Registry No.—**3**, 55711-80-3; **4**, 2565-18-6; **5**, 55711-81-4; **6**, 55711-82-5; **7**, 823-20-1; **8**, 55711-83-6; **9**, 55711-84-7; **10**, 55711-85-8; **13**, 41447-10-3; **13** carbobenzoxy derivative 55711-86-9; **14**, 55711-87-0; **15**, 55711-88-1; **16**, 55711-89-2; **17**, 55711-90-5; **18**, 55711-91-6; **20**, 55711-92-7; *cis*-β-iodoacrylyl chloride, 55711-93-8; *trans*-β-iodoacrylyl chloride, 55711-94-9; oxalyl chloride, 79-37-8; *cis*-β-iodoacrylic acid, 6214-35-3; dibutylamine, 111-92-2; 2,6-dimethylpiperidine, 504-03-0; acrylyl chloride, 814-68-6; dodecahydrocarbazole, 6326-88-1; 1,5-diazabicyclo[3.4.0]nonene-5, 3001-72-7; (±)-allosedridine, 26623-96-1; (±)-allosedridine carbobenzoxy derivative, 55711-95-0; 1-(2-pyridyl)-propan-2-ol 5307-19-7; benzyl chloroformate, 501-53-1; propionyl chloride, 79-03-8.

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Optically Active Amines. XX.[1,2] Application of the Salicylidenimino Chirality Rule to Cyclic Terpene Amines[3]

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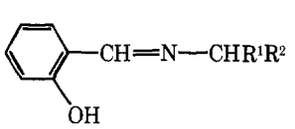
The signs of the Cotton effects near 255 and 315 nm observed in the circular dichroism spectra of the *N*-salicylidene derivatives of a group of cyclic terpene amines (menthane, thujane, and fenchane ring systems) correlate with the absolute configurations of the amines. The Cotton effects are generated by the coupled oscillator mechanism, and their signs are determined by the chirality (right-handed screw for positive chirality) of the vicinal carbon–carbon bonds and the attachment bond of the salicylidenimino chromophore.

Application of the salicylidenimino chirality rule to the establishment of the absolute configuration of *N*-salicylidene (Schiff base) derivatives (1) of chiral α- and β-arylalk-



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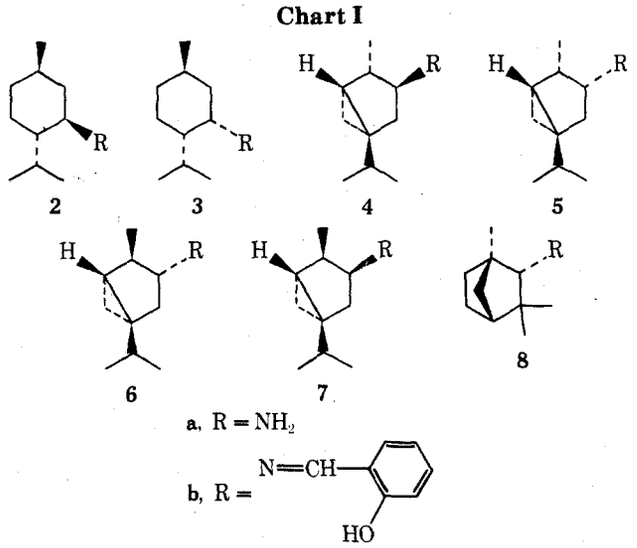
ylamines has been extensively documented.[1,6] The rule correlates the absolute configuration of these derivatives with their optical rotatory dispersion[7] (ORD) and circular dichroism[6] (CD) spectra. The magnitudes of the rotational strengths for the observed Cotton effects near 255 and 315 nm and the general features of the spectra indicate that the dominant mechanism operative in generation of the Cotton effects is electric transition moment dipole–dipole coupling of the aryl group with the salicylidenimino chromophore.[6] Positive chirality (right-handed screw) results in positive Cotton effects at 255 and 315 nm.

