In this reaction, the refluxing was allowed to continue until red oil appeared on the reaction mixture (the reaction had been completed at this point). Compound **5i** was synthesized by refluxing **1b** and benzoic acid in the dehydrated chloroform under nitrogen which was deoxygenated by using alkali pyrogallol and by crystallization of the resulting red oil with the absolute alcohol. Compound **2a** was also prepared in the same method as above. By employing the mild reaction conditions such as decreasing the amount of PPE, shortening the refluxing time, and increasing the amount of chloroform solvent, a small amount of **2** or **5** was collected together with the unreacted compound **1**, and the expected cyano thiazine derivatives could not be detected.

Nitrile Hydrolysis of 5-Cyano-6-methylthio-2-phenyl-1-oxo-1,3-thiazine-4-thione (5i).—A mixture of **5i** (1 g, 3.5 mmol) and polyphosphoric acid (PPA, 61 g) was heated at 80° for 3 hr. The reaction mixture was cooled and decomposed by adding ice–water (*ca.* 200 ml) and neutralized with KOH. The resulting brown crystals (0.8 g) were recrystallized from acetic acid to give brown plates: mp 223–224°; ir (KBr) 3440, 3400 (NH_2), 2920 (CH_3), 1640 (CO), 1580 (benzene ring), 1533 (hetero ring), 1444, 1415 (CH_3), 1119 (CS), 1002 cm^{-1} (SO); uv $\lambda_{max}^{99\%EtOH}$ 225 nm (log ϵ 4.14), 268 (4.29), 329 (3.78), 370 (4.48).

Anal. Calcd. for $C_{12}H_{10}N_2S_3O_2$: C, 46.43; H, 3.25; N, 9.03; mol wt, 310.42. Found: C, 46.51; H, 3.18; N, 8.98; mol wt, 310 (mass spectrum).

Registry No.—**1a**, 37614-61-2; **1b**, 29082-78-8; **2a**, 37614-62-3; **2b**, 37614-63-4; **2c**, 37614-64-5; **2d**, 37614-65-6; **2e**, 37614-66-7; **5f**, 37614-67-8; **5g**, 37614-68-9; **5h**, 37614-69-0; **5i**, 37614-70-3; **5j**, 37614-71-4; **5k**, 37614-72-5; benzoic acid, 65-85-0; *p*-hydroxybenzoic acid, 99-96-7; *p*-chlorobenzoic acid, 74-11-3; β-naphthoic acid, 93-09-4; furan-2-carboxylic acid, 88-14-2; phenylacetic acid, 103-82-2; acetic acid, 64-19-7; propionic acid, 79-09-4.

Transmission of Electronic Effects through the Cyclopropane Ring in Some Arylcyclopropanes

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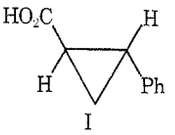
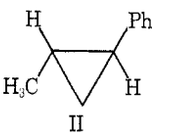
The possibility of electronic interaction between the cyclopropane ring and unsaturated groups has been of interest to several workers.[1-5] Some theoretical predictions[1] of Walsh for special geometric requirements for such interactions were tested[6] through the study of the ultraviolet spectra of a series of rigid arylcyclopropanes, but it was concluded that the steric relationship between a cyclopropane and benzene ring is of little consequence on the ultraviolet spectra.[6]

However, nmr evidence has been presented[7] showing that a conformation with the phenyl ring bisecting the three-membered ring is preferred in phenylcyclopropane. These results seem to imply that ultraviolet spectra are not sensitive to the relatively small conjugative effects in arylcyclopropanes.

This conclusion received indirect support by the recent report[8] that the ultraviolet and circular dichroism (CD) spectra of compounds I and II are very similar. In fact, this evidence was interpreted[8] as



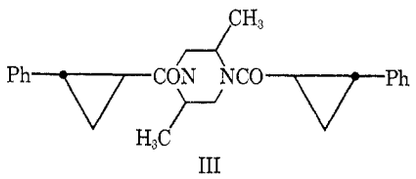
I



II

indicating that the carboxyl chromophore did not contribute significantly to the absorption, the latter being attributed exclusively to the benzene chromophore.

