**, 586 (1957); *Chem. Abstr.*, **53**, 18052 (1959).
(32) C. C. Cheng and L. R. Lewis, *J. Heterocycl. Chem.*, **1**, 260 (1964).
(33) H. Vorbrüggen and P. Strehlke, *Chem. Ber.*, **106**, 3039 (1973).

Use of *o*- and *p*-Hydroxybenzyl Functions as Blocking Groups Which Are Removable with Base

Lloyd D. Taylor,* J. Michael Grasshoff, and Milan Pluhar

Chemical Research Laboratories, Polaroid Corporation, Cambridge, Massachusetts 02139

Received May 23, 1977

The successful development of the *o*- and *p*-hydroxybenzyl functions and the corresponding esters thereof as blocking groups which are removable with base is described. Specific illustrative examples include protecting and subsequently releasing 1-phenyl-2-tetrazoline-5-thione and thiosulfate anions.

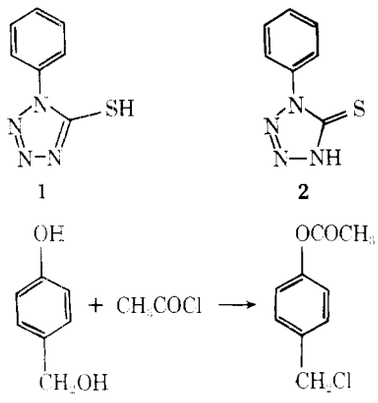
In photography many compounds are used which react in some way with silver halide either as silver precipitants, complexers, or solvents. For example, 1-phenyl-5-mercaptotetrazole (PMT) (1) is a development restrainer and forms a very insoluble silver salt.[1] On the other hand, sodium thiosulfate (hypo) is a silver solvent and is used for fixing emulsions (dissolving undeveloped silver halide).[2] We became interested in preparing derivatives of these types of compounds which would be stable in a film system before processing the system with a highly alkaline developer fluid, but during such processing these same derivatives would have to release the active photographic species.

Esters of PMT are not hydrolytically stable. For example, the acetyl derivative readily hydrolyzes, since the PMT anion is a very good leaving group. PMT is a fairly strong acid, having a pK_a of 3.65.[3] In the solid state, the compound exists as the tautomeric 1-phenyl-2-tetrazoline-5-thione (**2**).[4]

There is considerable literature on the base instability of *o*- and *p*-hydroxybenzyl groups,[5] the decomposition going through quinone methide intermediates.[6] We decided to prepare *o*- and *p*-hydroxybenzyl chlorides or the corresponding esters as reagents to generate alkali-removable blocking groups for photographically active compounds.

The reagents with which we did the most work were *o*- and *p*-acetoxybenzyl chlorides **3**. These compounds are prepared in one step by reaction of the *o*- and *p*-hydroxymethylphenols with with acetyl chloride.[7] The isomeric *m*-hydroxymethylphenol does not undergo this reaction. It is desirable to have

0022-3263/78/1943-1197$01.00/0

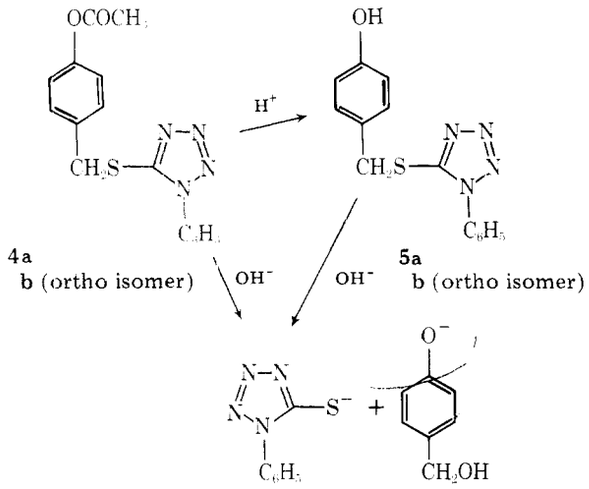


1 2

(also ortho isomer) 3a b (ortho isomer)

these esters, since the unsubstituted chloromethylphenols readily decompose and polymerize.