For the *N*-salicylidene derivatives of chiral alkylamines corresponding but less intense Cotton effects are observed.[8–11] As an extension of this work, we now report the CD spectra of the *N*-salicylidene derivatives of a group of cyclic terpene amines (**2a–8a**) (Chart I and Table I). In these spectra the signs of the observed Cotton effects near 255 and 315 nm, considered to be generated by the coupled oscillator mechanism,[15] correlate with the absolute configuration of the amine moiety.

Chart I



Results and Discussion

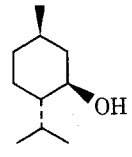
Configuration and Preferred Conformation. The absolute configurations of the *N*-salicylidene derivatives **2b–8b** follow from those of the respective amines. Both

Table I
Terpene Amines

Compd[a]	Present name	Previous name	$[\alpha]^{25}D$ of free base [or salt] used, deg
2a[b]	(−)-Menthylamine		−37 (*c* 2.0, $CHCl_3$)
3a[b]	(+)-Neomenthylamine		+15.5 (neat)
4a[c,d]	(+)-Thujylamine	(+)-Isothujylamine[b]	+114 (*c* 2.4, 95% C_2H_5OH)
5a[c,d]	(+)-Neothujylamine	(+)-Neoisothujylamine[b]	+53 (*c* 2.5, 95% C_2H_5OH)
6a[d]	(−)-Isothujylamine	(−)-Neothujylamine[b]	[+61 (*c* 1.0, H_2O)][e]
7a[d]	(−)-Neoisothujylamine	(−)-Thujylamine[b]	[−10 (*c* 1.0, H_2O)][f]
8a[g]	(−)-*endo*-Fenchylamine	(−)-α-Fenchylamine[g]	−25.3 (neat)

[a] References for sources of amines and further characterizations are footnotes. [b] Reference 12. [c] Reference 13. [d] H. L. Dickison and A.W. Ingersoll, *J. Am. Chem. Soc.*, 61, 2477 (1939). [e] (+)-Mandelate. [f] *p*-Toluenesulfonate. [g] Reference 14.

menthylamines (**2a** and **3a**) were prepared from (−)-menthone,[12] an oxidation product of (−)-menthol[16] (**9**), the rel-



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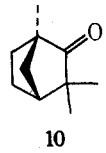

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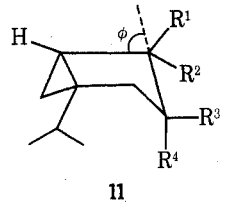
ative configurations of the amines following from their preparation[17] and interconversion.[12] The absolute configurations of the thujylamines (**4a** and **5a**) and isothujylamines (**6a** and **7a**) were also established earlier,[12,13] and their present names (Table I) now conform to the new rational nomenclature for the monoterpenes first suggested in connection with names for the isomeric menthols and carvomenthols[18] and later applied to the thujones and thujanols.[19] The absolute configuration of (−)-*endo*-fenchylamine (**8a**) follows from its preparation[20] from (+)-fenchone[16] (**10**) and the establishment of the amino group as endo.[21]

In the preferred conformation of the *N*-salicylidene derivatives of the menthylamines, the cyclohexane ring is a chair and the salicylidenimino moiety takes an equatorial (**2b**) or an axial (**3b**) position. For the thujylamines (**4b** and **5b**) and the isothujylamines (**6b** and **7b**), the ring of the amine moiety is preferably in a boat-like conformation[13,22] (**11**). For the alcohols corresponding to **4a** and **7a** (**11**, R^1



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and R^2 = H or CH_3; R^3 = OH; R^4 = H) the "flap angle"[22] (ϕ) has been found by ^1H NMR to be 20–30°. In the fenchylamine derivative (**8b**), the ring bearing the amino substituent is in rigid boat conformation with the salicylidenimino group axial.

