(10) H. Paul, R. D. Small, and J. C. Scaiano, *J. Amer. Chem. Soc.*, **100**, 4520 (1978).
(11) S. K. Wong, *J. Amer. Chem. Soc.*, **101**, 1235 (1979).
(12) L. Batt, R. D. McCulloch and R. T. Milne, *Int. J. Chem. Kinetics*, **6**, 945 (1974).
(13) L. Batt and R. D. McCulloch, *Int. J. Chem. Kinetics*, **8**, 911 (1976).
(14) R. L. East and L. Phillips, *J. Chem. Soc.*, **B**, 245 (1966).
(15) N. J. Quee and J. C. J. Tynne, *Trans. Faraday. Soc.*, **63**, 2970 (1967).
(16) A. C. Baldwin, J. R. Barker, D. M. Golden and D. G. Hendry, *J. Phys. Chem.*, **81**, 2483 (1977); L. Batt, *Int. J. Chem. Kinetics*, **11**, 977 (1979).
(17) K. Y. Choo and S. W. Benson, *Int. J. Chem. Kinetics*, **13**, 833 (1981).
(18) C. R. Park, S. A. Song, Y. E. Lee and K. Y. Choo, *J. Amer. Chem. Soc.*, **104**, 6445 (1982).
(19) E. Lissi, *Can. J. Chem.*, **52**, 2491 (1934).
(20) G. R. McMillan, *J. Amer. Chem. Soc.*, **82**, 2442 (1960).

# Synthesis of Nucleophilic Adducts of Thiols (V). Addition of Thioglycolic Acid to ω, ω-Diacetylstyrene Derivatives

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The addition reactions of thioglycolic acid to ω, ω-diacetylstyrene derivatives were investigated. ω, ω-Diacetylstyrene derivatives easily undergo addition reactions with thioglycolic acid to form s-(2, 2-diacetyl-1-phenylethyl)-thiogycolic acid, s-[2,2-diacetyl-1-(methyl) phenylethyl]-thioglycolic acid, s-[2,2-diacetyl-1-(p-methoxy) phenylethyl]-thioglycolic acid and s-[2, 2-diacetyl-1-(p-chloro) phenylethyl]-thioglycolic acid, respectively. The structures of these compounds were identified by neutralization equivalent, UV, IR, and NMR spectral data.

## Introduction

The Michael type addition, defined as the nucleophilic addition of an anion to the carbon-carbon double bond of α,β-unsaturated ketone, aldehyde, nitrile, or carboxylic acid derivatives, has been extensively used as an effective method for carbon-carbon bond formation.[1-3]

The addition of thiols to α, β-unsaturated compounds is interesting because much information has appeared in the literatures[4-7] concerning the antiviral and antitumor activities of their adducts.

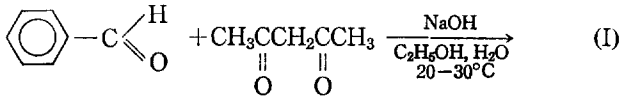
As a part of the series on the syntheses of nucleophilic adducts of thiols, the addition of cysteine[8] and thioglycolic acid[9] to β-nitrostyrene derivatives has been described recently.

We report here our investigation into Michael addition of thioglycolic acid to ω,ω-diacetylstyrene derivatives.

## Results and Discussion

The ω,ω-diacetylstyrene derivatives were attempted to prepare by Kohler's method.[11]

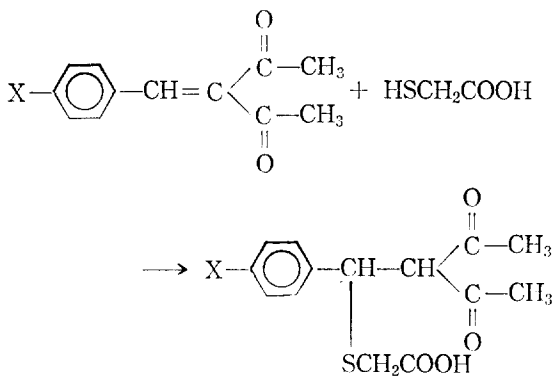
To a stirred solution of sodium hydroxide in ethanol and water was added benzaldehyde and acetylacetone. After stirring for 2 hours at 20-30°C, the mixture gave yellow precipitate, whose recrystallization from ethanol afforded yellow crystal (I). UV (330nm: *lit.*[10] 282nm), IR (1640cm$^{-1}$: *lit.*[10] 1690cm$^{-1}$), NMR (no-$COCH_3$ peaks) and Mass (MW 234) spectral data revealed that (I) was not ω,ω-diacetylstyrene. (I) was identified as dibenzylideneacetone, $C_6H_5$—CH=CH—C(=O)—CH=CH—$C_6H_5$ (mp 112 °C, *lit.*[12] 113 °C).



