[Chem. Pharm. Bull. 27(12)3186—3188(1979)]

UDC 579.279.52-128.04 : 547.539.04

Reaction of the α,α′-Dianion of β-Ketosulfoxide

Yasumitsu Tamura, Hirohisa Shindo, Jun-ichi Uenishi, and Hiroyuki Ishibashi

Faculty of Pharmaceutical Sciences, Osaka University[1]

(Received June 26, 1979)

The α,α′-dianion III or IV derived from the β-ketosulfoxide I or II reacted with alkyl halide, carbonyl compound, Schiff base, ester, and α,β-unsaturated carbonyl compound to give exclusively the α′-substituted β-ketosulfoxide V or VI.

Keywords——α,α′-dianion of β-ketosulfoxide; α′-substituted β-ketosulfoxides; acetonyl methyl sulfoxide; methyl phenacyl sulfoxide; butyllithium

Although the α,γ-dianion of β-ketosulfoxide has been extensively studied,[2] the corresponding α,α′-dianion has received scant attention.[2b] The present paper deals with the exclusive α′-alkylation and acylation of the α,α′-dianions III and IV derived from the β-ketosulfoxides I and II with alkyl halide, carbonyl compound, Schiff base, ester, and α,β-unsaturated carbonyl compound, leading to the α′-substituted β-ketosulfoxides V and VI.

$RCOCH_2SOCH_3$	$RCO\bar{C}HSO\bar{C}H_2\ 2Li^+$	$RCOCH_2SOCH_2R'$
I: R=CH_3	III: R=CH_3	V: R=CH_3
II: R=C_6H_5	IV: R=C_6H_5	VI: R=C_6H_5

Chart 1

Treatment of acetonyl methyl sulfoxide (I)[3] in tetrahydrofuran with 2.1 eq of butyllithium at −78° generated the dianion III. Benzylation of the solution of III in tetrahydrofuran

Table I. Reaction of the Dianions III and IV with Electrophiles

Dianion	Electrophile	Product No.	Product R′	Yield (%)	mp(°C) (Recrystn. solvent)
III	$C_6H_5CH_2Br$	Va	$-CH_2C_6H_5$	43	95—96 (C_6H_6-*n*-hexane)
IV	$C_6H_5CH_2Br$	VIa	$-CH_2C_6H_5$	95	73—74 (C_6H_6-*n*-hexane)
IV	$(C_6H_5)_2CO$	VIb	$-C(OH)(C_6H_5)_2$	70	154—155 (C_6H_6)
IV	C_6H_5CHO	VIc	$-CH(OH)C_6H_5$[a]	71	144—145 (C_6H_6)
IV	$C_6H_5CH=NC_6H_5$	VId	$-CH(C_6H_5)NHC_6H_5$[b]	75	190—192 (CH_2Cl_2)
IV	$C_6H_5COOC_2H_5$	VIe	$-COC_6H_5$	52	115—116 (C_6H_6)
IV	$C_6H_5COCH=CHC_6H_5$	VIf	$-C(OH)(C_6H_5)CH=CHC_6H_5$[a]	75	111—112 (C_6H_6-*n*-hexane)

a) A diastereomeric mixture (*ca.* 1:1).
b) Only one diastereomer.

1) Location: *133-1, Yamada-kami, Suita, Osaka, 565, Japan.*
2) a) I. Kuwajima and H. Iwasawa, *Tetrahedron Lett.*, **1974**, 107; P.A. Grieco and C.S. Pogonowski, *J. Org. Chem.*, **39**, 732 (1974); P.A. Grieco, D. Boxler, and C.S. Pogonowski, *J. Chem. Soc. Chem. Commun.*, **1974**, 497; J. Nokami, Y. Kusumoto, K. Jinnai, and M. Kawada, *Chem. Lett.*, **1977**, 715; b) P.A. Grieco and C.S. Pogonowski, *J. Chem. Soc. Chem. Commun.*, **1975**, 72.
3) M.E. Cain and J.I. Cunneen, *J. Chem. Soc.*, **1962**, 2959.

with 1.1 eq of benzyl bromide gave the α'-benzylated β-ketosulfoxide Va ($R'=CH_2C_6H_5$). The structure of Va was established by independent synthesis from sodium phenethyl mercaptide and chloroacetone, *via* oxidation with *m*-chloroperbenzoic acid. No α- or γ-benzylated β-ketosulfoxide was detected by thin layer chromatography (TLC) or nuclear magnetic resonance (NMR) spectroscopy of the crude reaction mixture.