Electronic Absorption and Circular Dichroism. The electronic (isotropic) adsorption (EA) and CD spectra of the *N*-salicylidene derivatives are summarized in Tables II and III. The EA spectra (Figure 1) are similar to those of other *N*-salicylidene derivatives.[1,6-11] In hexane, the spectra exhibit three broad absorption bands centered at about 315, 255, and 215 nm, designated as bands I, II, and III, respectively, and assigned to transitions of the intramolecularly hydrogen bonded salicylidenimino chromophore[6] (**12**). In polar solvents such as methanol and dioxane a broad band at 400 nm and a shoulder near 280 nm become evident in addition to a slight decrease in the intensity of the other three bands. The appearance of the 400- and 280-nm

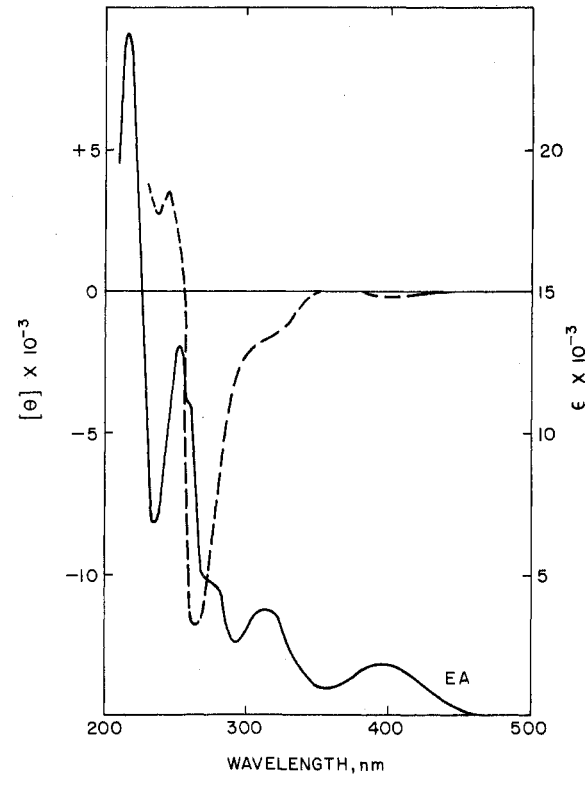
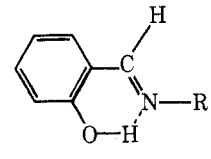


Figure 1. The EA and CD spectra of *N*-salicylidenementhylamine (**2b**) in methanol.

absorption bands has been attributed to the presence of a quinoid tautomer (**13**) in polar solvents.[23,24]



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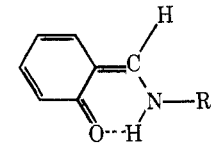

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The corresponding CD spectra are in general also similar to those of other *N*-salicylidene derivatives.[1,6-11] When a single CD maximum is associated with band I and with band II, these maxima are of the same sign. For **2b** and **5b**, which show S-shaped (double-humped[25]) CD curves associated with band II (Figure 1), the sign of the longer wavelength maximum is the same as that of the maximum associated with band I.

In the absence of exciton splitting, S-shaped CD curves associated with a single electronic transition have been interpreted in terms of conformational equilibria, the opposite signed maximum being due to a different conformer, or a solution equilibrium involving different solvated

Table II
Spectral Data for *N*-Salicylidene Derivatives of the Menthylamines and *endo*-Fenchylamine

