In the PMR spectrum of compound (VII), the methylene protons of the morpholine ring were manifested as a multiplet with a center at 4.05 ppm. IR spectrum, cm^{-1}: $\nu_{C=S}$ 570, ν_{C-O-C} 1120, $\nu_{C\equiv N}$ 2230. Found: C 46.70; H 5.14; N 17.80; S 20.51%. $C_6H_8N_2OS$. Calculated: C 46.14; H 5.18; N 17.93; S 20.52%. The IR spectrum of the recovered morpholine hydrochloride was completely identical to the IR spectrum of the certified specimen. Found: C 38.92; H 8.39; Cl 28.16; N 11.34%. $C_4H_{10}ClNO$. Calculated: C 38.88; H 8.16; Cl 28.69; N 11.33%. The bands in the IR spectra were assigned in accordance with [4].

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REGIO- AND STEREODIRECTIVITY IN THE REACTIONS OF ISOQUINOLINIUM YLIDES WITH UNSATURATED NITRILES

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Reactions of isoquinolinium ylides with arylmethylenemalonitriles involve 1,3-dipolar cycloaddition, with the highly regio- and stereoselective formation of 2-aryl-3-benzoyl(or carbamoyl)1,1-dicyano-2,3-trans-1,2,3,10b-tetrahydropyrrolo[2,1-a]isoquinolines. In contrast, N-phenacylisoquinolinium ylide reacts with arylmethylenecyanothioacetamides differently, proceeding regio- and stereoselectively to give 4-aryl-2-hydroxy-3-(1-isoquinolinio)-2-phenyl-3-cyano-3,4-trans-1,2,3,4-tetrahydropyridine-6-thiolates.

The reactions of azinium ylides with unsaturated compounds have been utilized for the synthesis of physiologically active indolizines, benzoindolizines, and other cyclazines [1-6]. It has been found that these reactions proceed by 1,3-dipolar cycloaddition to give hydrogenated cyclazines, and are frequently accompanied by side rections involving elimination, cycloelimination, or a variety of rearrangements [1, 2, 6]. There have been no reports up to the present time of the reactions of ylides with α, β-unsaturated nitriles.

We have examined the reactions of isoquinolinium ylides with arylmethylenemalononitriles and arylmethylenecyanothioacetamides, and established their regio- and stereodirectivity. The isoquinolinium ylides were not isolated, but were generated directly in the reaction mixture by treating the azinium salts (Ia, b) in ethanol with an equimolar amount of triethylamine. The subsequent reactions of the azinium ylides (IIa, b) with the unsaturated nitriles followed differing routes, depending on the substituents present in the unsaturated compounds (Scheme 1). The reactions of (IIa, b) with arylmethylenemalononitriles (IIIa-g) involved 1,3-dipolar cycloaddition regio- and stereoselectivity to give the tetrahydropyrrolo[2,1-a]isoquinolines (IV) and (V) (Tables 1 and 2). The high regio- and stereodirectivity of these reactions was confirmed by physicochemical studies. The IR spectra of (IV) showed several asbsorption bands corresponding to deformational and stretching vibrations of the $CONH_2$ group at 1635-1694 and 3180-3424 cm^{-1} (Table 2), and the IR spectra of (V) showed absorption of high intensity for the C=O group at 1685-1690 cm^{-1}. In addition, in the IR spectra of all the

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TABLE 1. Substituted 2-Aryl-1,1-dicyano-2,3-trans-1,2,3,10b-tetrahydropyrrolo[2,1-a]isoquinolines (IV) and (V)

Compound	Yield, %	Mp, °C	Empirical formula	Found/Calculated, %			
				C	H	Hal	N
(IVa)	76	165–166	$C_{21}H_{16}N_4O$	73,93 74,10	4,60 4.74		16,30 16,46
(IVb)	88	171–173	$C_{21}H_{15}FN_4O$	70,18 70,38	4,04 4.22	5,11 5,30	15,45 15,63
(IVc)	61	171–172	$C_{21}H_{15}ClN_4O$	67.24 67,29	3,97 4,03	9,35 9,46	14,82 14,95
(IVd)	82	175–177	$C_{21}H_{15}BrN_4O$	59.92 60,16	3,43 3,61	18,87 19,06	13,22 13,36
(IVe)	69	159–160	$C_{21}H_{15}FN_4O$	70,47 70,38	4.20 4,22	5,08 5,30	15,48 15,63
(IVf) *	96	148–149	$C_{21}H_{18}N_5O_2$	67,48 67,73	4.69 4,87		18,65 18,81
(Va)	98	122–123	$C_{27}H_{19}N_3O$	80.46 80,78	4,62 4.77		10,35 10,47
(Vb)	90	111–112	$C_{27}H_{18}FN_3O$	77,25 77,31	4,17 4,32	4,37 4,53	9,83 10,02
(Vc)	93	114–115	$C_{27}H_{18}ClN_3O$	74,25 74,40	4.02 4,16	8,12 8,13	9,40 9,64
(Vd)	92	116–117	$C_{27}H_{18}BrN_3O$	67,26 67,51	3,53 3,78	16,34 16,63	8,37 8,75
(Ve)	90	126–127	$C_{27}H_{18}FN_3O$	77,07 77,31	4,14 4,32	4,26 4,53	9,83 10,02
(Vf)	87	118–120	$C_{26}H_{18}N_4O$	77,43 77,60	4,38 4,51		13,78 13,92
(Vg)	74	108–110	$C_{25}H_{17}N_3OS$	73,48 73,69	4,06 4.21		10,16 10,31