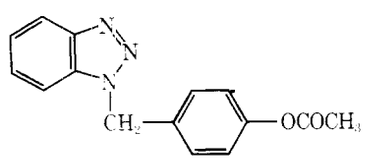
We found that the above compounds smoothly react to generate blocked PMT derivatives **4a,b,** which we formulate as the S-alkylated derivative. These ester derivatives can be hydrolyzed in acid to give the free hydroxybenzyl compounds **5a,b.** All of these compounds when treated with alkali rapidly



4a b (ortho isomer) 5a b (ortho isomer)

decompose to release the PMT anion. The quinone methide is converted to the anion of the hydroxymethylphenol. These reactions are readily followed by analysis of the products as well as by ^1H NMR and UV spectroscopy.

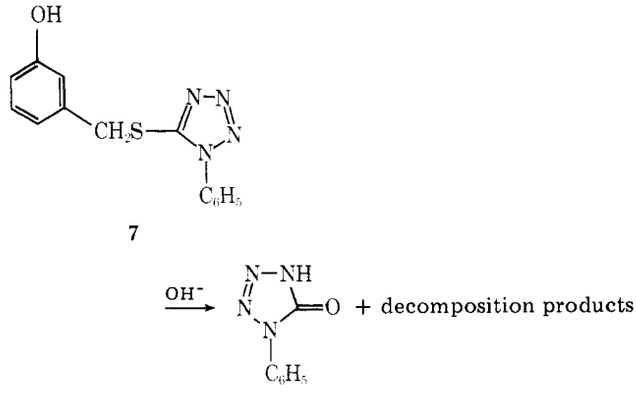
Although the cleavage reaction is very rapid in the case of PMT, a nitrogen analogue, 1-(*p*-acetoxybenzyl)benzotriazole (**6**), reacts much more slowly.



6

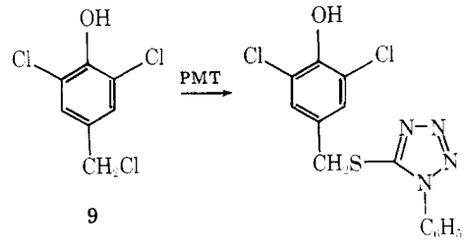
As a synthetic "proof" of the mechanism, we decided to prepare the meta derivative **7.** The intermediate, *m*-acetoxybenzyl chloride, was prepared in two steps.[8] The PMT derivative was found to undergo a very slow decomposition in alkali to yield a different product. Thus, instead of PMT anion being generated, the product was 1-phenyl-5-tetrazolone (**8**), the reaction most likely being attack of alkali on the tetrazole ring with cleavage of the sulfur bond in the opposite direction to that observed with the other isomers.

Another useful reagent was found to be the previously unreported 4-chloromethyl-2,6-dichlorophenol (**9**) readily prepared by chloromethylation of the phenol.[9] This compound



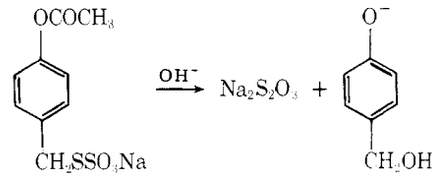
7 8

is quite stable and can be stored if kept dry. The PMT derivative **10** is readily prepared and deblocked with base.



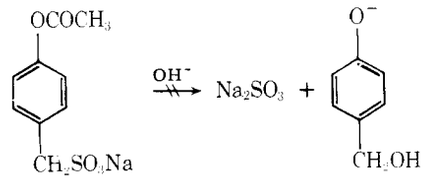
9 10

We then focused on the special Bunte salts based on this chemistry, by reaction of sodium thiosulfate with *p*-acetoxybenzyl chloride. We succeeded in preparing sodium *S*-(*p*-acetoxybenzyl)thiosulfate (**11**), and this compound does indeed release hypo when treated with alkali while the corresponding sodium *S*-benzylthiosulfate does not.