Compd (solvent)	Band assignment	EA max, λ, nm (ε[b])	CD,[a] λ, nm ([θ][c])
2b (hexane)	I	319 (5,400)	316 (–2,500)[d]
	II	261 (14,000)[d]	264 (–19,000) (max)
		255 (16,000)	245 (+1,200) (max)
			238 (+700) (min)
			233 (+2,300)
	III	217 (31,000)	
2b (MeOH)	Quinoid	401 (1,800)	400 (–150) (max)
	I	315 (3,700)	315 (–1,400)[d]
	Quinoid	276 (4,700)[d]	
	II	260 (11,000)[d]	267 (–12,000) (max)
		255 (13,000)	245 (+3,500) (max)
			237 (+2,700) (min)
			231 (+3,700)
	III	216 (24,000)	
3b (hexane)	I	319 (5,100)	315 (+680)[d]
	II	261 (14,000)[d]	264 (+9,700) (max)
		255 (15,000)	
			238 (+1,000) (min)
			233 (+3,100)
	III	217 (29,000)	
3b (MeOH)	Quinoid	399 (2,400)	396 (+860) (max)
	I	315 (3,100)	314 (+710)[d]
	Quinoid	276 (5,900)[d]	
	II	259 (11,000)[d]	264 (+6,500) (max)
		254 (12,000)	
			243 (+780) (min)
			230 (+4,100)
	III	217 (24,000)	
8b (hexane)	I	320 (5,400)	318 (+3,000) (max)
	II	264 (13,000)[d]	263 (+4,800) (max)
		258 (16,000)	
			242 (±0)
			233 (+5,200)
	III	223 (23,000)[d]	
		217 (25,000)	
8b (MeOH)	Quinoid	401 (2,100)	400 (+730) (max)
	I	315 (3,900)	316 (+2,700) (max)
	Quinoid	277 (5,600)[d]	
	II	256 (13,000)	259 (+7,100) (max)
			240 (+3,700) (min)
			235 (+4,200)
	III	215 (23,000)	

[a] Last entry for each spectrum is cut-off. [b] Molar absorptivity. [c] Molecular ellipticity. [d] Shoulder.

species.[26] However, the S-shaped CD curves for band II in **2b** and **5b** are interpreted in terms of vibronic coupling which also predicts alternate signed CD bands for a single electronic transition.[27,28] The S-shaped feature in band II may be the manifestation of the combined effect of an allowed progression of a totally symmetric vibrational mode and a forbidden progression of a possibly nontotally symmetric mode whose differential dichroic absorption maximum occurs at a shorter wavelength and borrows its intensity chiefly from the nearby intense band III.[27] In the EA spectra, the fine structure of band II, a shoulder near 260 nm with the absorption maximum near 255 nm, is evidence for the presence of these two vibrational progressions. An S-shaped CD curve for band II appears only when the two progressions have opposite signs and their rotational strengths are of approximately equal intensity.

The absence of S-shaped CD curves for band I indicates the relative unimportance of forbidden character in band I due to the absence of an intense band from which to borrow intensity.

In the absence of exciton splitting no S-shaped CD curve associated with band II was observed[1,6,7] for the *N*-salicylidene derivatives of aryl-substituted amines.

The sign of the CD maximum for band I and that of the CD maximum for band II (or that of the longer wavelength

Table III
Spectral Data for *N*-Salicylidene Derivatives of the Thujylamines and Isothujylamines

Compd (solvent)	Band assignment	EA λ, nm (ε[b])	CD,[a] λ, nm ([θ][c])
4b (hexane)	I	318 (5,300)	314 (+430)[d]
	II	262 (14,000)[d]	262 (+3,900) (max)
		254 (15,000)	
			238 (±0)
			230 (+2,100)
	III	216 (28,000)	
4b (MeOH)	Quinoid	400 (1,400)	398 (+400) (max)
	I	315 (4,100)	313 (+1,700) (max)
	Quinoid	278 (3,700)[d]	280 (+2,800)[d]
	II	260 (12,000)[d]	264 (+4,800) (max)
		254 (14,000)	
			238 (+1,700) (min)
			230 (+3,400)
	III	214 (25,000)	
5b (hexane)	I	320 (4,900)	315 (–1,700) (max)
	II	262 (13,000)[d]	272 (–5,800) (max)
		256 (14,000)	254 (+7,700) (max)
			238 (+2,700) (min)
			230 (+8,500)
	III	216 (28,000)	
5b (MeOH)	Quinoid	399 (1,400)	398 (–170) (max)
	I	314 (3,700)	315 (–630)[d]
	Quinoid	276 (4,000)[d]	
	II	259 (12,000)[d]	273 (–2,300) (max)
		254 (13,000)	254 (+8,800) (max)
			238 (+5,000) (min)
			230 (+9,000)
	III	215 (24,000)	
6b (hexane)	I	318 (4,800)	~315 (+) (max)[e]
	II	261 (12,000)[d]	
		256 (13,000)	
			230 (±0)
	III	216 (23,000)	
6b (MeOH)	Quinoid	399 (1,200)	~400 (+) (max)[e]
	I	316 (4,100)	~315 (+) (max)[e]
	Quinoid	280 (3,500)[d]	
	II	255 (14,000)	
			230 (±0)
	III	215 (26,000)	
7b (hexane)	I	319 (4,900)	315 (–1,200) (max)
	II	261 (12,000)[d]	255 (–3,600) (max)
		256 (13,000)	
			230 (±0)
	III	216 (24,000)	
7b (MeOH)	Quinoid	400 (2,100)	398 (–240)[d]
	I	315 (3,800)	314 (–2,000) (max)
	Quinoid	278 (9,100)[d]	
	II	255 (16,000)	254 (–6,500) (max)
			230 (±0)
	III	216 (26,000)	

