Synthesis Using Pyridinium Anhydrobases. Preparation of Indolizine Derivatives

P. Molina*, P. M. Fresneda and M. C. Lájara

Departamento de Química Orgánica, Facultad de Ciencias,
Universidad de Murcia, Murcia, Spain

Received May 8, 1984

A number of derivatives of indolizine ring system have been prepared from 1-substituted 4,6-diphenyl-2-phenacylidene-1,2-dihydropyridines either by metallation with LDA or acylation and further basic treatment. Similarly, 1-arylmethyl-4,6-diphenyl-2-dicyanomethylene-1,2-dihydropyridines by action of LDA undergo cyclization to the corresponding 2-amino-1-cyano-3-aryl indolizines.

J. Heterocyclic Chem., **22**, 113 (1985).

Several methods have been adopted for the synthesis of indazoline derivatives and have been comprehensively reviewed [1,2]; new routes continue to appear [3,4,5]. Intramolecular cyclization of 1-substituted 1,2-dihydropyridines is an useful standard method for preparing indazolines, thermal [6], alkaline [7] or acid [8] treatment have so far been the conditions of choice.

In continuation of the study on the chemistry of 2-functionalized pyridinium cations [9] and as part of a program designed to prepare bridgehead nitrogen heterocycles we have studied the preparation and cyclization reactions of the anhydrobases 1-substituted-4,6-diphenyl-2-phenacylidene-1,2-dihydropyridines **2** and 1-arylmethyl-4,6-diphenyl-2-dicyanomethylene-1,2-dihydropyridines **7**. 1-Substituted-4,6-diphenylpyridine-2-thiones, themselves readily available from 4,6-diphenylpyran-2-thione and primary amines [10], react with a series of phenacyl bromides in tetrahydrofuran at room temperature to yield the corresponding pyridinium bromides **1** as crystalline solids in high yields (Table 1).

The ir spectra of compounds **1** show absorption in the region 1650-1685 cm^{-1} due to the stretching vibration of the carbonyl group. The proton nmr spectra show among others a singlet at δ 5.5-5.8 ppm due to the S-CH_2-CO group, while the methylene group linked to the pyridine ring appears at δ 4.12-4.16 ppm for R = H and at δ 5.92-5.96 ppm for R = Ar. By thermal treatment the pyridinium bromides **1** decompose to 2-phenacylthio-4,6-diphenylpyridine and the bromide corresponding to the *N*-linked group, however, sodium benzenethiolate reacts on the *S*-linked methylene group of the pyridinium **1** to give α-phenylthioacetophenones and 1-substituted 4,6-diphenylpyridine-2-thiones respectively.

When ethanolic solutions of the pyridiniums **1** are treated with triethylamine the colour of the reaction mixture turns deep red indicating the formation of the anhydroba-

