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Preparation of New Nitrogen-bridged Heterocycles. 6.[1] First Synthesis of 2-Aroylfuro[2,3-*b*]indolizine Derivatives

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Alkaline treatment of 2-(aroylmethoxy)-3-(2,2-dicyanovinyl)indolizine derivatives, readily available from the step-by-step reactions of 1-(ethoxycarbonylmethyl)-2-picolinium salts with a base, (ethoxymethylene)malononitrile followed by some phenacyl bromides in ethanol, afforded smoothly the title compounds, 2-aroylfuro[2,3-*b*]-indolizine derivatives, in good yields. These furoindolizines could be also obtained directly from the pyridinium salts without the isolation of intermediate 3-vinylindolizines. Formation mechanisms and some physical properties of these furoindolizines are also discussed.

Recently, we have found a one-pot synthesis of 2-alkoxy- and 2-acyloxy-3-vinylindolizine derivatives using a single Michael addition of various vinylating agents onto 2(3*H*)-indolizinones generated in situ from the corresponding 1-(ethoxycarbonylmethyl)-2-picolinium salts.[1] Since effective functionalization of indolizine derivatives has been scarcely reported except the cyclization of 2-allylidenedihydropyridines[2] and 3-vinylation of 3-unsubstituted indolizines,[3] this route not only has high value from the stand of synthetic methodology, but also polyfunctionalized compounds, thus obtained, should be useful as a synthone for the transformations from them to fused heterocycles and other synthetic intermediates. In this paper we wish to report the syntheses of the indolizine molecules designed as both possessing an active methylene group and a 2,2-dicyanovinyl group as a masked carbonyl one and their successful transformations to furo[2,3-*b*]indolizine derivatives by an alkaline treatment.

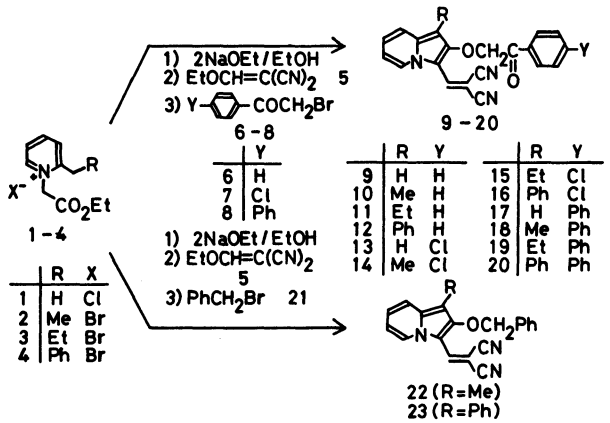
Results and Discussion

Preparations of 2-(Aroylmethoxy)- and 2-(Benzyloxy)-3-(2,2-dicyanovinyl)indolizine Derivatives. The reasons for the selection of 2-(aroylmethoxy)-3-(2,2-dicyanovinyl)indolizines as a model compound in this paper are following: a) The molecules have both a nucleophilic reaction center in the 2-substituent and a vinyl moiety which serves as a potential carbonyl group, and b) the subsequent reaction using these functional groups may provide a useful path to furan-fused heterocycles. These 2-(aroylmethoxy)-3-(2,2-dicyanovinyl)-indolizines **9**—**20** were synthesized from the reactions of 1-(ethoxycarbonylmethyl)pyridinium salts **1**—**4** in ethanol with base and (ethoxymethylene)malononitrile **5**, followed by the alkylations with phenacyl bromides **6**—**8** according to the procedure developed by us.[1] On the other hand, 2-benzyloxy derivatives **22** and **23** were also prepared by similar reactions of salts **2** and **4** using benzyl bromide **21** as an alkylating agent in order to compare their reactivities with those of 2-(aroylmethoxy)indolizines **9**—**20** (Scheme 1).