*This compound was a complex with ethylene glycol, $C_{20}H_{15}N_5O \cdot 0.5C_2H_6O_2$.

tetrahydropyrrolo[2,1-a]isoquinolines (IV) and (V) the C≡N absorption was of low intensity, and was shifted to higher frequencies (2247-2260 cm^{-1}) as compared with conjugated nitriles [7]. Hence, the IR spectra show that the functional groups C≡N, $CONH_2$, and COAr are bonded to sp^3-hybridized carbon atoms. The molecules of (IV) and (V) contain a hydrogenated pyrrole ring, and elimination of hydrogen or hydrogen cyanide does not occur in these cases.

The PMR spectra also indicate the high regio- and stereodirectivity of these reactions. The signals for the C^{2}H and C^{3}H protons are seen as two doublets at 4.42-4.68 and 4.79-6.08 ppm, with coupling constants $^3J_{H^2,H^3}$ = 6.4-7.9 Hz. The assignment of the signals for the C^{2}H and C^{3}H hydrogens was made by comparison with the PMR spectroscopic data for (IV) and (V).

The signal for the C^{3}H proton is shifted from 4.79-4.86 to 6.03-6.07 ppm ($\Delta\delta \approx 1.2$ ppm) on changing from 3-carbamoyl- to 3-benzoyltetrahydropyrrolo[2,1-a]isoquinolines, whereas the signal for the C^{2}H proton in unaffected (Table 2). In this transition, the ^3J values in the PMR spectra fall from 7.7-7.9 to 6.4-6.8 Hz, which should result in a decrease in the torsion angle ϕH—C^2-C^{3}H, stronger screening of the C^{3}H hydrogen, and a shift in its signal to higher field. The reverse of this behavior which is actually observed shows that the main contribution to the low-field shift of the C^{3}H hydrogen is made by electronic rather than steric factors, owing to polarization of the C^{3}H hydrogen by the stronger electron-accepting substituent COC_6H_5. In addition, the PMR spectra of (IV) and (V) show doublet signals for the C^{5}H and C^{6}H protons at 6.52-6.88 and 5.39-5.48 ppm with $^3J_{H^5,H^6}$ = 7.5-7.8 Hz, together with signals for the aromatic protons and the NH_2 group (Table 2).

The signal for the C^{10b}H proton is seen as a singlet at 5.54-5.78 ppm. This hydrogen is rigidly oriented in space, occupying a pseudoaxial position relative to the isoquinoline moiety. The strict spatial orientation of the C^{10b}H hydrogen results in its being sterically screened by the benzoyl group, so that on changing from (IV) to (V) the signal for this proton is shifted to higher field by $\Delta\delta$ = 0.20-0.22 ppm. These findings show that the substituent at C^3 and the C^{10b}H hydrogen atom lie in the same plane, and experience steric inter-

TABLE 2. IR and PMR spectra of 2-Aryl-1,1-dicyano-2,3-trans-1,2,3,10b-tetrahydropyrrolo[2,1-a]isoquinolines (IV, V)

