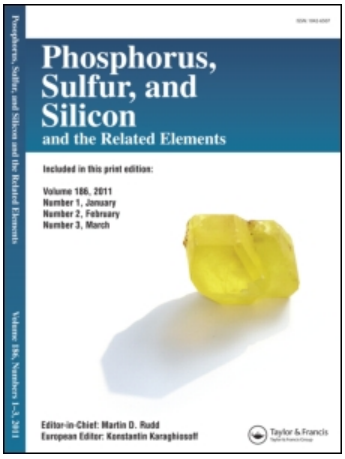

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

REACTIONS WITH α, β-SPIROEPOXY-ALKANONES. PART I. SYNTHESIS AND REACTIONS OF OXASPIRO(2,5)OCTA-4-ONES

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To cite this Article Yousif, N. M. , Gad, F. A. , Fahmy, A. F. M. , Amine, M. S. and Sayed, H. H.(1996) 'REACTIONS WITH α, β-SPIROEPOXY-ALKANONES. PART I. SYNTHESIS AND REACTIONS OF OXASPIRO(2,5)OCTA-4-ONES', Phosphorus, Sulfur, and Silicon and the Related Elements, 117: 1, 11 — 19
To link to this Article: DOI: 10.1080/10426509608038771
URL: http://dx.doi.org/10.1080/10426509608038771

Phosphorus, Sulfur, and Silicon, 1996, Vol. 117, pp. 11–19
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REACTIONS WITH α, β-SPIROEPOXY-ALKANONES. PART I. SYNTHESIS AND REACTIONS OF OXASPIRO(2,5)OCTA-4-ONES

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(Received 20 October 1994; Revised 10 April 1996; In final form 10 April 1996)

2-Aryl-1-oxaspiro(2,5)octa-4-ones Ia,b were synthesized and reacted with thiourea in ethanol to give hydroxy cyclohexanone derivatives IIa,b. Compounds IIa,b were readily cyclised into the corresponding 5-hydroxy quinazolines IIIa,b and their dehydrated derivatives IVa,b. A mixture of compounds III and IV were also prepared directly from the reaction of compounds Ia,b with thiourea in alkaline medium. Compounds Va,b were produced by reduction of corresponding IV. Compounds III or and V reacted with chloroacetic acid to give resp. VI and VII, which condensed with aromatic aldehydes to form resp. VIII and IX.

Keywords: Oxaspiro(2,5)octa-4-ones

INTRODUCTION

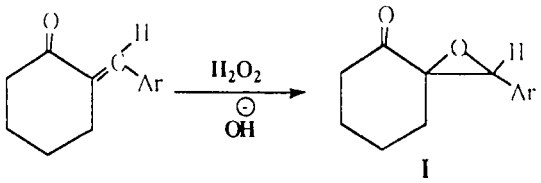
Epoxyketones are important in Organic synthesis.[1–3] In previous work the reaction of arylmetylene cycloalkanones with thiourea to form biologicaly active pyrimidinthiones and thiazolones was studied.[4–6] New derivatives from the reaction of thiourea with 2-aryl-1-oxaspiro(2,5)octa-4-ones were prepared.

*Corresponding author.

RESULTS AND DISCUSSION

Synthesis of 2-aryl-l-oxaspiro(2,5)octa-4-one

Hydrogen peroxide reacts with trans monoaryliden cyclohexanones[7] in alk. medium using different experimental conditions to produce three isomers of 2-aryl-1-oxaspiro (2,5)octa-4-one Ia,b. Mass and I.R. spectra of all isomers are nearly the same, but they are different in ^1H NMR spectra. ^1H NMR For isomer



I

a; Ar=C_6H_5 , b; Ar=C_6H_4-OCH_3 (P-)

1[8] and for isomers 2, and isomers 3 (table 2). Isomers 2 are thermally unstable, and they changed to the corresponding isomer 3. Theoretically, there are four steroisomers for compound I (one isomer R-R; two isomers R-S; and one isomer S-S). The determination of configuration of sterisomers for compound I is (1–3) still under investigation. Isomer 3 of compound I is used as a starting material in all reactions.