11

A similar release of sulfite ion was attempted. In this case, however, no sulfite ion could be detected after treatment for several hours with aqueous alkali.



12

Partial accounts of this work including applications have appeared in the patent literature.[10-13]

Experimental Section

***p*-Chloromethylphenyl Acetate (3a).** Acetyl chloride (300 mL) was stirred in an open beaker with ice cooling. *p*-Hydroxybenzyl alcohol (99.3 g, 0.8 mol) was added in small portions so as to keep the evolution of HCl at a moderate rate. The excess of acetyl chloride was allowed to evaporate overnight, whereupon the remainder was neutralized with concentrated sodium bicarbonate solution. The organic phase was separated and the aqueous layer extracted twice with ether. The combined organic layers were filtered and dried over Drierite. Vacuum distillation through a 12-in. severed Vigreux column yielded 81 g (55%) of a colorless liquid; bp 104–106 °C (1.5 mm); n^{25}_D

1.5290.

Anal. Calcd for $C_9H_9ClO_2$: Cl, 19.3. Found: 19.3.

o-Chloromethylphenyl Acetate (3b). Acetyl chloride and o-hydroxybenzyl alcohol were reacted in the same manner as described above to yield o-chloromethylphenyl acetate, bp 98–100 °C (1.5 mm), n^{25}_D 1.5235, in 75% yield.

Anal. Calcd for $C_9H_9ClO_2$: Cl, 19.3. Found: 19.3.

5-(o-Acetoxybenzylthio)-1-phenyltetrazole (4b). Sodium 1-phenyltetrazole-5-thiolate (45 g, 0.225 mol) and o-chloromethylphenyl acetate (41.5 g, 0.225 mol) were dissolved in 600 mL of acetone. The solution was refluxed for 2 h and then filtered. The filtrate was evaporated to dryness and the residue extracted with 3% aqueous $NaHCO_3$ solution. The remaining solid was washed with water and dried to render 72 g (98%) of white crystals, mp 103–105 °C.

Anal. Calcd for $C_{16}H_{14}N_4O_2S$: C, 59.0; H, 4.3; N, 17.2; S, 9.8. Found: C, 58.8; H, 4.6; N, 16.9; S, 9.7.

5-(p-Acetoxybenzylthio)-1-phenyltetrazole (4a). Similarly, the reaction of sodium 1-phenyltetrazolethiolate with p-chloromethylphenyl acetate gave the corresponding thioether, mp 71–72 °C, in 80% yield.

Anal. Calcd for $C_{16}H_{14}N_4O_2S$: C, 59.0; H, 4.3; N, 17.2. Found: C, 58.9; H, 4.3; N, 17.3.

5-(o-Hydroxybenzylthio)-1-phenyltetrazole (5b). 5-(o-Acetoxybenzylthio)-1-phenyltetrazole (57 g, 0.175 mol) was dissolved in 1.3 L of methanol containing 0.2% concentrated HCl. The solution was stirred at 55–57 °C under nitrogen for 3 h followed by solvent evaporation. The residue was powdered, extracted with warm dilute $NaHCO_3$ solution, washed with water, and finally dried. Recrystallization from benzene/hexane gave 40 g (80%) of colorless crystals, mp 102–103 °C.

Anal. Calcd for $C_{14}H_{12}N_4OS$: C, 59.2; H, 4.2; N, 19.7; S, 11.8. Found: C, 59.2; H, 4.3; N, 19.7; S, 11.8.

5-(p-Hydroxybenzylthio)-1-phenyltetrazole (5a). Acid hydrolysis of the corresponding acetate in the previously described manner gave the free phenol, mp 130–131 °C, in 70% yield: ^1H NMR (Me_2SO) δ 4.40 (CH_2), 6.58, and 7.12 (arom protons), 7.83 (C_6H_5), 9.37 (OH); UV (50% *tert*-butyl alcohol) λ_{max} 228 nm, ϵ 17 000.