We report here additional evidence on the uv and CD spectra of compound I, which indicates some electronic interaction between the benzene and carboxyl chromophores in this molecule. This result suggests some transmission of electronic effects through the cyclopropane ring in arylcyclopropanes. These effects are also present in the diamide III, derived from the acid I.

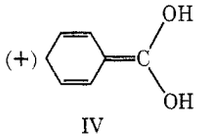


III

Results and Discussion

Relevant data on the uv, ORD, and CD spectra of compound I in tetramethylenesulfone (TMS) and methanesulfonic acid (MSA) are reported in Table I. The CD spectrum in TMS shows the typical vibrational structure of the ^1L_b benzene band in the 250–275-mμ region as well as a peak of higher intensity at 225 mμ which has been assigned[8] to the ^1L_a benzene transition. Although the TMS curve shows essentially the same features of the methanol spectrum previously reported,[8] a red shift is observed (Table I) in the MSA spectrum, with regard to the 225-mμ band.

This suggests that the 225-mμ band reflects an electronic interaction between the ^1L_a benzene transition and the carboxyl group, *via* the cyclopropane ring. In fact, red shifts of uv bands are known[9] to occur in aromatic carboxylic acids by addition of strong acids capable of protonating the carboxyl group, generating quinoid species such as IV absorbing at lower energy.[9]



IV

If the band at 225 mμ was entirely due to the ^1L_a benzene transition, it should not be drastically affected by the MSA addition. We have ascertained that phenylacetic acid shows a moderate blue shift in the corresponding uv absorption band in going from TMS (210 mμ) to MSA (204 mμ). However, the 280-mμ absorption of *trans*-cinnamic acid in TMS is shifted to about 325 mμ in MSA.

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TABLE I
OPTICAL DATA OF (−)-(*R*)-*trans*-2-PHENYLCYCLOPROPANECARBOXYLIC ACID (I)

Solvent	ORD λ, mμ	ORD *m*	CD λ, mμ	CD θ	Uv λ, mμ	Uv ε
TMS	274	−9,700 (t)[b]	273	−4,000 (M)[b]	273	350
	271	−9,500 (p)	269	−3,500 (m)		
	267	−10,500 (t)	265	−4,500 (M)	266	500
	264	−10,000 (p)	262	−3,500 (m)		
	259	−11,000 (s)	260	−4,000 (M)	260	500
	234	−37,500 (t)	254	−3,500 (m)		
	224	0	225	−61,000 (M)	223	13,000
	215	+27,500 (p)				
	207	0	211	−23,500 (m)		
	(200)	(−)	(205)	(−40,000)		
MSA	271[a]	−11,500 (t)				
	241	0	240[a]	−41,000	240	7,500
	217	+37,500 (p)	216	0		
			214	+3,500		
	205	+19,500 (t)	212	0		
	(200)	(+25,000)	(205)	(−14,000)		

[a] Very broad. [b] t, trough; p, peak; s, shoulder; M, + or − maximum; m, + or − minimum.

TABLE II
OPTICAL DATA OF (−)-(*R*)-Ph-C3·DMPIP DIAMIDE (III)

Solvent	ORD λ, mμ	ORD *m*	CD λ, mμ	CD θ	Uv λ, mμ	Uv ε
TMS	275	−10,500 (t)[b]	274	−5,500 (M)[b]	274	350
	272	−9,000 (p)	271	−2,500 (m)		
	268	−10,000 (t)	267	−6,000 (M)	267	500
	264	−9,000 (p)	264	−3,500 (m)		
	260	−10,500 (s)	261	−4,000 (M)	259	500
	237	−37,000 (t)	257	−3,000 (m)		
	229	0	230	−92,000 (M)		
	218	+72,000 (p)	218	0	221	23,000
			215	+12,000 (M)		
			212			
	(210)	(+33,000)	(210)	(−10,000)		
MSA	275	−16,500 (t)	272	−13,500 (s)		
	269	−15,000 (s)	265	−18,500 (s)		
	262	−11,500 (s)				
	248	0	247[a]	−30,000 (M)	242	9,000
	222	+39,500 (p)	225	0		
	213	0	217	+28,000 (M)		
	210	−6,500 (t)	211	0	207	26,000
	206	0				
	(200)	(+17,000)	(200)	(−38,000)		

[a] Very broad. [b] t, trough; p, peak; s, shoulder; M, + or − maximum; m, + or − minimum.