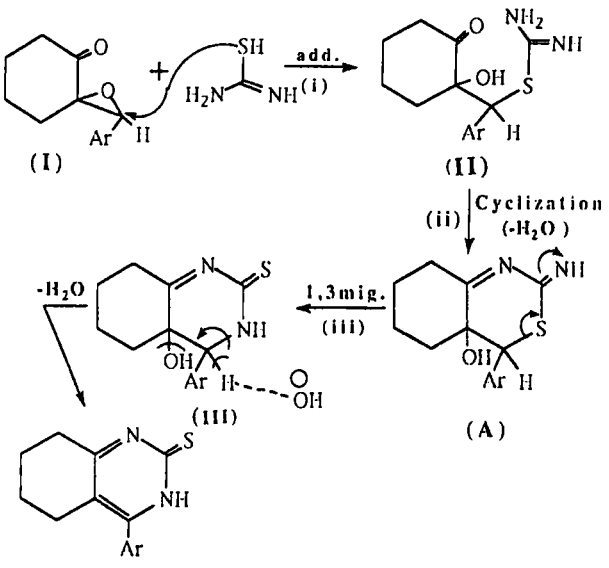
Synthesis of Quinazoline Thiones from Base-Catalyzed Reactions of Spirooctanones I With Thiourea

Spirooctanones Ia,b react with thiourea in the presence of alkali to give a mixture of the corresponding 5-hydroxy-quinazoline derivatives IIIa,b and their dehydrated derivatives IVa,b. The reaction takes place via the following mechanism (scheme 1):

In the first step the sulfur atom of the thiourea molecule attacks as a nucleophile[9] and opens the oxirane ring to form intermediate II. The second step is ring closure to form compound (A), which rearanges through 1,3-migration to give the final product III, or with elimination of a molecule of water to form product IV.

The above mechanism was proven by the following data

(i) the proposed intermediate compounds II can be separated if the reaction of compound I with thiourea takes place in absence of alkali.



a) Ar=C_6H_5 ; b) Ar=C_6H_4-OCH_3 (P-)

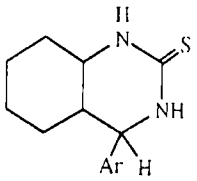
SCHEME 1

(ii) when the intermediate compound II was heated with alkali in ethanol, a mixture of compounds III and IV was obtained.
(iii) Compounds III were converted to the corresponding IV when heated with alkali.

The structure of compounds II–IV were proven from

(i) Elemental analysis and ^1H NMR (table 1,2). The IR spectra for compounds III showed absorption bands at 3674-3670 cm^{-1} (OH), and at 3484-3452 cm^{-1} (NH). The mass spectra for compounds II–IV continued to show the molecular ion peak M^+.
(ii) structure IV was proven chemically via reduction with Zn/acetic acid to give 4-aryl-decahydroquinazoline-2-thiones Va,b.

Structures IIIa,b and Va,b were proven chemically via the reaction with chloroacetic acid to give 5-aryl-6-hydroxy-2,3,6,7,8,9,10-hexahydro-5H-thiazolo-(2,3-b)quinazolin-3-ones VIa,b; and 5-aryl-2,3,4,5,6,7,8,9,10-octahydro-5H-thiazolo(2,3-b)quinazolin-3-ones VIIa,b. The mass spectra for compounds VI



(V a,b).

a; Ar=C_6H_5, b; Ar=C_6H_4-OCH_3 (P-)

and VII showed always the molecular ion peak at M^+. The IR spectra for the compounds showed absorption bands at 3572-3488 cm^{-1} (OH), and at 1775–1735 cm^{-1} (C=O).