Anal. Calcd for $C_{14}H_{12}N_4OS$: C, 59.2; H, 4.2; N, 19.7. Found: C, 59.2; H, 4.4; N, 19.7.

Alkaline Hydrolysis of o- and p-Hydroxybenzylthio-1-phenyltetrazoles. The free phenols as well as their acetates were stirred in 5% aqueous NaOH at 25–30 °C for about 2 h. The reaction mixture was centrifuged and repeatedly extracted with ether. Acidification with HCl gave a voluminous, slightly yellow precipitate, which was recrystallized from benzene. The product was identified by means of elemental and spectral analysis as pure 1-phenyltetrazoline-5-thione. The ^1H NMR spectrum of the compounds in Me_2SO-d_6 containing KOD showed a complex aromatic signal and a shift of 0.3 ppm from δ 4.4 (CH_2S) to 4.1 ppm (CH_2O). Although in the parent compounds we have no direct proof of S-alkylation, we feel that not only is it the predictable isomer but also that the chemical shift for CH_2N would be more like that of compound **6**, δ 5.7.

1-(p-Acetoxybenzyl)benzotriazole (6). To a solution of 2.5 g (2.06 mmol) of 2,4,6-trimethylpyridine in 50 mL of diethyl ether was added with stirring a solution of 3.5 g (1.89 mmol) of p-acetoxybenzyl chloride in 10 mL of ether. The hazy reaction mixture was refluxed overnight, followed by solvent evaporation and extraction with 10 mL of water and 50 mL of ether. The ether phase was washed with water and dried with anhydrous Na_2SO_4. Solvent evaporation yielded a pale-yellow oil which solidified on treatment with a hexane/methanol mixture. Recrystallization from hexane/methanol gave 2 g (40%) of white crystals; mp 89 °C; ^1H NMR (CD_3OD) δ 2.0 (CH_3), 5.7 (CH_2N), multiple signals at 6.6, 7.0, 7.4, and 7.8 ppm (aromatic ring systems).

Anal. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.4; H, 4.9; N, 15.8. Found: C, 67.3; H, 5.2; N, 15.6.

Alkaline cleavage: to the CD_3OD solution was added 5 wt % of KOD, followed by heating at 70 °C for 4 h. The following changes in the ^1H NMR spectrum were recorded: decrease in the intensity of the signal at δ 5.7 (CH_2N) and appearance of new signal at δ 4.1 ppm (CH_2O); signal strength ratio 3:1 (25% cleavage).

5-(m-Hydroxybenzylthio)-1-phenyltetrazole (7). A solution of sodium 1-phenyltetrazole-5-thiolate (4.5 g, 22.5 mmol) and m-chloromethylphenyl acetate[6] (4.15 g, 22.5 mmol) in acetone (200 mL) was heated to reflux for 2 h. Filtration and solvent evaporation yielded a pale-yellow oil. The latter was heated at 54 °C in methanol in the presence of HCl to give a solid which was recrystallized from benzene: white crystals, mp 111 °C, yield 2 g (31%).

Anal. Calcd for $C_{14}H_{12}N_4OS$: C, 59.2; H, 4.2; N, 19.7. Found: C, 59.1; H, 4.2; N, 19.8.

Alkaline Hydrolysis of m-Hydroxybenzylthio-1-phenyltetrazole. Unlike the ortho and para isomer, the meta-substituted derivative was not changed by dilute aqueous NaOH at room temperature. Heating at 50–60 °C with 10% NaOH gave a clear odorous solution. The pH was adjusted to 8, followed by ether extraction. The aqueous layer was evaporated to dryness, and the solid was extracted with ether and recrystallized from 2-propanol/water. The colorless crystalline product melted at 190 °C and was found to be identical with 1-phenyl-5-tetrazolone (**8**).[14]

Anal. Calcd for $C_7H_6N_4O$: C, 51.9; H, 3.7; N, 34.6. Found: C, 52.2; H, 3.7; N, 34.5.