A similar benzylation of the dianion IV derived from methyl phenacyl sulfoxide (II)[4] gave the α'-benzylated β-ketosulfoxide VIa ($R'=CH_2C_6H_5$), which was identical with an authentic sample prepared by the reaction of sodium phenethyl mercaptide and phenacyl bromide followed by oxidation with *m*-chloroperbenzoic acid.

When a tetrahydrofuran solution of the dianion IV was treated with benzophenone, benzaldehyde, benzalaniline, ethyl benzoate, or benzalacetophenone, facile reaction occurred to yield the α'-substituted β-ketosulfoxide VIb—f (Table I). That the reaction occurred only at the α' carbon was confirmed by the following evidence. The NMR spectrum ($CDCl_3$) of the starting material II has a two-proton AB quartet (δ 4.37) due to the α-methylene protons and a three-proton singlet (δ 2.75) due to the α'-methyl protons, but the spectra of VIa—f have only the former signal (δ ~4.3—4.6), and not the latter (Table II). Further, TLC and NMR spectroscopy of the crude reaction mixtures failed to detect any α-substituted β-ketosulfoxide.

Table II. Spectral and Analytical Data for Va and VIa—f

Comp. No.	IR ν_{max}^{KCl} cm^{-1}		NMR ($CDCl_3$,[a] δ, J in Hz)	Formula	Analysis(%) Calcd. (Found) C	H	N
Va	1705	1045	2.32 (s, $COCH_3$), 3.08(s, $-CH_2CH_2-$), 3.72 (ABq, $COCH_2$, $J=13.5$), 7.23 (s, arom)	$C_{11}H_{14}O_2S$	62.84 (62.85)	6.71 (6.66)	
VIa	1670	1045	3.14 (s, $-CH_2CH_2-$), 4.36 (ABq, $COCH_2$, $J=14$), 7.23—8.00 (m, arom)	$C_{16}H_{16}O_2S$	70.57 (70.45)	5.92 (5.95)	
VIb	3380 1060	1670	3.85 [ABq, $SOCH_2C(OH)$, $J=14$], 4.42 (s, $COCH_2$), 5.25 (bs, OH), 7.13—7.95 (m, arom)	$C_{22}H_{20}O_3S$	72.51 (72.71)	5.53 (5.60)	
VIc	3310 1050	1670	3.22 and 3.24 (d, $SOCH_2CH<$, $J=7$), 3.95 and 3.98 (bs, OH), 4.58 and 4.62 (s, $COCH_2$), 5.40and 5.45 (t, $CH_2CH<$, $J=7$), 7.38—8.01 (m, arom)	$C_{16}H_{16}O_3S$	66.66 (66.38)	5.59 (5.63)	
VId	3220 1020	1670	3.37 (d, $SOCH_2CH<$, $J=7$), 4.71 (s, $COCH_2$), 4.93 (t, $CH_2CH<$, $J=7$), 6.50—8.05 (m,arom)	$C_{22}H_{21}NO_2S \cdot 1/4H_2O$[b]	71.81 (72.06)	5.89 (5.73)	3.81 (3.89)[c]
VIe	1660	1050	4.57 (ABq $COCH_2$, $J=14$), 7.35—8.01 (m, arom)	$C_{16}H_{14}O_3S$	67.12 (66.97)	4.93 (4.92)	
VIf	3380 1060	1670	3.50 and 3.57 [ABq, $SOCH_2C(OH)$, $J=16$] 4.40 (s, $COCH_2$), 5.06 and 5.13 (s, OH), 6.37 and 6.58 (d, $C_6H_5CH=$, $J=16$), 6.69 and 6.87 [d, $C(OH)CH=$, $J=16$], 7.12—7.88 (m, arom)	$C_{24}H_{22}O_3S$	73.83 (74.04)	5.68 (5.59)	

a) The spectrum of VId was measured in DMSO-d_6.
b) Mass spectrum, *m/e* 363 (M^+, $C_{22}H_{21}NO_2S$).
c) Similar values were obtained in another run, C, 72.06; H, 5.68; N, 3.84.

Experimental[5]

General Procedure for α'-Substituted β-Ketosulfoxides Va and VIa—f——Butyllithium in hexane (2.9 ml of 1.59 M, 4.6 mmol) was added dropwise (*via* a syringe) to a stirred solution of the β-ketosulfoxide I or II

4) E.J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1345 (1965).
5) All melting points are uncorrected. NMR spectra were measured on a Hitachi R-20A spectrometer using tetramethylsilane as an internal standard. IR spectra were recorded on a Hitachi EPI-G2 spectrophotometer.