Structural elucidation of these indolizines **9**—**20**, **22**, and **23** were achieved by their elementary analyses and by their spectral comparisons with those of known 1- and 3-vinylindolizine derivatives.[1-3]

Facile Formation of Furo[2,3-b]indolizine Derivatives. When the retro-aldol reaction of the 2,2-dicyanovinyl group in indolizine **9** to a formyl group was examined in ethanol with an aqueous alkali,[4] the direct formation of 2-benzoylfuro[2,3-*b*]indolizine **25**, red prisms, mp 124—127 °C, was observed instead of initially expected 3-formylindolizines such as **24**. Similar treatment of 2-(aroylmethoxy)indolizines **10**—**20** afforded the corresponding 2-aroylfuro[2,3-*b*]indolizine derivatives **26**—**36** as red crystals in comparatively good yields. On the other hand, the reactions of 2-(benzyloxy)indolizines **22** and **23** with an aqueous alkali did not give furoindolizines such as **39** at all, but yielded 2-(benzyloxy)-3-formylindolizines **37** and **38** as colorless oil and crystals in 79 and 75% yields, respectively. Furthermore, our attempts to prepare 2-phenylfuro[2,3-*b*]indolizine derivatives such as **39** from these 3-formylindolizines **37** and **38** under various basic conditions were unsuccessful (Schemes 2 and 3). Next, we examined the possibility of one-pot synthesis from pyridinium salts **1**—**4** to **25**—**36**, since both formation reactions of 3-vinylindolizines **9**—**20** and furoindolizines **25**—**36** took place always in the same solvent such as ethanol. As might be expected, the same products **25**—**36** could be obtained directly in 10—57% yields by the successive reactions of salt **1**—**4** with sodium ethoxide, (ethoxymethylene)malononitrile **5**, bromides **6**—**8**, and aqueous alkali. Similar furoindolizines **41**—**44** were also formed from the reactions of salt **1**—**4** by using *p*-methylphenacyl bromide **40** as an alkylating agent (Scheme 4).

The structures of furoindolizines **25**—**36** and **41**—**44** were mainly determined by the physical and spectral



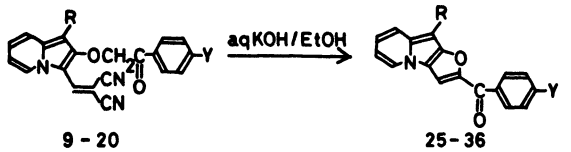
	Y
6	H
7	Cl
8	Ph

	R	Y
9	H	H
10	Me	H
11	Et	H
12	Ph	H
13	H	Cl
14	Me	Cl

	R	Y
15	Et	Cl
16	Ph	Cl
17	H	Ph
18	Me	Ph
19	Et	Ph
20	Ph	Ph

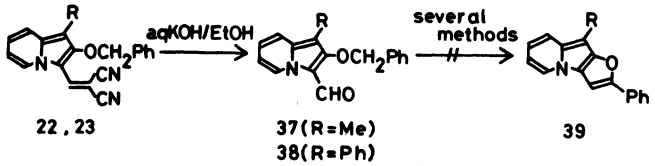
	R	X
1	H	Cl
2	Me	Br
3	Et	Br
4	Ph	Br

Scheme 1.

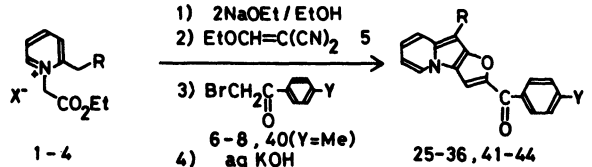


	R	Y		R	Y
25	H	H	31	Et	Cl
26	Me	H	32	Ph	Cl
27	Et	H	33	H	Ph
28	Ph	H	34	Me	Ph
29	H	Cl	35	Et	Ph
30	Me	Cl	36	Ph	Ph

Scheme 2.



Scheme 3.



	R	Y		R	Y
25	H	H	33	H	Ph
26	Me	H	34	Me	Ph
27	Et	H	35	Et	Ph
28	Ph	H	36	Ph	Ph
29	H	Cl	41	H	Me
30	Me	Cl	42	Me	Me
31	Et	Cl	43	Et	Me
32	Ph	Cl	44	Ph	Me

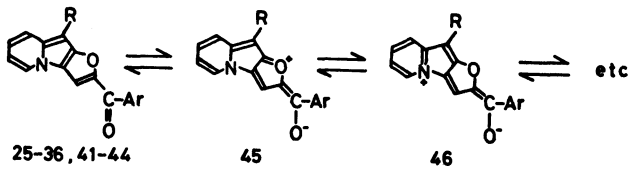
Scheme 4.