4-Chloromethyl-2,6-dichlorophenol (9). 2,6-Dichlorophenol (41.8 g, 0.256 mol) was dissolved in heptane (300 mL) with heating and stirring under a nitrogen blanket. A mixture of 37% aqueous formaldehyde solution (250 mL, 3.1 mol) and concentrated HCl (500 mL) was prepared, three quarters of which was added to the phenol solution. The remainder was introduced after letting the reaction mixture reflux for 8 h. Simultaneously, the introduction of HCl gas was started. The reflux conditions were maintained for a total of 24 h. The organic layer was separated, the aqueous layer was extracted with ether, and the extracts were combined with the oil phase. Recrystallization of the evaporation residue gave 35 g (64%) of white needles, mp 87.5–89 °C.

Anal. Calcd for $C_7H_5Cl_3O$: C, 39.7; H, 2.4; Cl, 50.3. Found: C, 39.4; H, 2.4; Cl, 50.6.

5-(3,5-Dichloro-4-hydroxybenzylthio)-1-phenyltetrazole (10). A solution of sodium 1-phenyltetrazole-5-thiolate (3 g, 0.015 mol) in acetone (20 mL) was treated with 4-chloromethyl-2,6-dichlorophenol (3.2 g, 0.015 mol) in acetone (20 mL). Immediate precipitation of NaCl was noticed. The mixture was refluxed for 2 h and then filtered and evaporated to yield a white solid, mp 127–130 °C. Recrystallization from benzene/hexane gave the pure compound, mp 132–134 °C, in 90% yield (4.8 g).

Anal. Calcd for $C_{14}H_{10}Cl_2N_4OS$: C, 47.6; H, 2.9; N, 15.8; Cl, 20.2; S, 9.0. Found: C, 47.7; H, 3.0; N, 15.7; Cl, 19.9; S, 8.9.

Sodium S-(p-Acetoxybenzyl) Thiosulfate (11). To a solution of $Na_2S_2O_3 \cdot 5H_2O$ (27.3 g, 0.11 mol) in H_2O (60 mL) was added ethanol (5 mL). The mixture was heated at 55–65 °C and p-chloromethylphenyl acetate (18.45 g, 0.1 mol) in 60 mL of ethanol was added from a dropping funnel over a period of 45 min. The clear solution was stirred at 65–70 °C for another 45 min. Then the solvent was evaporated and the residue extracted with hot ethanol (about 700 mL). The extract was filtered hot and refrigerated to give a crystalline material (19 g, 75%): mp 220 °C (decomposition); UV (in ethanol) λ_{max} 265, 272 nm (ϵ 435, 325).

Anal. Calcd for $C_9H_9S_2O_5Na$: C, 38.1; H, 3.2; S, 22.5. Found: C, 37.9; H, 3.2; S, 22.4.

Treatment of the compound with aqueous NaOH gave a white precipitate. The supernatant liquid acted as silver complexing agent, solubilizing silver ion in alkaline solution.

Sodium S-Benzyl Thiosulfate. By use of the above procedure substituting p-chloromethylphenyl acetate with benzyl chloride, sodium S-benzyl thiosulfate was isolated as white platelets, mp ~210 °C (decomposition). Aqueous NaOH caused an oily brown precipitate to form. Silver ion was not solubilized, indicating hypo was not released.

Sodium p-Acetoxybenzyl Sulfonate (12). To a solution of 6 g (0.048 mol) of Na_2SO_3 in 30 mL of water was added at 70–73 °C a solution of 8.8 g (0.048 mol) of p-chloromethylphenyl acetate in 30 mL of ethanol. The hazy solution was diluted with 50 mL of ethanol and stirred at 75 °C for 2 h. A small amount of a white solid settled out. The clear supernatant was freed of solvent to render a white crystalline residue which was recrystallized twice from ethanol. The yield was 2 g of an extremely hygroscopic solid. The IR spectrum showed only a very weak carbonyl absorption band at 1720 cm^{-1}. Elemental analysis showed the solid to be a mixture of the p-acetoxy and p-hydroxybenzyl sulfonates. When the solid was treated with aqueous alkali, no evidence of sulfite release was found, as evidenced by a negative iodine test. Since neither the hydroxy compound nor its acetate released sulfite, no further work was done to separate these compounds into pure components.