So other method[10] was tri ed. To a stirred mixture of benzaldehyde and acetylacetone was added piperidine. The mixture was allowed to stand at 0−10 °C for 3 days. The resulting yellow precipitate was washed successively with ether, diluted HCl solution and water. Recrystallization from ethanol gave white crystal (II). In view of the presence of the sharp peak at 3440 $cm^{-1}$ (OH stretching) and the absence of the peak at 1600 $cm^{-1}$ (C=C stretching), (II) was identified as 2,2-diacetyl-1-phenyl-1-ethanol, $C_6H_5$-CH(OH)-CH$(COCH_3)_2$.

As the third trial, the mixture of benzaldehyde, acetylacetone and piperidine was allowed to stand at 10-15 °C for 3 days. The resulting precipitate (III) was identified as the desired product.

Then the nucleophilic adducts were prepared by the typical Micheal type reaction of thioglycolic acid to ω,ω-diacetylstyrene derivatives.



X=H, Me, MeO, Cl

Since the conjugated system of ω, ω-diacetylstyrene disappears by forming adduct, the products were easily confirmed by UV, IR and NMR spectra. The maximum absorption at 282nm was not observed at the adduct. The absorption at 1600$cm^{-1}$ (C=C stretching) disappeared and broad band at 2500-3300 $cm^{-1}$ (carboxylic OH stretching) appeared. A singlet at 7.30ppm (-CH=C-) was replaced by two doublets at 4.30 and 4.80 ppm(-CH—CH-). And two singlets at 3.06 ($S-CH_2$-) and 9.00 ppm (-COOH) were observed in the adduct. The integral ratio of the peaks was 3(—C(=O)—$CH_3$): 3(C(=O)—$CH_3$): 2($SCH_2$): 1(CH-CH): 1(CH-CH): 5(Ar): 1(COOH) which is well in consistent with the structure.

## Experimental

Melting points were determined on a Fisher-Johns apparatus. Ultraviolet spectra were recorded on a Beckman Model 26 spectrometer. Infrared spectra were obtained on a Hitachi EPI-G2 or Perkin Elmer 710B spectrometer and are reported in wave numbers($cm^{-1}$). Proton magnetic resonance spectra were recorded with a Varian Model E.M. 360 (60 MHz) spectrometer and are reported in parts per million (δ) downfield from tetramethylsilane.

Neutralization equivalents were determined by a potentiometric titration with 0.092*N* sodium hydroxide solution.

*ω,ω-Diacetylstyrene*[10]. To a stirred mixture of benzaldehyde (10.6g, 0.1mol) and acetylacetone (10.0g, 0.1mol) was added piperidine (1m*l*) at 10-15 °C. After standing at the same temperature for 3days, the mixture was extracted with ether. The extract was washed successively with dilute hydrochloric acid, dilute sodium hydroxide solution and water. After drying ($Na_2SO_4$) and removal of solvent, ω,ω-diacetylstyrene (bp 168−170 °C/760 mmHg) was obtained. (12.5g, 35.5 %) Table 1 shows the physical data of ω, ω-diacetylstyrene derivatives.

*s-(2,2-Diacetyl-1-phenylethyl)-thioglycolic Acid.* To a stirred solution of ω,ω-diacetylstyrene (8.0g, 0.043mol) and thioglycolic acid (8.0g, 0.086mol) in actone (20m*l*) was added triethylamine (2.0g, 0.02mol) at room temperature. After stirring for 2 hours at the same temperature, cold dilute hydrochloric acid was added to the solution. The mixture was allowed to stand in refrigerator overnight. The resulting precipitates were collected by filtration. Recrystallization from $CCl_4$ gave white crystal of s-(2,2-diacetyl-1-phenylethyl)-thioglycolic acid (8.1g, 68%): mp 108-109 °C: UV ($CH_3OH$) $\lambda_{max}$ 294nm: IR (KBr disc) 1690, 2500-3300$cm^{-1}$: NMR ($CDCl_3$) 1.90(3H, *s*), 2.40 (3H, *s*), 3.06 (2H, *s*), 4.30 (1H, *d*), 4.80(1H, *d*), 7.40 (5H, *s*), 9.00 (1H, *s*).