means and by the mechanistic consideration of the reactions. In particular, the elementary analyses of **25**—**36** and **41**—**44** were in good accord with the proposed compositions but not with those of initially expected 3-formylindolizines **24** at all. This fact was also supported clearly by the molecular ions in the Mass spectra of 2-benzoylfuro[2,3-*b*]indolizine derivatives **25**—**28**. In the NMR spectra of **25**—**36** and **41**—**44**, all of the skeletal proton signals appeared in an aromatic region and any other signals due to the formyl and the methylene protons could not be detected. For example, the NMR spectrum of **25** exhibited proton signals at δ=6.33 (1H, s), 6.62 (1H, dd, J=7.0 and 1.5 Hz), 6.95 (1H, br t, J=9.0 and 7.0 Hz), 7.58 (1H, s), and 7.3—8.2 (7H, m) due to the 9-H, 6-H, 7-H, 3-H, and 5-, 8-, and phenyl-H, respectively. Similar signal patterns and chemical shifts supporting the furoindolizine structure were always observed in the NMR spectra of compounds **26**—**36** and **41**—**44** (See Table 1). Furthermore, the qualitative tests (Ehrlich, Shear, and Liebermann-Burchard reactions) for furan rings were positive in all cases. Interestingly, the carbonyl absorption bands in the IR spectra of these furoindolizines **25**—**36** and **41**—**44** appeared in extremely lowered region (1592—1618 cm^{-1}), suggesting maybe large contribution of delocalized structures **45** and/or **46** as shown in Scheme 5.

TABLE 1. NMR SPECTRA OF FURO[2,3-*b*] INDOLIZINE DERIVATIVES

Compd No	C-3	C-6	C-7	C-9		C-5,8 and Phenyl-H	
25	7.58	6.62	6.95	6.33		7.3—8.2	
	s	dt	br t	s		m	
26	7.54	6.53	6.88	2.43		7.2—8.2	
	s	dt	br t	s		m	
27	7.57	6.54	6.86	1.40	2.94	7.3—8.2	
	s	dt	br t	t	q	m	
28	b)	6.65	7.02	7.3—8.2		7.3—8.2	
		dt	br t	m		m	
29	7.62	6.60	6.92	6.30		7.3—8.2	
	s	dt	br t	s		m	
30	7.56	6.57	6.92	2.44		7.3—8.3	
	s	dt	br t	s		m	
31	7.58	6.57	6.92	1.41	2.91	7.3—8.2	
	s	dt	br t	s	q	m	
32	b)	6.68	7.02	7.3—8.3		7.3—8.3	
		dt	br t	m		m	
33	7.67	6.59	6.90	6.33		7.3—8.3	
	s	dt	br t	s		m	
34	7.60	6.54	6.88	2.43		7.3—8.3	
	s	dt	br t	s		m	
35	7.62	6.50	6.83	1.39	2.88	7.3—8.3	
	s	dt	br t	s	q	m	
36	b)	6.65	7.00	7.3—8.3		7.3—8.3	
		dt	br t	m		m	
41	7.54	6.57	6.87	6.30		7.1—8.2	2.44[c]
	s	dt	br t	s		m	s
42	7.54	6.52	6.87	2.43		7.1—8.2	2.43[c]
	s	dt	br t	s		m	s
43	7.60	6.56	6.90	1.43	2.93	7.1—8.2	2.48[c]
	s	dt	br t	t	q	m	s
44	7.70	6.67	7.02	7.2—8.3		7.2—8.3	2.48[c]
	s	dt	br t	m		m	s

a) The coupling constants of these molecules were as follows; $J_{5,6}=J_{6,7}=7.0$ Hz, $J_{7,8}=9.0$ Hz, $J_{6,8}=1.5$ Hz, and $J_{Et}=7.0$ Hz. b) Overlapped with the phenyl signals. c) The methyl signal of the *p*-methylbenzoyl group.

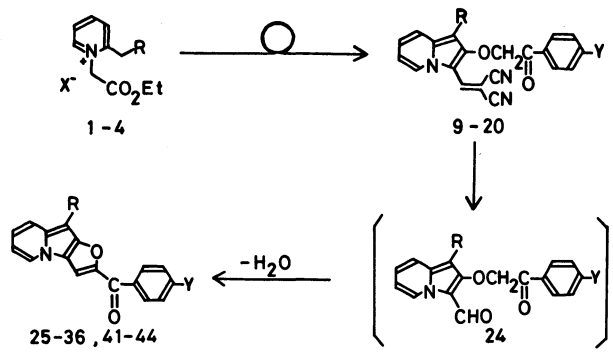


Scheme 5.