Compound	IR spectrum, ν, cm^{-1}		PMR spectrum									$\varphi_{H-C^2-C_3-H}$ deg
			δ, ppm							³J, Hz		
	R	C≡N	C²H (d)	C³H (d)	C⁵H (d)	C⁶H (d)	C¹⁰ᵇH (s)	NH₂ (s)	Ar, R, C⁷H, C⁸H, C⁹H (m)	J_{H^2, H^3}	J_{H^5, H^6}	
(IVa)	1636, 1654, 1692, 3240, 3420	2260	4,42	4,83	6.56	5,41	5,77	7,78 (1H)	7,09–7,60 (10H)	7,9	7,6	137
(IVb)	1640, 1656, 1688, 3235, 3424	2258	4,45	4.79	6,55	5,41	5,75	7,77 (1H)	7,05–7.70 (9H)	7,8	7,7	136
(IVc)	1638, 1652, 1690, 3230, 3420	2255	4,43	4,82	6.53	5,40	5,74	7,74 (1H)	7,07–7,65 (9H)	7,9	7.6	137
(IVd)	1635, 1653, 1687. 3242, 3415	2253	4,43	4,80	6,52	5,39	5,75	*	7,08–7,71 (10H)	7,7	7.6	135
(IVe)	1638, 1650, 1694, 3190, 3410	2258	4,48	4,85	6,57	5,42	5,76	*	7,06–7,73 (10H)	7,7	7,8	135
(IVf)	1636, 1652, 1692. 3180, 3424	2260	4,50	4,86	6,54	5,43	5.78	*	7,30–8,75 (10H)	7,9	7,6	137
(Va)	1690	2245	4.64	6,07	6,88	5,48	5,58		7,08–7,93 (14H)	6.8	7,7	131
(Vb)	1687	2248	4,68	6.08	6,87	5,48	5.57		7,12–7,92 (13H)	6,4	7,6	128
(Vc)	1688	2250	4,67	6,07	6.86	5,47	5,56		7.12–7,93 (13H)	6,4	7,6	128
(Vd)	1685	2247	4,68	6,06	6.86	5,48	5,55		7.10–7,91 (13H)	6.5	7,5	129
(Ve)	1690	2248	4,65	6,03	6,85	5,45	5,54		7,12–7,90 (13H)	6,6	7,6	130
(Vf)	1685	2247	4,68	6,08	6,87	5,47	5,56		6,30–8,75 (13H)	6,5	7,5	129
(Vg)	1688	2248	4.67	6,07	6,85	5.45	5,55		7.22–7,94 (12H)	6,4	7,6	128

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*Overlaps signals for aromatic protons.

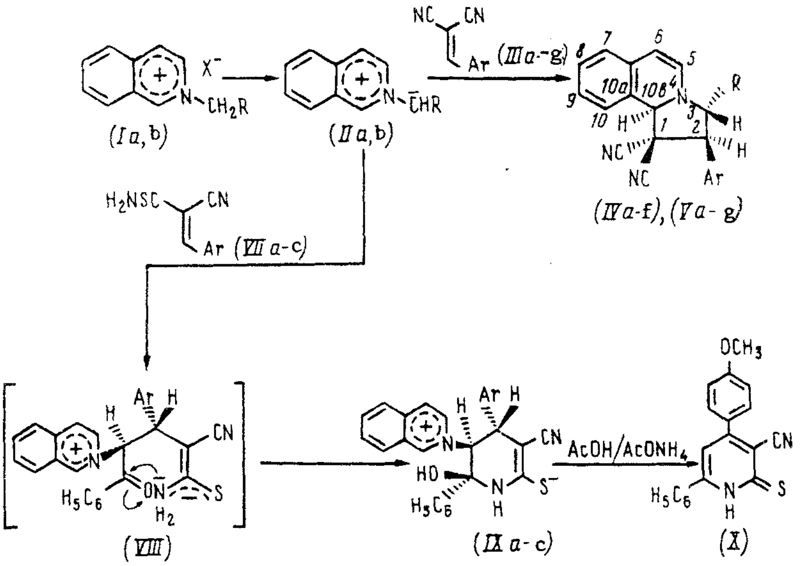
TABLE 3. 4-Aryl-2-hydroxy-3-(1-isoquinolinio)-2-phenyl-5-cyano-3,4-trans-1,2,3,4-tetrahydropyridine-6-thiolates (IX)

Compound	Yield, %	Mp, °C	Empirical formula	Found/Calculated, % C	H	N	S
(IXa)	87	128–129	$C_{28}H_{23}N_3O_2S$	72,02 72,23	4,72 4,96	8,82 9,03	6,74 6,89
(IXb)	90	140 (dec.)	$C_{26}H_{20}N_4OS$	71,32 71,53	4,30 4,62	12,62 11,84	7,57 7,35
(IXc)	88	135–136	$C_{25}H_{19}N_3OS_2$	67,82 68,00	4,16 4,34	9,37 9,52	14,31 14,52

TABLE 4. IR and PMR Spectra of 4-Aryl-2-hydroxy-3-(1-isoquinolinio)-2-phenyl-5-cyano-3,4-trans-1,2,3,4-tetrahydropyridine-6-thiolates (IX)