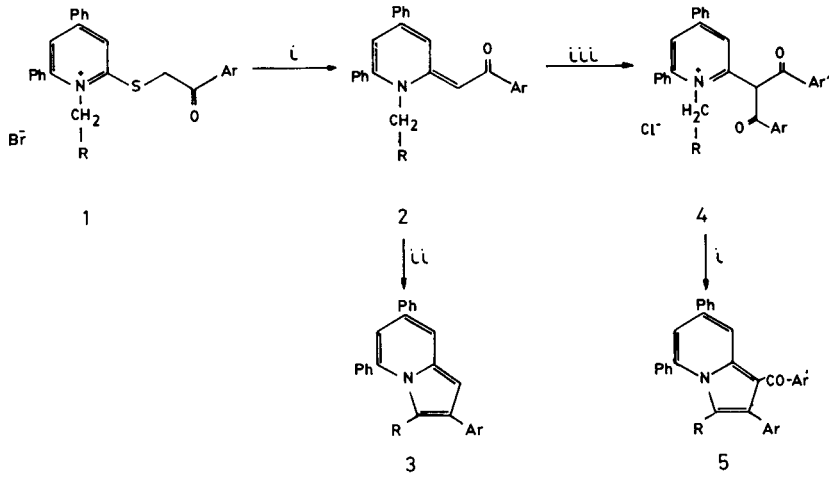
Table 1

1-Substituted 4,6-Diphenyl-2-phenacylthiopyridinium Bromides **1**

Compound No.	R	Ar	Yield (%)	Mp (°C)	Molecular Formula	Analysis % Calcd./Found C	H	N
1a	C_6H_5	C_6H_5	83	151	$C_{32}H_{26}BrNOS$	69.56	4.74	2.54
					(552.54)	69.50	4.63	2.45
1b	C_6H_5	4-Br-C_6H_4	95	145	$C_{32}H_{25}Br_2NOS$	60.87	3.99	2.22
					(631.44)	60.77	3.88	2.10
1c	4-Cl-C_6H_4	C_6H_5	99	107	$C_{32}H_{25}BrClNOS$	65.48	4.29	2.38
					(586.98)	65.35	4.31	2.26
1d	4-Cl-C_6H_4	4-Br-C_6H_4	88	132-134	$C_{32}H_{24}Br_2ClNOS$	57.71	3.63	2.10
					(665.98)	57.60	3.74	2.14
1e	4-H_3C-C_6H_4	C_6H_5	92	120	$C_{33}H_{28}BrNOS$	69.96	4.98	2.47
					(566.57)	69.92	4.95	2.43
1f	4-H_3C-C_6H_4	4-Br-C_6H_4	94	125-127	$C_{33}H_{27}Br_2NOS$	61.41	4.22	2.17
					(645.47)	61.37	4.28	2.05
1g	H	C_6H_5	98	162	$C_{26}H_{22}BrNOS$	65.48	4.65	2.94
					(476.44)	65.38	4.69	2.85
1h	H	4-Br-C_6H_4	97	187	$C_{26}H_{21}Br_2NOS$	56.23	3.81	2.52
					(555.34)	56.31	3.89	2.48
1i	H	4-Cl-C_6H_4	98	189	$C_{26}H_{21}BrClNOS$	61.12	4.14	2.74
					(510.89)	61.02	4.20	2.70
1j	H	4-CH_3O-C_6H_4	91	121	$C_{27}H_{24}BrNO_2S$	64.03	4.77	2.76
					(506.47)	63.98	4.81	2.75

Table 1 (Continuation)

Compound No.	IR (ν cm^{-1}) (Nujol)	^{1}H-NMR δ (ppm) (Deuteriochloroform)
1a	1670, 1605, 1595, 1535, 1450, 1380, 1300, 1285, 1160, 1000, 970, 770, 740, 700, 690	8.7 (1H, s), 8.5 (1H, s), 8.0-8.7 (20H, m), 5.9 (2H, s), 5.80 (2H, s)
1b	1690, 1610, 1580, 1540, 1450, 1390, 1375, 1200, 1160, 995, 820, 770, 760, 730, 700	8.7 (1H, s), 8.5 (1H, s), 8.0-7.0 (19H, m), 6.0 (2H, s), 5.85 (2H, s)
1c	1680, 1605, 1535, 1490, 1380, 1215, 1150, 1090, 780, 770, 710, 690	8.7 (1H, s), 8.4 (1H, s), 8.0-6.9 (19H, m), 5.95 (2H, s), 5.8 (2H, s)
1d	1680, 1610, 1595, 1535, 1490, 1450, 1395, 1375, 1205, 1150, 1070, 990, 810, 780, 770, 700, 680	8.7 (1H, s), 8.5 (1H, s), 8.0-6.8 (18H, m), 6.0 (2H, s), 5.85 (2H, s)
1e	1676, 1614, 1546, 1461, 1376, 1319, 1291, 1211, 1155, 996, 769, 685	8.7 (1H, s), 8.5 (1H, s), 8.0-6.9 (19H, m), 5.95 (2H, s), 5.85 (2H, s), 2.3 (3H, s)
1f	1700, 1620, 1590, 1550, 1470, 1390, 1280, 1225, 1200, 1180, 1075, 1000, 900, 840, 785, 780, 775, 715	8.7 (1H, s), 8.5 (1H, s), 8.0-6.7 (18H, m), 5.9 (2H, s), 5.8 (2H, s), 2.3 (3H, s)
1g	3050, 1675, 1610, 1590, 1540, 1400, 1375, 1210, 1175, 1090, 990, 775, 760, 700, 685	8.4 (1H, s), 8.1 (1H, s), 8.0-7.54 (15H, m), 5.74 (2H, s), 4.16 (3H, s)
1h	3050, 1675, 1610, 1590, 1540, 1470, 1400, 1380, 1210, 1100, 1075, 1000, 820, 770, 705	8.5 (1H, s), 8.2 (1H, s), 8.0-7.5 (14H, m), 5.7 (2H, s), 4.15 (3H, s)
1i	3050, 1670, 1615, 1590, 1570, 1540, 1375, 1200, 1090, 895, 825, 780, 770, 705, 700	8.4 (1H, s), 8.1 (1H, s), 8.1-7.4 (14H, m), 5.6 (2H, s), 4.16 (3H, s)
1j	3050, 1665, 1615, 1600, 1540, 1470, 1370, 1270, 1210, 1175, 990, 835, 785, 780, 770, 710	8.3 (1H, s), 8.1 (1H, s), 7.9-6.8 (14H, m), 5.58 (2H, s), 4.12 (3H, s), 3.82 (3H, s)