TABLE I Physical and Analytical Data for the Prepared Compounds

comp.	*M.P. °C Mol.Form.* *sol. of cry. Mol.Wt.*		*Yield* %	*Analysis* *C*	*H*	*calc./Found* *N*	*S*
Ia-isomer 2	78–79	$C_{13}H_{14}O_2$	60	77.20	6.98	–	–
	B.pet.	202.2		77.3	7.0		
Ib-isomer 2	60–61	$C_{14}H_{16}O_3$	65	72.39	6.94	–	–
IIa	B.pet.	232.3		72.5	7.0		
	96	$C_{14}H_{18}N_2O_2S$	77	60.40	6.52	10.06	11.52
	E-W	278.4		60.7	6.5	9.9	11.7
b	92	$C_{15}H_{20}N_2O_3S$	70	58.41	6.54	9.09	10.40
	E-W	308.4		58.6	6.5	9.0	10.3
IIIa	138	$C_{14}H_{16}N_2OS$	40	64.58	6.20	10.76	12.31
	E	260.4		64.8	6.1	10.9	12.5
b	110	$C_{15}H_{18}N_2O_2S$	35	62.05	6.25	9.65	11.03
	E-W	290.3		62.0	6.3	9.9	10.8
IVa	153	$C_{14}H_{14}N_2S$	50	69.38	5.82	11.56	13.23
	B	242.3		69.6	5.9	11.8	12.9
b	127	$C_{15}H_{16}N_2OS$	50	66.14	5.92	10.29	11.77
	E	272.4		66.5	6.0	10.4	10.5
Va	197	$C_{14}H_{18}N_2S$	80	68.24	7.36	11.37	13.02
	A-M	246.4		68.4	7.3	11.5	12.8
b	178	$C_{15}H_{20}N_2OS$	80	65.18	7.29	10.14	11.60
	E	276.4		65.4	7.3	10.0	11.4
VIa	138–139	$C_{16}H_{16}N_2O_2S$	50	63.97	5.37	9.33	10.67
	M-W	300.4		64.1	5.4	9.4	10.4
b	131–132	$C_{17}H_{18}N_2O_3S$	50	61.80	5.49	8.48	9.70
	E-W	330.4		62.0	5.6	8.5	9.7
VIIa	163–164	$C_{16}H_{18}N_2OS$	55	67.10	6.33	9.78	11.20
	M	286.4		67.3	6.3	9.6	11.0
VIIb	152–153	$C_{17}H_{20}N_2O_2S$	55	64.52	6.37	8.86	10.13
	E	316.4		64.7	6.3	8.9	10.0

TABLE I (Continued)

comp.	M.P. °C sol. of cry.	Mol.Form. Mol.Wt.	Yield %	Analysis C	H	calc./Found N	S
VIIIa	224–225	$C_{23}H_{20}N_2O_2S$	60	71.11	5.19	7.21	8.25
	E	388.5		71.3	5.0	7.1	8.2
b	205–206	$C_{24}H_{22}N_2O_3S$	60	68.87	5.30	6.70	7.66
	B	418.5		69.0	5.3	6.6	7.5
c	216–217	$C_{23}H_{19}Cl_2N_2O_2S$	60	65.31	4.53	6.63	7.58
	B	422.9		65.5	4.5	6.4	7.4
d	197–199	$C_{24}H_{22}N_2O_3S$	60	68.87	5.30	6.70	7.66
	E	418.5		69.0	5.4	6.6	7.5
e	243–244	$C_{25}H_{24}N_2O_4S$	70	66.94	5.39	6.25	7.15
	B	448.5		67.1	5.3	6.2	7.0
f	231–232	$C_{24}H_{21}N_2O_3S$	65	63.64	4.67	6.19	7.08
	E	452.9		63.9	4.9	6.0	6.9
IXa	186–187	$C_{23}H_{22}N_2OS$	50	73.76	5.92	7.48	8.56
	E-W	374.5		73.9	6.0	7.3	8.4
b	198–199	$C_{24}H_{24}N_2O_2S$	55	71.25	5.98	6.93	7.94
	E-W	404.5		71.4	6.0	7.0	8.0
c	198–199	$C_{23}H_{21}ClN_2OS$	55	67.55	5.17	6.85	7.84
	E	408.9		67.8	5.0	6.4	7.6
d	197–198	$C_{24}H_{24}N_2O_2S$	50	71.25	5.98	6.93	7.94
	E	404.5		71.4	6.0	7.0	8.0
e	217–218	$C_{25}H_{26}N_2O_3S$	55	69.10	6.03	6.45	7.38
	E	434.5		69.0	6.0	6.3	7.2
f	209–210	$C_{24}H_{23}ClN_2O_2S$	60	65.66	5.28	6.38	7.30
	E	439.0		65.9	5.1	6.2	7.2

A = acetic acid, B = benzene, E = ethanol, M = methanol, M = methanol, W = water.

U.V. spectra for compounds VI and VII showed absorption at λ_{max}, 290–300 nm (ϵ 22000–25000), and in their ^1H NMR spectra there is a deshielding for the CHAr proton, so the structures VI and VII are more favored than the structures VI and VII.

Compounds VIa,b and VIIa,b contain active methylene group, and condensed with aromatic aldehydes to yield the corresponding products VIIIa–f and IXa–f.

The mass spectra for compounds VIII and IX always showed the molecular ion peak M^+. The IR spectra for compounds VIII showed absorption bands at 3594–3590 cm^{-1}, and at 1722-1708 cm^{-1} (C=O).