[a] Last entry for each spectrum is cut-off. [b] Molar absorptivity. [c] Molecular ellipticity. [d] Shoulder. [e] The anisotropy factor ($\Delta\epsilon/\epsilon$) for this band was such that the CD measurement was not quantitatively significant.

Table IV
N-Salicylidene Derivatives of Terpene Amines

Compd	Mp [bp], °C	$[\alpha]^{25}D$, deg (solvent)[a]
2b[b]	56–58	−119 ($CHCl_3$)
3b[c]	94–96	+33 ($CHCl_3$)
4b[d]	[176 (4.5 mm)]	+91 (CH_3OH)
5b[e]	85–86	+8 (CH_3OH)
6b[f]	62–63	−17 (heptane)
7b[f,g]	65–66[h]	−5 (hexane)
8b[i]	95–96	+74 (CH_3OH)

[a] 1.0–2.0 g/100 ml. [b] Lit.[17] mp 57–58°; $[\alpha]D$ −119.2° ($CHCl_3$). [c] Lit.[17] mp 99–100°, $[\alpha]^{15}D$ + 30.0° ($CHCl_3$). [d] Oil, $n^{25}D$ 1.5444. Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01. Found: C, 79.28; H, 9.18. [e] Anal. Found: C, 79.67; H, 8.82. [f] Sublimed at 60° (0.005 mm). [g] Anal. Found: C, 79.80; H, 8.72. [h] Kofler hot stage. [i] Lit.[14] mp 95.5°; $[\alpha]D$ +73.5° (*c* 4, CH_3OH).

portion of band II) are the same since the electronic transition moments of bands I and II, although not coinciding exactly with each other, are both almost parallel to the chromophore attachment bond.[6] There are, however, a few reported[10,11] CD spectra of *N*-salicylidene derivatives for which the signs of band I and band II are not the same. This is probably a consequence of the slightly different orientation of the respective transition moments.

Menthylamines (Table II). In the preferred conformation of **2b** and **3b,** the cyclohexane ring is symmetrically disposed with respect to the attachment bond of the salicylidenimino group. Further, if the effect due to the polarizability of carbon–hydrogen bonds is assumed to be negligible,[29] only the attached methyl and isopropyl groups will be effective in inducing differential dichroic absorption in the chromophore. The methyl group attachment bond to the cyclohexane ring and the methyl group attachment bonds in the isopropyl substitutent are all separated from the chromophore by a substantial distance. Thus their contribution to the CD will be small compared to that of the isopropyl group attachment bond. Consequently, it appears that the sign of the CD maximum associated with bands I and II (or the longer wavelength portion of band II) is largely determined by the orientation of the isopropyl group attachment bond with respect to the chromophore attachment bond, since the purely electronic transition moments of bands I and II of the chromophore are approximately parallel to its attachment bond,[6] and the chirality rule developed for the *N*-salicylidene derivatives of β-arylalkylamines[6] will be applicable.