Reagents : i) Et_3N ; ii) LDA/THF-78°C ; iii) Ar'-COCl

Scheme 1

ses 1-substituted-2-phenacylidene-1,2-dihydropyridines **2**, which are isolated as crystalline solids in very good yields (Table 2). The reaction seems to be applicable for R = H and R = Ar, however, when R = 4-$CH_3OC_6H_4$, 2-phenacylthio-4,6-diphenylpyridine and *p*-methoxybenzyl bromide were found to be the only reaction products.

Support for the formulation of **2** is clearly provided by their spectral data. The ir spectra show a combination of variable absorptions in the region 1560-1630 cm^{-1} due to the conjugated alkene stretching vibration and α,β-unsaturated ketone stretching. Comparison of the proton nmr spectra of these compounds with those of the parent pyridiniums **1** is instructive. In particular, the peak for the *S*-methylene group has disappeared and the signal corresponding to the =CH-CO- group now appears near to the aromatic proton signals. Mass spectra show the expected molecular ion peak and the fragmentation pattern is in accord with the proposed structure (Table 2).

Metallation of **2** (R = Ar) with lithium diisopropylamide at −78° leads to the corresponding 2,3-diarylindolizines **3**, which are isolated as yellow crystals in excellent yields (Table 3), however, attempts at cyclization of **2** (R = H) failed because of the comparatively poor reactivity of the *N*-methyl group. Treatment of the anhydrobases **2** with ar-

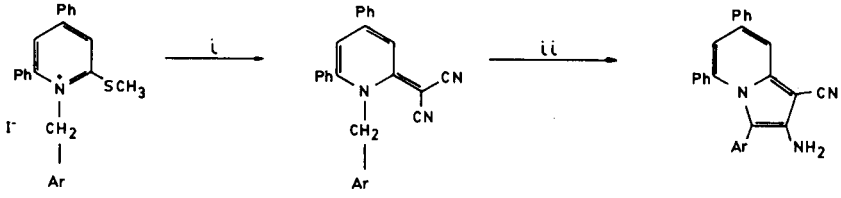
oyl chlorides lead to the pyridinium chlorides **4** which are isolated as crystalline solids. When pyridinium **4** (R = Ar = Ar' = C_6H_5) is treated with triethylamine, the corresponding indolizine derivative **5** is isolated in moderate yield (Table 4).

When Ar and Ar' are different in pyridinium **4**, only one regioisomer is isolated as reaction product. Thus, the pyridinium **4** (Ar = 4-BrC_6H_5, Ar' = C_6H_5) leads to 1-(*p*-bromobenzoyl)-2,3,5,7-tetraphenylindolizine, whereas the pyridinium **4** (Ar = C_6H_5, Ar' = 4-$CH_3C_6H_4$) gave 1-benzoyl-2-(*p*-methylphenyl)-3,5,7-triphenylindolizine.