On the other hand, compounds **37** and **38** were determined to be 2-benzyloxy-3-formylindolizine derivatives, since their NMR spectra showed the presences of the formyl protons (δ=9.73 (**37**) and 9.79 (**38**)) and the methylene protons (δ=5.22 (**37**) and 4.88 (**38**)), and the elementary analysis of **38** were in accord with the suggested structure.

Mechanistically, the formation reaction of furoindolizines **25**—**36** and **41**—**44** can be explain reasonably by the intermediacy of 2-(aroylmethoxy)-3-formylindolizines such as **24** *via* the retro-aldol reaction of 2-(aroylmethoxy)-3-(2,2-dicyanovinyl)indolizine deriva-

tives and subsequent intramolecular aldol reaction between the 2- and 3-substituents in **24** (Scheme 6). Since 2-(benzyloxy)-3-fromylindolizines **37** and **38** from 3-vinylindolizines **22** and **23** were actually isolated and the utility of the 2,2-dicyanovinyl group as a masked carbonyl is extensively realized,[4] the former hypothesis seems to be undoubtful. The latter reaction is also one of the most important methods for the syntheses of fused furans.[5] The failure to obtain 2-phenylfuro[2,3-*b*]-indolizines such as **39** from 2-(benzyloxy)-3-formylindolizines **22** and **23** must be owing to low acidity of the methylene group of the 2-substituent in contrast with that of the 2-aroylmethoxy group in indolizine derivatives such as **9**—**20**.



Scheme 6.

Experimental

Melting points were measured with a Yanagimoto MP-S3 micromelting point apparatus and are uncorrected. Microanalyses were carried out on a Perkin-Elmer 240 elemental analyzer. NMR spectra were determined with a Varian EM360A NMR spectrometer in deuteriochloroform with tetramethylsilan as an internal standard, chemical shifts expres-

Table 2. Some data of 3-vinylindolizinederivatives

Compd No.	Reactant	Yield %	Mp θ_m/°C	KBr $\nu_{C=O}$ cm^{-1}	KBr ν_{CN} cm^{-1}	Formula	Calcd (%) C	Calcd (%) H	Calcd (%) N	Found (%) C	Found (%) H	Found (%) N
9	**1 5 6**	19	211—213	1687	2200	$C_{20}H_{13}N_3O_2$	73.38	4.00	12.84	73.53	4.10	12.60
10	**2 5 6**	61	225—227	1690	2195	$C_{21}H_{15}N_3O_2$	73.89	4.43	12.31	73.81	4.37	12.44
11	**3 5 6**	49	203—207	1696	2200	$C_{22}H_{17}N_3O_2$	74.35	4.82	11.82	74.28	4.93	11.78
12	**4 5 6**	56	198—201	1688	2195	$C_{26}H_{17}N_3O_2$	77.41	4.25	10.42	77.37	4.19	10.51
13	**1 5 7**	3	243—245	1690	2200	$C_{20}H_{12}N_3O_2Cl$	66.40	3.34	11.61	66.29	3.48	11.58
14	**2 5 7**	39	217—219	1697	2201	$C_{21}H_{14}N_3O_2Cl$	67.12	3.76	11.18	66.89	3.84	11.32
15	**3 5 7**	32	202—204	1699	2207	$C_{22}H_{16}N_3O_2Cl$	67.78	4.14	10.78	67.89	4.17	10.70
16	**4 5 7**	53	182—184	1691	2199	$C_{26}H_{16}N_3O_2Cl$	71.32	3.68	9.60	71.48	3.72	9.56
17	**1 5 8**	2	240—243	1691	2210	$C_{26}H_{17}N_3O_2$	77.41	4.25	10.42	77.21	4.33	10.53
18	**2 5 8**	69	218—221	1689	2195	$C_{27}H_{19}N_3O_2$	77.68	4.59	10.07	77.72	4.63	9.99
19	**3 5 8**	57	199—202	1696	2210	$C_{28}H_{21}N_3O_2$	77.94	4.91	9.74	78.12	5.01	9.46
20	**4 5 8**	48	188—191	1698	2201	$C_{32}H_{21}N_3O_2$	80.15	4.41	8.76	79.94	4.57	8.93
22	**2 5 21**	65	140—142	—	2206	$C_{20}H_{15}N_3O$	76.66	4.83	13.41	76.73	4.95	13.21
23	**4 5 21**	68	170—172	—	2185	$C_{25}H_{17}N_3O$	79.98	4.56	11.19	79.86	4.70	11.17