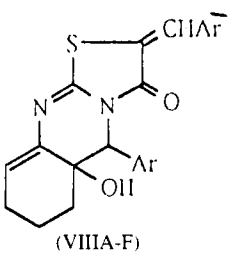
EXPERIMENTAL

Melting points were uncorrected. The IR spectra were recorded on a Beckman IR-18 spectrometer. Mass spectra were recorded on a micromass 7070 f spec-

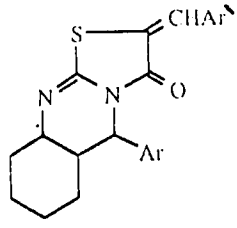
TABLE II ^{1}H NMR Spectra for some Prepared Compounds

product	*^{1}H NMR (ppm)*
Ia-isomer 2.	1.5–1.7(2H, m, CH_2); 1.8–1.9(2H, m, CH_2); 2.3–2.6(4H, m, CH_2); 3.6(1H, s, CHAr); 7.2–8(5H, m, arom.).
Ia-isomer 3.	1.5–1.7(2H, m, CH_2); 1.7–1.9(4H, m, CH_2); 2.5–2.9(2H, m, CH_2); 3.7(1H, s, CHAr); 7–7.5(5H, m, arom.).
Ib-isomer 2.	1.8–2.6(8H, m, CH_2); 3.5(1H, s, CHAr); 3.8(3H, s, OCH_3); 6.6–7.1(4H, m, arom.).
Ib-isomer 3.	1.5–2.7(8H, m, CH_2); 3.7–3.9(4H, br, OCH_3 + CHAr); 6.7–7.5(4H, m, arom.).
IIb	1.5–2(8H, m, CH_2); 2.6–3.5(2H, br, OH+CHAr); 3.6–4(4H, m, OCH_3+NH); 6.7–7.7(6H, m, arom. +NH_2).
IIIa	1.5–2.5(8H, m, CH_2); 4.8(1H, s, CHAr); 6.5–7.5(6H, m, arom. +OH); 7.7–7.8(1H, br, NH).
IIIb	1.5–2.5(9H, m, CH_2 +OH); 3.5–3.7(4H, m, OCH_3 +NH); 4.8(1H, s, CHAr); 6.7–7.5(4H, m, arom.).
VIa	1.5–2.5(6H, m, CH_2); 2.5–4.5(4H, m, CH_2S +CH=C + OH); 5.4–5.6(1H, br, CHAr); 7–7.8(5H, m, arom.).
VIIa	1.5–3(10H, m, CH_2 +CHN + CHC); 4.3–5.2(3H, br, CH_2S + CHAr); 6.5–7.7(5H, br, arom.).
VIIIb	1.5–3(7H, m, CH_2 +OH); 3.6–4(7H, m, OCH_3 +CH=C); 6.5–7.8(10H, m, arom. +CHAr + CH=C).
IXa	1.5–3(10H, br, CH_2 +CHCN + CHN); 5.4–5.7(1H, br, CHAr); 6.8–7.9(11H, m, arom. +CH=C).

The solvent used for ^{1}H NMR spectra is $CDCl_3$ for all compounds except for compounds IIb and VIa is d-acetone.



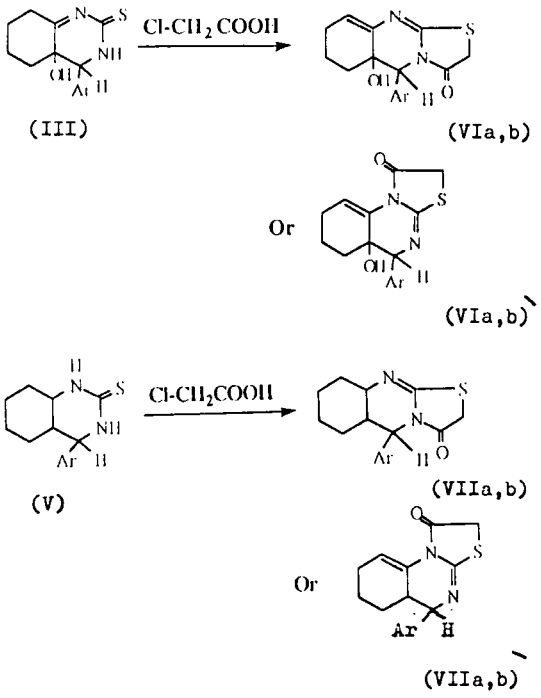
(VIIIA-F)