Neutralization equivalent. Calculated for $C_{14}H_{16}O_4S$: 280.36. Found: 276.47. Anal. Calcd for $C_{14}H_{16}O_4S$: C, 60.01 %; H, 5.71 % Found: C, 59.83 %; H, 5.67 %

*s-[2,2-Diacetyl-1-(p-methyl)phenylethyl]-thioglycolic Acid.* To a stirred solution of *p*-methyl-ω, ω-diacetylstyrene (2.0g) and thioglycolic acid (1.8g) in acetone (20m*l*) was added triethylamine (0.5g) at room temperature. Work-up as above gave white precipitate, whose recrystallization from $CCl_4$ afforded s-[2,2-diacetyl-1-(*p*-methyl)-phenylethyl]-thioglycolic acid (2.8g, 95.2 %): mp 97-98 °C: UV($CH_3OH$) $\lambda_{max}$ 294nm: IR(KBr disc) 1690, 2500-3300$cm^{-1}$: NMR ($CDCl_3$) 1.90(3H, *s*), 2.33(3H, *s*), 3.00(2H, *s*), 4.30(1H, *d*), 4.80 (1H, *d*), 7.20(4H, *d*), 9.70(1H, *s*).

Neutralization equivalent. Calculated for $C_{15}H_{18}O_4S$: 294.39. Found: 291.55. Anal. Calcd for $C_{15}H_{18}O_4S$: C, 61.23 %; H, 6.12 % Found: C, 61.12 %; H, 6.28 %

*s-[2,2-Diacetyl-1-(p-methoxy) phenylethyl]-thioglycolic Acid.* To a stirred solution of *p*-methoxy-ω,ω-diacetylstyrene (1.1g) and thioglycolic acid (0.9g) in acetone (20m*l*) was added triethylamine (0.25g) at room temperature. Work-up as above gave white precipitate, whose recrystallization from $CCl_4$ afforded s-[2,2-diacetyl-1-(*p*-methoxy) phenylethyl]-thioglycolic acid (0.4g, 12.8 %): mp 111-112 °C: UV($CH_3$ OH) $\lambda_{max}$ 318nm: IR(KBr disc) 1705, 1720, 2500-3300$cm^{-1}$: NMR ($CDCl_3$) 1.90(3H, *s*), 2.35(3H, *s*), 3.00(2H, *s*), 3.85 (3H, *s*), 4.20(1H, *d*), 4.80(1H, *d*), 7.10(4H, *m*).

Neutralization equivalent. Calculated for $C_{15}H_{18}O_5S$: 310.39. Found: 317.28. Anal Calcd for $C_{15}H_{18}O_5S$: C, 58.08 %;H, 5.80 % Found: C, 59.26 %; H, 5.94 %

*s-[2,2-Diacetyl-1-(p-chloro)phenylethyl]-thioglycolic Acid.* To a stirred solution of *p*-chloro-ω,ω-diacetylstyrene (2.2g) and thioglycolic acid (1.8g) in acetone (20m*l*) was added triethylamine (0.5g) at room temperature. Work-up as above

**TABLE 1: Physical and Spectral Data of ω, ω-Diacetylstyrene Derivatives**

| Derivaties | mp ( °C) | max(nm) | IR ($cm^{-1}$) | NMR (ppm) |
|---|---|---|---|---|
| H | 168–170 | 282 | 1690 | 2.10 (*s*) |
| | | | 1940 | 2.30 (*s*) |
| | | | 1600 | 7.25 (*s*) |
| | | | | 7.30 (*s*) |
| *p*-$CH_3$ | 41–42 | 294 | 1690 | 2.33 (*s*) |
| | | | 1640 | 2.40 (*d*) |
| | | | 1600 | 7.25 (*s*) |
| | | | | 7.45 (s) |
| *p*-$CH_3O$ | 67–68 | 318 | 1690 | 2.30 (*d*) |
| | | | 1640 | 3.85 (*s*) |
| | | | 1580 | 6.90 (*s*) |
| | | | | 7.40 (*d*) |
| *p*-Cl | 72–73 | 286 | 1700 | 2.30 (*d*) |
| | | | 1640 | 7.35 (*s*) |
| | | | 1600 | 7.40 (*s*) |