Structural elucidation of indolizines **3** and **5** were achieved by their elementary analyses and by their spectral data. In particular mass spectrometry has been an useful tool in this study and provides a decisive method for structural assignments for compounds **5**. Thus, the mass spectra of **5** show the expected molecular ion as the base peak, peaks are also found at m/e M^+-ArCO and at m/e Ar-CO^+, by contrast peaks corresponding to the fragments Ar'CO and M^+-Ar'CO are absent.

The preparation of compounds **3** and **5** provides a route to indolines which involves ring closure at the 2,3-position in the indolizine ring by an intramolecular aldol-type condensation. This method is conceptually similar to the Chichibabin synthesis based on the quaternisation of derivatives of α-picoline with α-halogenocarbonyl compounds and treatment of the salts with bases and acetic anhydride.

On the other hand, 1-arylmethyl-4,6-diphenyl-2-methylthiopyridinium iodides **6**, readily available from 1-arylmethyl-4,6-diphenylpyridine-2-thiones and methyl iodide



6 7 8

Reagents: i) $CH_2(CN)_2$ / Et_3N ; ii) LDA / THF - 78°C

Scheme 2

Table 2

1-Substituted 4,6-Diphenyl-2-phenacylidene-1,2-dihydropyridines **2**

Compound No.	R	Ar	Yield (%)	Mp (°C)	Molecular Formula	Analysis % Calcd./Found C	H	N
2a	C_6H_5	C_6H_5	92	173	$C_{32}H_{25}NO$	87.44	5.73	3.18
					(439.56)	87.52	5.60	3.14
2b	C_6H_5	4-Br-C_6H_4	95	186	$C_{32}H_{24}BrNO$	74.13	4.67	2.70
					(518.46)	74.10	4.53	2.82
2c	4-Cl-C_6H_4	C_6H_5	76	167	$C_{32}H_{24}ClNO$	81.09	5.10	2.95
					(474.00)	81.19	5.12	2.90
2d	4-Cl-C_6H_4	4-Br-C_6H_4	71	188	$C_{32}H_{23}BrClNO$	69.52	4.19	2.53
					(552.90)	69.40	4.14	2.62
2e	4-CH_3-C_6H_4	C_6H_5	73	185	$C_{33}H_{27}NO$	87.38	6.00	3.09
					(453.58)	87.30	5.90	3.03
2f	4-CH_3-C_6H_4	4-Br-C_6H_4	85	188	$C_{33}H_{26}BrNO$	74.44	4.92	2.63
					(532.50)	74.32	4.83	2.60
2g	H	C_6H_5	53	217	$C_{26}H_{21}NO$	85.91	5.82	3.85
					(363.46)	86.00	5.77	3.82
2h	H	4-Br-C_6H_4	50	250	$C_{26}H_{20}BrNO$	70.59	4.55	3.16
					(442.36)	70.46	4.52	3.18
2i	H	4-Cl-C_6H_4	50	246	$C_{26}H_{20}ClNO$	78.48	5.06	3.52
					(397.9)	78.36	5.10	3.48
2j	H	4-CH_3O-C_6H_4	53	210	$C_{27}H_{23}NO_2$	82.41	5.89	3.56
					(393.48)	82.36	5.94	3.57

Table 2 (Continuation)