Table 3. Some data of furo[2,3-*b*]indolizine derivatives

Compd No.	Reactant No. (No.)[a]	Yield % (%)[a]	Mp θ_m/°C	KBr $\nu_{C=O}$ cm^{-1}	Formula	Calcd (%) C	Calcd (%) H	Calcd (%) N	Found (%) C	Found (%) H	Found (%) N
25	**9 (1 5 6)**	97 (12)	124—127	1618	$C_{17}H_{11}NO_2$	78.15	4.24	5.36	77.90	4.27	5.57
26	**10 (2 5 6)**	95 (57)	119—121	1609	$C_{18}H_{13}NO_2$	78.52	4.75	5.08	78.36	4.83	5.17
27	**11 (3 5 6)**	82 (46)	117—119	1595	$C_{19}H_{15}NO_2$	78.87	5.22	4.84	78.68	5.36	4.88
28	**12 (4 5 6)**	99 (46)	186—188	1600	$C_{23}H_{15}NO_2$	81.88	4.48	4.15	81.75	4.65	4.11
29	**13 (1 5 7)**	73 (17)	185—187	1608	$C_{17}H_{10}NO_2Cl$	69.05	3.41	4.74	68.82	3.47	4.68
30	**14 (2 5 7)**	88 (39)	197—199	1602	$C_{18}H_{12}NO_2Cl$	69.80	3.91	4.52	69.71	3.87	4.61
31	**15 (3 5 7)**	84 (42)	188—190	1604	$C_{19}H_{14}NO_2Cl$	70.48	4.36	4.33	70.32	4.37	4.47
32	**16 (4 5 7)**	51 (31)	227—229	1595	$C_{23}H_{14}NO_2Cl$	74.30	3.80	3.77	74.04	3.89	3.87
33	**17 (1 5 8)**	60 (14)	171—173	1605	$C_{23}H_{15}NO_2$	81.88	4.48	4.15	81.86	4.59	4.07
34	**18 (2 5 8)**	76 (49)	200—203	1596	$C_{24}H_{17}NO_2$	82.03	4.88	3.99	81.93	4.89	4.07
35	**19 (3 5 8)**	65 (25)	154—156	1597	$C_{25}H_{19}NO_2$	82.17	5.24	3.83	82.08	5.30	3.87
36	**20 (4 5 8)**	50 (28)	208—210	1594	$C_{29}H_{19}NO_2$	84.24	4.63	3.39	84.01	4.62	3.18
41	**(1 5 40)**	(11)	154—156	1597	$C_{18}H_{13}NO_2$	78.53	4.76	5.09	78.53	4.80	5.04
42	**(2 5 40)**	(44)	135—137	1592	$C_{19}H_{15}NO_2$	78.87	5.22	4.84	78.68	5.24	4.86
43	**(3 5 40)**	(25)	153—155	1598	$C_{20}H_{17}NO_2$	79.19	5.65	4.62	79.40	5.63	4.42
44	**(4 5 40)**	(41)	212—213	1595	$C_{24}H_{17}NO_2$	82.03	4.88	3.99	82.09	4.89	3.92

a) One-pot synthesis.

sed in terms of δ, mass spectra done with a JEOL LMS-01SG-2 mass spectrometer with a JEC-6 spectrocomputer attached, and IR spectra taken with a Hitachi 260-10 Infrared spectrophotometer.

Preparations of 3-(2,2-Dicyanovinyl)indolizine Derivatives ***9—20, 22, and 23.*** *General Method*: To an ethanolic solution (70 ml) of 1-(ethoxycarbonylmethyl)-2-picolinium salt (3 mmol), an ethanolic sodium ethoxide (6 ml, 6 mmol), (ethoxymethylene)malononitrile **5** (3 mmol), and phenancyl bromide (3.5 mmol) were added step-by-step at intervals of 3 min at 60—70 °C. After kept for an hour at this temperature, the reaction mixture was chilled to room temperature. Because of the extremely low solubility of 3-(2,2-dicyanovinyl)indolizines **9—20**, **22**, and **23**,[6] their isolations were carried out by filtrating crude indolizines precipitated from the reaction solution or separated by pouring into water (200 ml). Recrystallizations of the crude compounds from ethanol or chloroform gave pure **9—20**, **22**, and **23** as yellow needles. These results and some properties are given in Table 2.