It seems reasonable to conclude that the 225-mμ band in compound I arises from the ^1L_a benzene transition modified by the electronic interaction with the cyclopropane ring. Accordingly, the fact that the methyl derivative II is isospectral to I does not necessarily imply the absence of interaction between phenyl and carboxyl, but rather indicates the presence of electronic interaction between benzene and cyclopropane rings in both compounds I and II.

A behavior similar to that observed for compound I is shown by the uv, ORD, and CD spectra of the diamide III, reported in Table II. The CD spectrum in TMS shows the typical vibrational structure of the ^1L_b benzene band in the 250–280-mμ region, and this fine structure is still detectable in MSA, superimposed by a long wavelength "tail" of the red-shifted (conjugation) band (Table II). We interpret this red shift as due to the protonation of the amide linkage by MSA. Thus benzamide is reported to be completely protonated in 59% H_2SO_4,[10] and its absorption maximum is considerably red shifted.[11] Aliphatic amides do not show this behavior; thus only minor changes in the intensity of these bands are observed.[11] The data suggest an electronic interaction from the benzene ring to the amide unit through the "conducting" cyclopropane bridge.

The presence of this electronic interaction poses the question of the identity of the preferred conformation for this system. It has been proposed[12] that the cyclopropylthioamides exist in a preferred conformation where the endo orbitals of the cyclopropane rings overlap with the adjacent π orbital of the thiocarbonyl group in the thioamide unit, so that the latter bisects exactly the cyclopropane ring. Since there are no appreciable differences in going from thioamides to amides, the above conformation should be also preferred in the case of cyclopropylamides.

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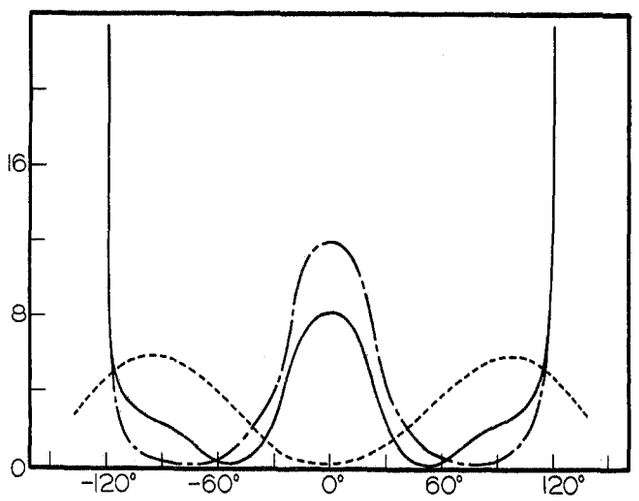

Figure 1.—Energy profiles as a function of the twist angle ϕ, for diamide III (half-molecule): — — —, nonbonded atoms interactions; – – – –, conjugative energy; ————, relative conformational energy. The 0° position is that where the carbonyl bisects the cyclopropane ring (maximum orbitals overlap).

However, if it is true that the geometrical arrangement with the amide (or thioamide) unit bisecting the cyclopropane ring meets the Walsh[1] requirements for the maximum overlap of cyclopropyl and carbonyl orbitals, an inspection of molecular models reveals that the nonbonded atom interactions are very unfavorable. As a consequence, a preferred conformation has to be assessed taking into account both conjugative and steric factors.