Registry No.—**3a,** 39720-27-9; **3b,** 15068-08-3; **4a,** 39720-25-7; **4b,** 39720-28-0; **5a,** 39720-23-5; **5b,** 39720-24-6; **6,** 64706-07-6; **7,** 64706-08-7; **8,** 5097-82-5; **9,** 45952-61-2; **10,** 64706-09-8; **11,** 39941-32-7; **12,** 64706-10-1; acetyl chloride, 75-36-5; p-hydroxybenzyl alcohol, 623-05-2; o-hydroxybenzyl alcohol, 90-01-7; sodium 1-phenyltetrazole-5-thiolate, 15052-19-4; 1-phenyltetrazoline-5-thione, 86-93-1; m-chloromethylphenyl acetate, 4530-44-3; 2,6-dichlorophenol, 87-65-0; formaldehyde, 50-00-0.

References and Notes

(1) T. H. James, in "The Theory of the Photographic Process", 3rd ed, C. E. K. Mees and T. H. James, Ed., Macmillan, New York, N.Y., 1966, pp 344–346.
(2) G. T. Eaton, in "The Theory of the Photographic Process", 3rd ed, C. E. K. Mees and T. H. James, Ed., Macmillan, New York, N.Y., 1966, pp 398–405.
(3) E. Lieber, J. Ramachandran, C. N. R. Rao, and C. N. Pillai, *Can. J. Chem.*, **37**, 563 (1959).
(4) E. Lieber, C. N. R. Rao, C. N. Pillai, J. Ramachandran, and R. D. Hites, *Can. J. Chem.*, **36**, 801 (1958).
(5) A. Meriljan and P. D. Gardner, *J. Org. Chem.*, **30**, 3965 (1965).
(6) L. J. Filar and S. Winstein, *Tetrahedron Lett.*, **25**, 9 (1960).
(7) T. Zawadowski, *Rocz. Chem.*, **42**, 297 (1968).
(8) R. Grice and L. N. Owen, *J. Chem. Soc.*, 1947 (1963).
(9) N. P. Newreiter, *J. Org. Chem.*, **28**, 3486 (1963).
(10) J. M. Grasshoff and L. D. Taylor, U.S. Patent 3 698 898 (1972).
(11) J. M. Grasshoff and L. D. Taylor, U.S. Patent 3 674 478 (1972).
(12) J. M. Grasshoff and L. D. Taylor, U.S. Patent 3 685 991 (1972).
(13) J. M. Grasshoff and L. D. Taylor, U.S. Patent 3 932 480 (1976).
(14) J. P. Horwitz, B. Fisher, and A. Tomasewski, *J. Am. Chem. Soc.*, **81**, 3076 (1959).

Synthesis of γ- and δ-(1,3-Dithianyl) β-Keto Esters[1]

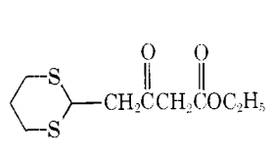
Edward C. Taylor* and John L. LaMattina[2]

Department of Chemistry, Princeton University, Princeton, New Jersey 08540

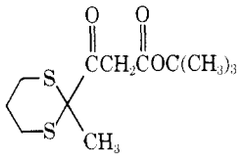
Received September 21, 1977

The preparations of ethyl γ-(1,3-dithian-2-yl)acetoacetate (**1**), *tert*-butyl 3-oxo-4-trimethylenedithiopentanoate (**2**), and ethyl 5-benzyloxy-3-oxopentanoate (**3**) are described. Some additional reactions relevant to the chemistry of dithiane are also discussed.