(IXA-F)

a) Ar=Ar'=C_6H_5
b) Ar=$C_{6\,6}H_{4\,3}$(P)
c) Ar=C_6H_5, Ar'=C_6H_4Cl.(P)
d) Ar=$C_6H_4OCH_3$(P), Ar'=C_6H_5
e) Ar=Ar'=$C_6H_4OCH_3$.(P)
f) Ar=$C_6H_4OCH_3$.(P), Ar'=C_6H_4Cl.(P)

trometer operating at 70 ev using direct inlet. ^{1}H NMR spectra were recorded at 180 MHZ on a Varian EM 360 spectrometer. TMS is used as internal standard and chemical shifts are expressed in δ values. UV spectra are recorded on Shimadzu UV visible recording spectrometer UV 240.



a) Ar=C_6H_5 ; b) Ar=C_6H_4-OCH_3 (P-)

Synthesis of 2-aryl-l-oxaspiro(2,5)octa-4-ones Ia,b

Hydrogen peroxide (8 ml, 36%) was added portion-wise to a mixture of trans 2-arylmethylenecyclohexanone[10,11] (0.01 mol) in 30 ml acetone, 10 ml methanol containing 1 g KOH, at 20–25°C with stirring. The reaction mixture was left overnight. The solvent was evaporated under reduced pressure at 60°C, extracted with ether to produce a mixture of two isomers Ia,b. Recrystallized from benzene-pet ether to give colorless needles of the isomer I-2. Concentration of the mother liquor gave an oil for the isomer I-3.

isomer	M.P.	Yield
Ia-2	78–79	15
Ia-3	oil	60
Ib-2	60–61	10
Ib-3	oil	65

Isomers Ia,b-1 were prepared by the method of House[8].

Formation of Isomer 3 from Isomer 2 for Compound Ia Isomer 2 for compound Ia (1.01 g, 0.005 mol) in 30 ml benzene was heated under reflux for 10 hours. The product was purified on a silica gel column using of ether as eluent to give isomer 3 for compound Ia in 50% yield.

General Procedure for the Synthesis of Compounds IIa-b Compounds Ia,b (0.01 mol) were added to thiourea (0.01 mol) in 20 ml ethanol. The reaction mixture was refluxed for 3 hours, then concentrated and the residue was purified by crystallization to give the products IIa-d.

General Procedure for the Synthesis of Compounds IVa,b and IIIa, b Compounds Ia, b (0.01 mol) were added to thiourea (0.8 g, 0.01 mol) in 20 ml ethanol contain 1 g KOH. The reaction mixture was refluxed for 3 hours, the solvent removed under reduced pressure, after acidification with cold HCl. The residue was purified by crystallization from ethanol to give the products IVa, b. The filtrate was concentrated and crystallized from the proper solvent to give IIIa, b.

Cyclisation for Compounds IIa, b A mixture of compounds IIa, b (0.01 mol) in 20 ml ethanol containing 1g KOH was refluxed for 2 hours. The ethanol was evaporated to half its volume and acidified with cold HCl, the precipitate was filtered off. The residue was purified by fractional crystallization as before to give a mixture of compounds IIIa, b and IVa, b. Melting points and mixed melting point not depressed.

Reduction of Compounds IVa, b Compounds IVa, b (0.01 mol) in 20 ml acetic acid was heated at 100°C, then 5 g zinc dust was added gradually during 1/2 hour with stirring. The reaction mixture was kept at 100°C for 2 hours, then poured into water. The solid formed was collected and crystallized to give the products Va, b.

Reaction of Chloroacetic Acid with Compounds IIIa, b or and Compounds Va, b A mixture of compounds IIIa, b and/or compounds Va, b (0.01 mol), 1g of chloroacetic acid, 4 g fused sodium acetate, 10 ml acetic acid, and 5 ml acetic anhydride was refluxed for 3 hours and left to cool. The reaction mixture was poured into water and crystallized from the proper solvent to give the corresponding compounds VIa, b and VIIa, b resp.

Reaction of Aromatic Aldehydes with Compounds VIa, b or and Compounds VIIa, b A mixture of compounds VIa, b or and VIIa, b (0.01 mol), 0.01 mol of the aromatic aldehyde, 2 g of fused sodium acetate, 10 ml acetic acid, and 5 ml

acetic anhydride was refluxed for 2 hours. The reaction mixture was poured into cold water and the solid formed was collected and crystallized to give the products VIIIa–f and IXa–f resp.

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