*Preparations of 2-Aroylfuro[2,3-*b*]indolizine Derivatives* ***25—36 and 41—44.*** *Method A*: To an ethanolic suspension (50 ml) of 2-(aroylmethoxy)-3-(2,2-dicyanovinyl)indolizine (1 mmol), aqueous potassium hydroxide (2 g in 5 ml of water) was added rapidly. After the suspended indolizine was completely disappeared and the resulting solution turned red (about 3—5 min), the reaction mixture was poured into 200 ml of water, neutralized carefully with diluted hydrochloric acid, and extracted twice with chloroform (100 ml). The combined extract was filtered through phase separating filter and the resulting filtrate concentrated at reduced pressure. Recrystallizations of crude products from ethanol or chloroform gave the corresponding 2-aroylfuro[2,3-*b*]indolizines **25—36** as red or dark red crystals. These results and some properties are shown in Tables 1 and 3.

Method B: To the reaction mixture described in the preparations of 3-vinylindolizines **9—20**, aqueous potassium hydroxide (2 g in 5 ml of water) was added and, after 5 min, the resulting reddish solution was poured into 200 ml of water. The aqueous solution was neutralized with diluted hydrochloric acid, extracted twice with chloroform (100 ml), and the combined solution was filtered through phase separating filter and then the filtrate concentrated at reduced pressure. The residue was separated by column chromatography (alumina) using ether and then chloroform as eluents. Recrystallizations from ethanol or chloroform gave the corresponding furoindolizines **25—36**. Similar treatment of the reaction mixtures using *p*-methylphenacyl bromide **40** as an alkylating agent gave furoindolizines **41—44**. These results and some properties are summarized in Tables 1 and 3.

Preparations of 2-(Benzyloxy)-3-formylindolizines ***37*** *and* ***38.*** These 3-formylindolizines were prepared according to the procedure (Method A) described above. Some data of compounds **37** and **38** are as follows: **37**: 79%, colorless oil, ν (Neat) 1620 cm^{-1} (C=O), $\delta(CDCl_3)=2.23$ (3H, s, 1-Me), 5.22 (2H, s, OCH_2), 6.7—7.6 (8H, m 6-, 7-, 8-, and phenyl-H), 9.61 (1H, d, $J=7.0$ Hz, 5-H), and 9.73 (1H, s, CHO). Because of its unstability, pure specimen for its elemental analysis could not be obtained.

38: 75%, colorless prisms, mp 106—107 °C, ν(KBr) 1668 cm^{-1} (C=O), $\delta(CDCl_3)=4.88$ (2H, s, OCH_2), 6.7—7.8 (13H, m, 6-, 7-, 8-, and two phenyl-H), 9.62 (1H, d, $J=7.0$ Hz, 5-H), and 9.79 (1H, s, CHO). Found: C, 80.72; H, 5.40; N, 4.18%. Calcd for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23; N, 4.28%.

Furthermore, our attempts to obtain 2-phenylfuroindolizines such as **39** from these compounds **37** and **38** under some alkaline conditions (ethanolic sodium ethoxide, potassium *t*-butoxide, and potassium acetate–acetic anhydride) were unsuccessful.

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6) The NMR spectra of 2-(aroylmethoxy)-3-vinylindolizine derivatives **9—20** except 2-benzyloxy analogs **22** and **23** could not be measured from the same reason. The NMR spectra of **22** and **23** were as follows: **22**: $\delta(CDCl_3)=2.20$ (3H, s, 1-Me), 5.24 (2H, s, OCH_2), 6.7—7.6 (9H, m, 6-, 7-, 8-, vinyl-, and phenyl-H), and 8.30 (1H, br d, $J=7.0$ Hz, 5-H). **23**: $\delta(CDCl_3)=4.92$ (2H, s, OCH_2), 6.7—7.7 (14H, m, 6-, 7-, 8-, vinyl-, and two phenyl-H), and 8.30 (1H, br d, $J=7.0$ Hz, 5-H).