(264 mg of I or 400 mg of II, 2.2 mmol) in anhydrous tetrahydrofuran (20 ml) at −78° under an argon atmosphere. The reaction mixture was stirred at the same temperature for 20 min, then an appropriate electrophile (2.4 mmol, or 1: 1 mmol of ethyl benzoate) was added (*via* a syringe) and the mixture was allowed to warm to room temperature during 1 hr, with stirring. The reaction was quenched by the addition of wet silica gel (10 g, 70—230 mesh), which was removed by filtration. The solvent was evaporated off, and the residue was chromatographed[6] on silica gel, using ethyl acetate as an eluent, to give the α′-substituted β-ketosulfoxide Va or VIa—f.

Independent Syntheses of α′-Benzylated β-Ketosulfoxide Va and VIa——A solution of sodium hydroxide (1.38 g, 35.5 mmol) in water-methanol (15 ml+25 ml) was added to a stirred solution of phenethyl mercaptan (4.14 g, 30 mmol) in methanol (10 ml) at 0°. The reaction mixture was stirred at the same temperature for 30 min, a solution of chloroacetone (2.78 g, 30 mmol) or phenacyl bromide (5.97 g, 30 mmol) in methanol (40 ml) was added dropwise at 0°, and stirring was continued at 50—60° for 1 hr. The reaction mixture was poured into ice-water (100 ml) and extracted with ethyl acetate. The extract was washed with 10% hydrochloric acid and dried ($MgSO_4$). The solvent was removed by evaporation, and the residue was distilled *in vacuo* to give acetonyl phenethyl sulfide (4.72 g, 88%, bp 142°/6 mmHg) or phenacyl phenethyl sulfide (6.68 g, 87%, bp 188°/0.3 mmHg). Oxidation of the resulting β-ketosulfide with an equimolar amount of *m*-chloroperbenzoic acid in methylene chloride followed by usual work-up gave the corresponding β-ketosulfoxide Va (69%, mp 94—95°) or VIa (70%, mp 73—74°), which gave spectral data identical with those of the material obtained by benzylation of the dianion III or IV, respectively.

6) The compound VId was obtained by recrystallization of the residual mass from methylene chloride.

[Chem. Pharm. Bull. 27(12)3188—3192(1979)]

UDC 615.451.23.011.3.014.23 : 615.31.014.23.073

Detoxication Capacity of a Multiple (w/o/w) Emulsion for the Treatment of Drug Overdose: Drug Extraction into the Emulsion in the Gastro-intestinal Tract of Rabbits

YASUNORI MORIMOTO, KENJI SUGIBAYASHI, YUKIYA YAMAGUCHI, and YOSHIO KATO

Faculty of Pharmaceutical Sciences, Josai University[1]

(Received July 23, 1979)

The drug extraction ability of water-in-oil-in-water emulsion was evaluated *in vitro* and *in vivo*. *In vitro* drug extraction into the emulsion was determined using a dialysis system and was significant compared to the control. Blood concentration of salicyclic acid, selected as a model drug, co-administered with the multiple emulsion to rabbits was significantly lower than that in the control. The *in vitro* and *in vivo* experimental results suggest that the emulsion may be useful for the emergency treatment of drug overdose.

Keywords——w/o/w emulsion; detoxication; drug overdose; drug extraction; salicylic acid; emergency treatment for drug overdose; rabbit

Poisoning due to drug overdose is a continuing problem. The present modes of emergency treatment are aimed at removal of the drug from the body by various methods, *e. g.* peritoneal dialysis, ingestion of adsorbants such as activated charcoal, and administration of emetics. However, these methods have limitations.

Water-in-oil-in-water (w/o/w) emulsion represents a potential new drug-carrier system with the ability to facilitate gastro-intestinal absorption.[2] Asher *et al.*[3] also showed the

1) Location: *1-1, Keyakidai, Sakado, Saitama, 350-02 Japan.*

2) R.H. Engel, S.J. Riggi, and M.J. Fahrenbach, *Nature* (London), **219**, 856 (1968).

3) W.J. Asher, K.C. Bovee, J.W. Frankenfeld, R.W. Hamilton, L.W. Henderson, P.G. Holtzapple, and N.N. Li, *Kidney Int.*, **7**, s-409 (1975).