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ALICYCLIC TERPENOIDS FROM CYCLOCITRAL PHENYL SULFIDES. I. ACID-CATALYZED CYCLIZATION OF GERANYL PHENYL SULFIDES TO CYCLOCITRAL DERIVATIVES. A SYNTHESIS OF α- AND β-IONONES

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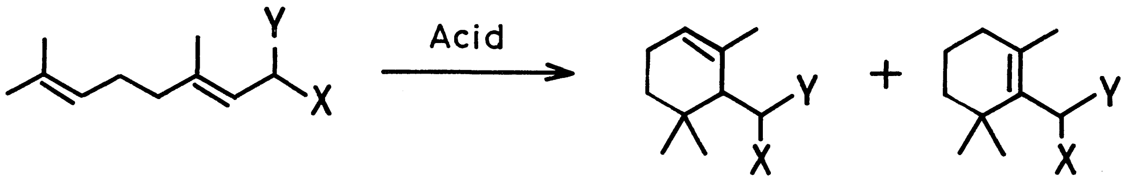
Cyclocitryl phenyl sulfides (IIa and IIIa) and sulfones (IIb and IIIb) were efficiently prepared by acid-catalyzed cyclization of geranyl phenyl sulfide (Ia) and sulfone (Ib). The sulfones (IIb and IIIb) could be converted into α- and β-ionones. The cyclization of citral diphenylthioacetal (Ic) afforded the tricyclic compound (VI). The detailed cyclization conditions are discussed.

In connection with the synthesis of terpenoids and steroids the acid-catalyzed cyclization of functionalized polyisoprenes has been well reviewed.1) Considering versatile application of cyclocitral derivatives 2) as a synthon for terpenoid syntheses, a device on introduction of a suitable functional group to cyclocitryl moiety would be prerequisite. Here, we designed sulfur modified cyclocitrals (IIa, IIb, IIIa, and IIIb), which can be used for α- and β-ionones syntheses. This paper deals with an efficient cyclization of geranyl phenyl sulfide (Ia) and the sulfone (Ib) to cyclic compounds (IIa, IIb, IIIa, and IIIb) and involves the conversion of (IIb) and (IIIb) into α- and β-ionones.



Ia X = H, Y = SPh IIa IIIa

Ib X = H, Y = SO_2Ph IIb IIIb

Ic X = SPh, Y = SPh IIc IIIc

The sulfide (Ia) and the sulfone (Ib) were subjected to cyclization in the different conditions as shown in Table 1. Among the acids examined boron trifluoride provided the most favourable result in the formation of (IIa) and (IIIa), since treatment of (Ia)[3)] with 0.5 eq. amount of boron trifluoride[4)] in refluxing benzene for 30 min afforded a 1:3 mixture of α- and β-cyclocitral phenyl sulfides (IIa) and (IIIa) in 91% yield along with a trace amount of (IV) arising from further ring constraction via a cation (V). Similarly, geranyl phenyl sulfone (Ib)[5)] afforded a 6:1 mixture of (IIb) and (IIIb) in 93% yield. On the other hand, similar treatment of citral diphenylthioacetal (Ic)[6)] could let to provide the tricyclic compound (VI) in 80% yield instead of the expected compounds (IIc) and (IIIc). This result suggests that the catalyst would induce elimination of one of the phenylthio groups to give a geranyl cation (VII) stabilized by the divalent sulfide group.[7)]

Particularly noteworthy is both the solvent effect and the influence of catalysts for the improvement of yield and the isomer selectivity in the cyclization reaction. Thus, both n-hexane and dioxane with boron trifluoride facilitated the preferential formation of the α-isomer from (Ia). Combination of acetic acid and concentrated sulfuric acid also induced the formation of the α-isomer from (Ia). The sulfone (Ib) could be cyclized successfully with concentrated sulfuric acid in acetic acid to afford a 1:4 mixture of (IIb) and (IIIb) in 94% yield. In contrast to this, the low concentration of sulfuric acid enabled to produce the α-isomer, effectively.