The sign of the CD maxima for bands I and II (or the longer wavelength portion of band II) is determined by the chirality (right-handed screw for positive chirality) of the vicinal carbon–carbon bond and the attachment bond of the chromophore. For **2b** in its preferred conformation, this chirality between the salicylidenimino and the isopropyl group attachment bonds is negative and thus negative allowed vibrational progressions for bands I and II are predicted. The latter allowed progression coupled with a positive nontotally symmetric vibrational progression results in a strong negative CD maximum near 265 nm and a moderately positive maximum centered at 245 nm. For **3b,** the chirality between the salicylidenimino and the isopropyl group attachment bonds is positive. Positive allowed progressions are predicted for bands I and II. Band II augmented by a positive forbidden progression results in a single positive maximum at 264 nm.

Thujyl and Isothujylamines (Table III). For these derivatives the bicyclic carbon skeleton is also symmetrically disposed with respect to the salicylidenimino group attachment bond, and the sign of the CD associated with allowed vibrational progressions of bands I and II is largely determined by the chirality of the attachment bonds of the vicinal methyl group and the chromophore. For **4b** in a boat-like conformation, this chirality is positive and positive CD maxima near 315 and 264 nm are observed. For **7b** in a boat-like conformation, this chirality is negative in agreement with the observed negative CD maxima for bands I and II.

For **5b,** an S-shaped CD curve appears for band II, indicating that the two vibrational progressions for this band have opposite signs. However, the signs for band I and the longer wavelength portion of band II are both negative in agreement with the negative chirality of the attachment bonds of the vicinal methyl group and the chromophore for **5b** in a boat-like conformation. The large magnitude of the shorter wavelength portion of band II is related to the high rotational strength associated with band III as indicated by the molecular ellipticity shown by **5b** at 230 nm (cut-off). That the sign of the forbidden vibrational progression for **2b–5b** and **8b** agrees with the sign of band III lends support to the conclusion that the rotational strength of this progression is borrowed mainly from band III.

In the preferred, boat-like conformation of **6b,** the attachment bonds of the vicinal methyl group and the chromophore are almost antiparallel to each other (**11**, R^1 = CH_3; R^4 = chromophore). As a result, the coupled oscillator contribution of the vicinal carbon–carbon bond to the differential dichroic absorption will be small, and the contribution due to other carbon–carbon bonds must be taken into account. This analysis is in agreement with the observation that the rotational strengths for bands I and II are very small.

Fenchylamine (Table II). The interpretation of the CD spectrum of **8b** is complicated by the fact that the bicyclic carbon skeleton of **8b** is not symmetrically disposed with respect to the salicylidenimino group attachment bond. However, if only the nearest neighboring carbon–carbon bonds are considered, more bonds have positive chirality with respect to the chromophore attachment bond. Thus positive allowed vibrational progressions for bands I and II are predicted, and the observed CD maxima are positive.

Experimental Section

Melting points were taken in open capillary tubes unless otherwise noted, and are corrected. The boiling point is also corrected. Optical rotations at the sodium D line were measured using a visual polarimeter and a 1-dm sample tube. Isotropic electronic absorption (EA) spectra were obtained with a Cary Model 14 spectrophotometer with the normal variable slit and matched 1-cm cells. Circular dichroism (CD) spectra were measured with a Cary Model 60 spectropolarimeter with a CD Model 6001 accessory at 25–28° using a 1-cm cell. The slit was programmed for a spectral band width of 1.5 nm. The sample concentrations were 2.41×10^{-3} to 2.64×10^{-2} g/100 ml, and cut-off was indicated when the dynode voltage reached 400 V. Elemental analyses were done by Galibraith Laboratories, Inc., Knoxville, Tenn.

***N*-Salicylidene Derivatives.** The derivatives were formed and purified as outlined previously.[30] In cases where they did not crystallize (**4b, 6b,** and **7b**), the methanol was evaporated and the residue was distilled (**4b**) or sublimed (**6b** and **7b**). Details are given in Table IV.