Compound	IR spectrum, ν, cm⁻¹			PMR spectrum					$\varphi_{H-C^2-C^3-H}$, deg
				δ, ppm				$^3J_{H^2,H^3}$, Hz	
	C≡N	NH	OH	C^3H (d)	C^4H (d)	NH, OH (br.s)	aromatic protons (m)		
(IXa)	2170	3337	3418	4,76	5,25	5,83	7,10–8,80 (16H)	11,2	156
(IXb)	2168	3285	3424	4,93	5,39	6,05	7,05–8,45 (16H)	11,4	158
(IXc)	2167	3278	3408	4,35	5,18	5,93	6,68–8,20 (15H)	11,5	158

Scheme 1

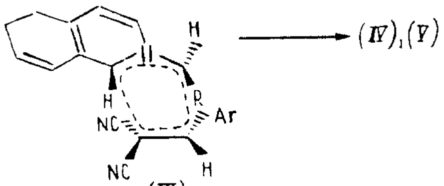


(IV): R = $CONH_2$, Ar = C_6H_5 (a), 4-FC_6H_4 (b), 4-ClC_6H_4 (c), 4-BrC_6H_4 (d) 3-FC_6H_4 (e), 3-C_5H_4N (f); (V): R = COC_6H_5, Ar = C_6H_5 (a), 4-FC_6H_4 (b), 4-ClC_6H (c), 4-BrC_6H_4 (d), 3-FC_6H_4 (e), 3-C_5H_4N (f) 2-C_4H_3S (g); (VII), (IX): Ar = 4-$CH_3OC_6H_4$ (a), 3-C_5H_4N (b), 2-C_4H_3S (c).

action. Consequently, the C^3H hydrogen lies in the opposite plane relative to the $C^{10b}H$ hydrogen, and occupies a pseudoaxial position in the hydrogenated pyrrole moiety in (IV) and (V).

The torsion angles, calculated using the Karplus–Conroy equation [8] on the basis of coupling constant $^3J_{H^2,H^3}$, have two values: $\varphi^1_{H-C^2-C^3-H} = 128-137°$ and $\varphi^2_{H-C^2-C^3-H} = 35-45°$. Consequently, the C^2H and C^3H hydrogens may be oriented either pseudoaxially, or pseudoequatorilly. Bearing in mind the characteristic J values for previously prepared tetrahydroindolizines (^3J = 6.5-9 Hz) [3-5], and comparing these with the $^3J_{C^2H,C^3H}$ values for (TV) and (V), it will be seen that the C^2H and C^3H hydrogens are located trans-pseuodequatorially, with torsion angle $\varphi_{H-C^2-C^3-H}$ = 128-137°. The C^2H hydrogen occupies a cis-pseudoaxial position relative to the $C^{10b}H$ hydrogen.

With these considerations in mind, it may be assumed that the reaction of isoquinolinium ylides (II) with arylmethylenemalonitriles (III) involves synchronous 1,3-dipolar cycloaddition in a highly regio- and stereoselective manner with the formation of 2,3-trans-1,2,3,10b-tetrahydropyrrolo[2,1-a]isoquinolines (IV, V).



(VI)

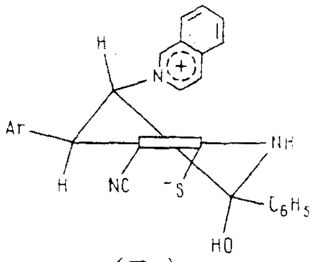
The regiodirectivity of these reactions is governed by dipole–dipole interactions and the strict orientation of the molecules of the starting material with respect to each other in space. The stereodirectivity of the reactions is governed by steric interactions of the substituents in the molecules of starting material in the transition state (VI). These factors make it possible to state with some confidence that the above reactions involve the endo-addition of the arylmethylenmalononitriles (III) to the anti-form of the isoquinolinium ylide via the transition state (VI), with retention of orbital symmetry.

In contrast, the reaction of the ylide (IIb) with arylmethylenecyanothioacetamides (VIIa-c) in ethanol at 25°C results in the formation of the 3-(1-isoquinolinio)-3,4-trans-1,2,3,4-tetrahydropyridine-6-thiolates (IXa-c). This reaction may be rationalized as a predominant Michael addition of the ylide (IIb) to (VII) in preference to 1,3-dipolar cyloaddition, with the formation of the Michael adduct (VIII) followed by heterocyclization to the tetrahydropyridine-6-thiolates (IXa-c).