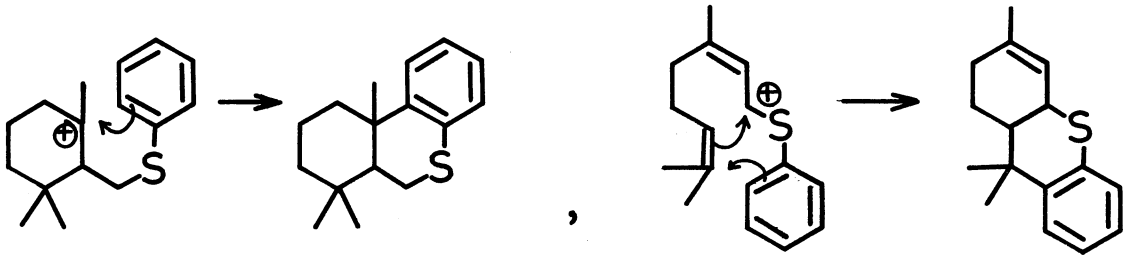
The advantage of (IIb) and (IIIb) as a synthetic intermediate can be verified by facile conversion to α- and β-ionones. Namely, the reaction of a 6:1 isomeric mixture of (IIb) and (IIIb) with n-butyl lithium in HMPA-THF (1/5) at -70° followed by treatment with propylene oxide at 15° for 30 hr gave the alcohol (VIII) in 90% yield. Oxidation of (VIII) with chromic anhydride in pyridine at 15° for 40 hr afforded the corresponding ketone (IX) in 73% yield. Finally, treatment of (IX) with sodium methoxide in dry tert-butanol at 15° for overnight gave a 10:1 mixture of α- and β-ionones in a quantitative yield.[8)] Successful conversion of the isomeric mixture to β-ionone was accomplished by stirring the mixture in concentrated sulfuric acid and acetic acid (2:1).[9)]

Studies on the versatile use of the sulfur functionalized cyclocitrals for terpenoid syntheses are going on.

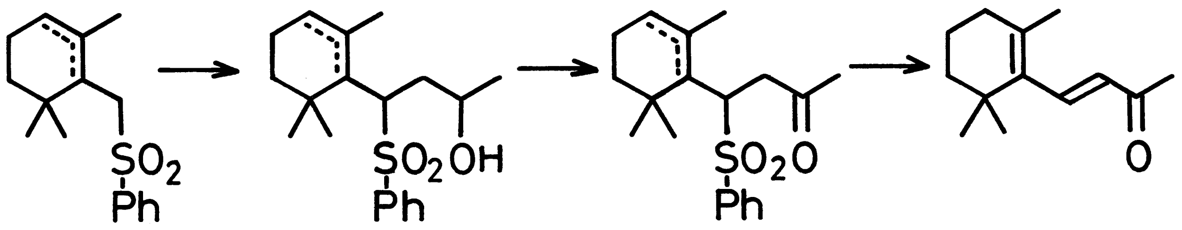
TABLE 1 Cyclization Conditions and Results

Compound	Solvent	Acid (eq)	React. Time hr	Yield %	Product Ratio,% (II)	(III)	(IV)
Ia	Benzene*	BF_3 (0.5)	0.5	91	24	75	1
		BF_3 (1.5)	1.5	75	19	76	5
		BF_3 (4)	1.5	67	14	70	15
	Toluene*	BF_3 (4)	4	68	43	57	0
	Chloroform*	BF_3 (4)	1	70	30	60	10
	n-Hexane*	BF_3 (8)	15	69	67	18	15
	Dioxane*	BF_3 (6)	5	60	71	24	4
	AcOH**	H_2SO_4 (8)	20	79	67	33	0
Ib	Benzene*	BF_3 (1)	0.5	93	83	17	—
	AcOH**	H_2SO_4 (32)	0.5	94	20	80	—
	AcOH**	H_2SO_4 (9)	60	87	92	8	—
Ic	Benzene*	BF_3 (1)	0.5	80***	—	—	—

*) At refluxing temperature in the solvent. **) At 12-15°. ***) Product isolated is the tricyclic sulfide (VI).



V IV , VII VI



IIb, IIIb VIII IX X

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