Registry No.—**2b,** 56087-03-7; **3b,** 56087-04-8; **4b,** 56087-05-9; **5b,** 56087-06-0; **6b,** 56087-07-1; **7b,** 56087-08-2; **8b,** 56087-09-3.

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(4) (a) Vanderbilt University; (b) Tennessee State University.
(5) National Defense Education Act Fellow, 1961–1964.
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Synthesis of Condensed Heterocyclic Systems. VI.[1a] Some Ring Closure Reactions Involving 1-Hydrazinophthalazine

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The acylation of 1-hydrazinophthalazine (**1**, hydralazine) with mono-, di-, tri-, and tetracarboxylic acids and acid derivatives gave 3-substituted *s*-triazolo[3,4-*a*]phthalazines; use of *p*-nitrophenol esters of carboxylic acids facilitates the dehydrative cyclization reaction and enlarges the scope of this type of reaction considerably. Though the annelation of five-membered rings to the phthalazine ring proceeds with exceptional ease, fusion of a six-membered ring to this system proceeds with difficulties only. Annelation of larger rings met with failure.

As the result of work by our group[2–5] and others[6–8] on the determination and clarification of the structure of human metabolites of **1**, a common hypotensive agent, we were prompted to investigate in detail the reaction between **1** and a variety of acylating agents. Originally,[7] it had been proposed that **1** undergoes enzymatic acetylation to give 1-(2-acetylhydrazino)phthalazine (**2**, R = CH_3; R′ = H). However, it has subsequently been shown independently by two groups[3,8] that enzymatic acetylation instead leads to 3-methyl-*s*-triazolo[3,4-*a*]phthalazine (**3**, R = CH_3; R′ = H). It has also been found that attempts to synthesize **2** under a variety of conditions[3] failed and always yielded the cyclized product **3**. This seems to be unique for the phthalazine system. In other cases, e.g., the acylation of 1-aminomethylisoquinoline[9] and corresponding benzoisoquinoline and benzoquinoline compounds,[10] the expected amides were obtained as stable and isolable compounds. These amides underwent dehydrative cyclization only upon catalysis by strong mineral or Lewis acids. It was, therefore, decided to investigate the acylation of **1** with a variety of acids and acid derivatives to determine whether ring closure to 3-substituted *s*-triazolo[3,4-*a*]phthalazines is in all cases the product in this type of reaction or if it is only typical for the acetylation reaction. Consequently, the acylation of **1** was studied using a variety of mono-, functional mono-, and dicarboxylic acids and derivatives as well as a tri- and a tetracarboxylic acid ester. In addition, attempts were made to fuse six-, seven-, and eight-membered rings to the phthalazine system.

In agreement with earlier investigators[11] we also found that the acid chloride–$POCl_3$ method for achieving dehydrative cyclization to yield the *s*-triazolo system is not a general one and often not suitable at all owing to instability of the acid chlorides. We found that *p*-nitrophenol esters of such acids are excellent materials for the projected reaction, undergoing amide formation and ring closure under very mild conditions. Use of these esters extends the scope of this cyclization reaction considerably.

***s*-Triazolo[3,4-*a*]phthalazines from Monocarboxylic Acid Derivatives.** In every case, the reaction of monocarboxylic acids or acid derivatives with widely varying R groups (Table I) led to the formation of 3-substituted *s*-triazolo[3,4-*a*]phthalazines (**3**, R′ = H) (Scheme I). The scope of this reaction is shown by the substituents in **3** shown in Table I. A unique acylation agent, trichloroacetonitrile, was also used to prepare 3-trichloromethyl-*s*-triazolo[3,4-*a*]phthalazine although in poorer yield than with the acid. This reaction involving the nitrile is analogous to the formation of **3** (R = NH_2; R′ = H) from cyanogen bromide.[11]

In agreement with previous work,[11] the acylation of 1,4-dihydrazinophthalazine (**1**, R = R′ = $NHNH_2$) does not yield by a double ring closure reaction the bis-*s*-triazolo[3,4-*a*:4,3-*c*]phthalazine system (**4**, R = CF_3), but a mixture of