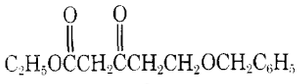
Previous papers from this laboratory have described an unambiguous approach to the synthesis of 6-substituted pteridines by guanidine cyclization of 2-amino-3-cyano (or alkoxycarbonyl) pyrazines suitably substituted at position 5. These latter critical intermediates were prepared in turn by cyclization of aminomalononitrile (or esters of α-aminocyanoacetic acid) with an α-ketoaldoxime, followed by deoxygenation of the resulting pyrazine 1-oxide (see Scheme I).[3] In this sequence, the group α to the carbonyl of the α-ketoaldoxime becomes the C-6 substituent on the final pteridine. Since the α-ketoaldoximes are themselves prepared from β-keto esters by hydrolysis, oximation, and subsequent decarboxylation, the preparation of a specific C-6 substituted pteridine requires an appropriately substituted β-keto ester. Our current interest in the preparation of certain 2,4-diaminopteridines carrying side chains at position 6 substituted with carbonyl groups thus necessitated the preparation of a variety of β-keto esters containing a (potential) carbonyl at either the γ or δ position. This paper describes our efforts to prepare β-keto esters **1**, **2**, and **3**.



1

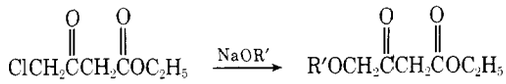


2



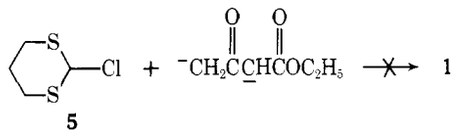
3

Initial approaches to **1** attempted to attach the dithiane moiety directly to the γ position of an appropriately substituted acetoacetic ester. A promising model was the successful conversion of ethyl γ-chloroacetoacetate (**4**) with excess alkoxide to yield γ-alkoxy derivatives in good yield.[4] Unfortunately, however, no reaction occurred between 2-lithio-1,3-dithiane and **4** (as its sodium salt). The dithiane anion is apparently not sufficiently nucleophilic to displace the γ-chloro substituent.[5] Attempts to carry out this reaction in the presence of 1 equiv of sodium iodide[6] resulted only in self-condensation of **4**.



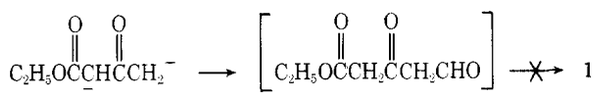
4

An alternative approach to **1** involves treatment of 2-chloro-1,3-dithiane (**5**)[7] with the dianion of ethyl acetoacetate.[8] No displacement of halide ion occurred; instead, the dianion was protonated by **5**, leading to the recovery of ethyl acetoacetate and to the decomposition of the dithiane moiety.



5

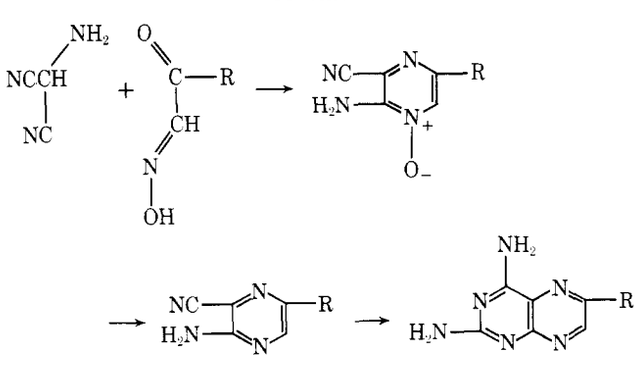
Since direct linkage of 1,3-dithiane with the γ position of ethyl acetoacetate did not seem feasible, an attempt was made to incorporate this moiety indirectly. Treatment of the dianion of ethyl acetoacetate with methyl formate gave the unstable aldehyde **6**,[9] but attempted reaction of this material with



6

propane-1,3-dithiol resulted only in the formation of an intractable tar; no **1** could be isolated.

Scheme I



0022-3263/78/1943-1200$01.00/0