According to physicochemical methods of analysis, this reaction is regio- and stereoselective. In the IR spectra of (IX), strong C≡N absorption is seen at 2167-2170 cm^{-1} (Tables 3 and 4). The high intensity and low-frequency position of the nitrile group absorption indicates partial redistribution of the negative charge in the grouping $N{\equiv}C{-}C{-}C{-}S^-$. It appears that in the 3-(1-isoquinolinio)tetrahydropyridine-6-thilates (IX) the sulfur atom bears a formal negative charge, as in tetrahydropyridine-2-thiolate salts [9-11].

In the PMR spectra of (IXa-c), the signals for the C^3H and C^4H hydrogens are seen as two doublets at 4.35-4.76 and 5.18-5.39 ppm, with $^3J_{H^3H^4}$ = 11.2-11.5 Hz. The torsion angle calculated using the Karplus–Conroy equation [8] for such values of the coupling constants has the single value $\varphi_{H-C^3-C^4-H}$ = 156–158° (Table 4). This shows that the C^3H and C^4H hydrogen atoms are located trans-pseudoaxially, and consequently the isoquinolinium and aryl substituents occupy trans-pseudoequatorial positions. Bearing in mind that the $N{-}C{-}C{-}C{-}S^-$ grouping contains a highly developed conjugated electronic system, it will be seen that the fragment $N^1{-}C^6{=}C^5{-}C^4$ is coplanar. The above physicochemical data, together with construction of Stuart–Briegleb models, and earlier data on the structures of tetrahydropyridine-2-thiolates [9-12], show that tetrahydropyridine-6-thiolate molecules exist in the semi-chair conformation, as in the case of cyclohexene [13], with atoms C^2 and C^3 departing from the plane of the the coplanar fragment $N^1{-}C^6{=}C^5{-}C^4$ on opposite sides (IX , A). In this conformation of the tetrahydropyridine ring and the steric disposition of the substituents attached to it, the hydroxyl group attached to C^2 occupies the trans-pseudoaxial position relative to the C^3H hydrogen. The phenyl substituent attached to C^2 occupies the most sterically favored trans-pseudoequatorial position relative to the isoquinolinium cation.

The structures of the products (IX) were also confirmed chemically. On heating the tetrahydropyridine-6-thiolate (IXa) in acetic acid in the presence of ammonium acetate, water and quinoline were eliminated to give the known 4-(4-methoxyphenyl)-6-phenyl-3-cyano-2(1H)-pyridinethione (X) [14].



(IXA)

EXPERIMENTAL

The IR spectra of the compounds were obtained on a Specord M-80 in KBr disks. PMR spectra were recorded on a Bruker WM-250 (250 MHz) in solution of DMSO-d_6, with TMS as internal standard. TLC was carried out in the system acetone:hexane (3:5) for (IV) and (V), and DMSO:hexane (2:5) for (IX).

2-Aryl-3-(benzoyl or carbamoyl)-1,1-dicyano-2,3-trans-1,2,3,10b-tetrahydropyrrolo[2,1-a]isoquinolines (IV) and (V). To a mixture of 10 mmoles of the isoquinolinium salt (I) and 10 mmoles of the arylmethylenemalononitrile (III) in 20-25 ml of ethanol was added with stirring 10 mmoles of triethylamine, and the mixture stirred for 4-5 h at ∿25°C The solid was filtered off, washed with ethanol and hexane, and recrystallized from ethanol or methanol. The yields, constants, elemental analyses, IR and PMR spectra for (IV) and (V) are given in Tables 1 and 2.

4-Aryl-2-hydroxy-3-(1-isoquinolinio)-2-phenyl-5-cyano-3,4-trans-1,2,3,4-tetrahydropyridine-6-thiolates (IX). To a mixture of 10 mmoles of the isoquinolinium salt (Ib) and 10 mmoles of the arylmethylenecyanothioacetamide (VII) in 30-40 ml of ethanol was added 10 mmoles of triethylamine, and the mixture stirred for 3-4 h at 25°C. The solid was then filtered off, and washed with ethanol and hexane. For analytical purposes, the compounds (IX) were recrystallized from nitromethane. The yields, constants, elemental analyses, IR and PMR spectra of the compounds (IX) are given in Tables 3 and 4.

4-(4-Methoxyphenyl)-6-phenyl-3-cyano-2(1H)pyridinethione (X). A mixture of 5 mmoles of (IXa) and 15 mmoles of ammonium acetate in 10 ml of acetic acid was boiled for 8 h. The reaction mixture was poured onto 100 g of ice, and the solid filtered off, washed with water and ethanol, and twice recrystallized from nitromethane with decolorizing charcoal to give 68% of (X), mp 225-227°C, the IR spectrum and melting point of which were identical to those previously reported for (X) [14].

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