gave white precipitate, whose recrystallization from $CCl_4$ afforded s-[2,2-diacetyl-1-(chloro)-phenylethyl]-thioglycolic acid (2.4g, 78.8 %): mp 115–116 °C: UV($CH_3OH$) $\lambda_{max}$ 286nm: IR(KBr disc) 1670, 2500–3300 $cm^{-1}$: NMR ($CDCl_3$) 1.90(3H, *s*), 2.35(3H, *s*), 3.00(2H, *s*), 4.20(1H, *d*), 4.80(1H, *d*), 7.30(4H, *s*).

Neutralization equivalent. Calculated for $C_{14}H_{15}O_4SCl$: 314.78. Found: 308.21. Anal. Calcd for $C_{14}H_{15}O_4SCl$: C, 53.44 %; H, 4.77 % Found: C, 53.12 %; H, 4.86 %

## References


(1) E. D. Bergman, D. Ginsberg and R. Pappo, *Org. React.*, **10**, 179 (1955).

(2) R. K. Boeckman, Jr., *J. Amer. Chem. Soc.*, **96**, 6179 (1974).

(3) G. Stork and J. Singh, *J. Amer. Chem. Soc.*, **96**, 6181 (1974).

(4) R. A. Alarcon and J. Meinhofer, *Nature*, **233**, 250 (1971).

(5) H. Zoller, *Biochem. Pharmacol.*, **22**, 1171 (1973).

(6) R. W. Kims and D. R. Morris, *Biochem. Biophys. Acta*, **228**, 235 (1971).

(7) P. J. Conroy, J. T. Nodes, T. F. Slator and G. W. White, *Europ. J. Cancer*, **11**, 231 (1971).

(8) T. R. Kim and S. Y. Choe, *Bull. Korean Chem. Soc.*, **2**, 4, 125 (1981).

(9) T. R. Kim, T. S. Huh and I. S. Han, *J. Korean Chem. Soc.*, **25**, 6, 390 (1981).

(10) M. E. McEntee and A. R. Pinder, *J. Chem. Soc.*, 4419 (1957).

(11) E. P. Kohler and H. M. Chadwell, "Org. Syn., Coll." Vol. I,78, (1958).

(12) Handbook of Chemistry and Physics, CRC, 55, 72 (1974–1975).


# The Crystal and Molecular Structure of Phthalylsulfacetamide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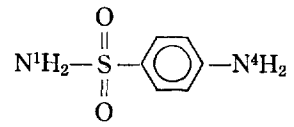
The crystal structure of phthalylsulfacetamide, one of the long-acting 'sulfa' drugs, has been determined by the X-ray diffraction methods. The crystal is monoclinic with cell dimensions of $a = 7.980(3)$, $b = 12.784(2)$, $c = 18.064(7)$ Å and $\beta = 112.94(2)°$, space group $P2_1/c$ and $Z=4$. The structure was solved by the direct methods and refined to $R = 0.048$. The sulfonylacetamide moiety is folded with respect to the central phenyl ring and the benzamide and benzoyl planes are nearly perpendicular to each other. This conformation is consistent with those of the relevant molecules containing the corresponding moieties. All of the molecules in the crystal lattice are connected by a three-dimensional hydrogen bonding network.


## Introduction

Phthalylsulfacetamide (PSA), $N^1$-acetyl-$N^4$-phthalylsulfanilamide, is one of the long-acting 'sulfa' drugs where both $N^1$ and $N^4$ of sulfanilamide (I) are substituted.[1]

Although numerous crystal structures of 'sulfa' drugs usually designated for the $N^1$-substituted sulfanilamide derivatives have been determined,[2] only one crystal structure of an $N^1$, $N^4$-substituted 'sulfa' drug, succinylsulfathiazole (SST), has been determined to date.[3] We now report the first crystal structure of an $N^4$-phthalyl derivative of a 'sulfa' drug.




(I)