The conjugative ability of cyclopropane and carbonyl groups at the "maximum overlap" conditions has been estimated[4,5] to be about 6.0 kcal/mol in cyclopropanecarboxaldehyde, a system reasonably free from steric restraints. Assuming[4,5] a cosine[2] dependence of the conjugative energy from the angle of twist ϕ, the latter energy can be calculated for each ϕ value.

In Figure 1 are reported, as a function of the twist angle ϕ, the nonbonded interactions,[13] the conjugative energy, and the resultant relative conformational energy curves, relative to the half-molecule of diamide III.

It is apparent that the conformational minima are removed about 50–60° from the maximum-overlap position; this would still allow more than one-half of the maximum conjugative energy to be present.

This simple analysis appears to provide a more realistic basis to rationalize the transmission of electronic effects observed in the case of diamide III. Thus, it is not necessary to have coincidence between the maximum orbital overlap and the actual preferred conformation in order to get a sizable conjugative interaction and, therefore, the transmission of electronic effects through the cyclopropane ring.

Experimental Section

Spectra were recorded on a Jasco-Durrum ORD/CD/UV-5 spectropolarimeter; concentration 10^{-2}–10^{-3} M, cell length 0.1–1.0 mm, temperature 20–25°. All ORD/CD data are given in deg cm²/dmole of substrate.

Tetramethylenesulfone (Aldrich Chemical Co.) and methanesulfonic acid (Eastman Kodak Co.) were used without further purification.

(−)-(1*R*,2*R*)-*trans*-2-Phenylcyclopropanecarboxylic Acid (I).—(−)-(1*R*,2*R*)-*trans*-2-Phenylcyclopropanecarboxylic acid (I) was prepared as previously described:[15] mp 48.5–49.5° [petroleum ether (bp 30–60°)]; $[\alpha]^{20}D$ −410° ($CHCl_3$, 1.0 g/dl) [lit.[14a] mp 51–52°; $[\alpha]^{24}D$ −368° ($CHCl_3$, 0.931 g/dl)].

Bis-1,4-[(−)-(1*R*,2*R*)-2-phenylcyclopropanecarbonyl]-2,5-dimethylpiperazine (III).—(−)-(*R*)-*trans*-2-Phenylcyclopropanecarboxylic acid and a catalytic amount of anhydrous zinc chloride were added to thionyl chloride (120% excess relative to carboxyl groups) at room temperature. The mixture was stirred at 40° for 3 hr. The excess thionyl chloride was then removed under reduced pressure and the residue was fractionated to afford an 85% yield of the acid chloride, bp 80° (0.25 mm).

A mixture of 0.193 g (1.69 mmol) of *trans*-2,5-dimethylpiperazine (DMPIP), 9.32 ml (3.63 mmol) of 0.4 N aqueous NaOH solution, and 35.5 ml of methylene chloride was precooled to 0° in a Waring semimicro blender. This mixture was cooled in ice and vigorously stirred during the addition of 0.641 g of acid chloride and for an additional 10 min. The reaction mixture was filtered through a medium sintered glass funnel and the methylene chloride phase was separated and evaporated to dryness to afford 0.68 g (~100% based on DMPIP) of crude III which was purified by column chromatography (Florisil 60–100 mesh and 160 ml, MeOH 60 ml/hr, room temperature, retention volume 140–200 ml) and two recrystallizations from *n*-hexane, mp 120–121°.

Anal. Calcd for $(C_{10}H_9O_2)_2(C_6H_{12}N_2)$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.76; H, 7.64; N, 6.84.

Registry No.—I, 3471-10-1; I (acid chloride), 37107-48-5; III, 37107-49-6.

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A Convenient Synthesis of β-Halopyruvaldoximes

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In order to further our recent studies on unequivocal syntheses of 6-substituted pteridines,[1,2] we required large quantities of 2-amino-3-cyano-5-chloromethylpyrazine 1-oxide (**1**), obtained in good yield by condensation of aminomalononitrile with β-chloropyruvaldoxime (**2**). The preparation of **2** had previously been accomplished by chlorination of pyruvaldoxime in dilute chloroform solution,[3] but this proved to be a tedious and unpredictable reaction. Major problems

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