Compound No.	IR (ν cm^{-1}) (Nujol)	^{1}H-NMR δ (ppm) (Deuteriochloroform)	MS m/e (%)
2a	1630, 1595, 1565, 1530, 1500, 1480, 1380, 1360, 1320, 1260, 1220, 1155, 1080, 1065, 1030, 900, 880, 845, 775, 760, 740, 730, 710	8.2-7.1 (21H, m), 6.7 (1H, s), 6.1 (1H, d), 5.1 (2H, s)	439 (10), 438 (10), 422 (11), 421 (35), 353 (38), 352 (45), 335 (13), 334 (44), 320 (18), 230 (19), 202 (26), 189 (11), 171 (11), 115 (18), 105 (100), 102 (12), 91 (82), 77 (84)
2b	1630, 1600, 1579, 1555, 1505, 1475, 1380, 1370, 1335, 1255, 1150, 1075, 1010, 900, 875, 845, 840, 790, 770, 760, 740, 705	7.8-7 (20H, m), 6.7 (1H, s), 5.65 (1H, d), 5.1 (2H, s)	519 (12), 518 (17), 517 (12), 516 (17), 501 (17), 500 (14), 499 (17), 335 (27), 334 (100), 230 (5), 215 (12), 203 (14), 202 (22), 189 (10), 185 (60), 183 (63), 157 (32), 155 (32), 115 (11), 105 (5), 104 (11), 102 (10), 91 (92), 77 (23)
2c	1630, 1570, 1560, 1530, 1510, 1490, 1480, 1410, 1380, 1260, 1230, 1155, 1080, 1010, 880, 850, 840, 760, 710	8.1-7.2 (20H, m), 6.75 (1H, s), 5.75 (1H, d), 5.15 (2H, s)	475 (1), 473 (3), 456 (4), 455 (5), 454 (2), 368 (2), 320 (8), 230 (4), 331 (3), 215 (3), 203 (6), 202 (8), 189 (3), 125 (23), 115 (10), 106 (8), 105 (100), 102 (5), 91 (14), 89 (11), 77 (70)
2d	1630, 1570, 1560, 1530, 1510, 1490, 1480, 1410, 1380, 1260, 1230, 1155, 1080, 1010, 880, 850, 840, 760, 710	7.8-7.1 (19H, m), 6.75 (1H, s), 6.1 (1H, d), 5.1 (2H, s)	554 (6), 553 (10), 552 (13), 551 (7), 550 (9), 537 (14), 536 (19), 535 (50), 534 (30), 533 (37), 532 (13), 371 (9), 370 (35), 369 (28), 368 (100), 319 (5), 317 (6), 230 (7), 215 (11), 203 (16), 202 (33), 201 (12), 189 (16), 185 (82), 183 (83), 155 (41), 157 (43), 127 (26), 125 (54), 104 (13), 77 (28)
2e	1625, 1568, 1528, 1483, 1477, 1325, 1251, 1217, 1155, 1064, 843, 764, 735, 713, 690	7.8-7.1 (20H, m), 6.75 (1H, s), 5.85 (1H, d), 5.15 (2H, s), 2.4 (3H, s)	454 (4), 453 (13), 452 (15), 435 (10), 349 (20), 348 (65), 320 (4), 215 (5), 203 (5), 202 (8), 189 (3), 106 (10), 105 (100), 103 (6), 91 (4), 77 (45)
2f	1635, 1560, 1530, 1500, 1480, 1460, 1425, 1375, 1330, 1260, 1220, 1160, 1080, 1015, 910, 880, 850, 800, 770, 710, 690	7.8-6.95 (19H, m), 6.75 (1H, s), 5.7 (1H, s), 5.1 (2H, s), 2.35 (3H, s)	533 (8), 532 (12), 531 (9), 530 (10), 516 (5), 515 (10), 514 (7), 513 (10), 512 (4), 349 (31), 348 (100), 230 (4), 215 (7), 204 (3), 203 (9), 202 (14), 201 (3), 185 (30), 183 (32), 157 (19), 155 (20), 105 (76), 91 (7), 77 (20)
2g	3060, 1630, 1470, 1380, 1290, 1260, 1230, 1200, 1150, 1070, 1025, 895, 880, 780, 770,	8.01-7.3 (16H, m), 6.65 (1H, s), 5.79 (1H, s), 3.4 (3H, s)	363 (77), 335 (26), 321 (26), 277 (100), 258 (55), 244 (42), 215 (25), 202 (20), 105 (31), 77 (26)
2h	3060, 1635, 1500, 1470, 1380, 1265, 1230, 1205, 1155, 1010, 880, 775, 770, 760, 750	8.1-7.3 (15H, m), 6.7 (1H, s), 5.7 (1H, s), 3.4 (3H, s)	442 (100), 440 (87), 424 (6), 412 (16), 414 (16), 363 (3), 332 (3), 277 (53), 257 (41), 215 (6), 127 (57), 125 (23), 105 (6), 77 (6)
2i	3060, 1630, 1620, 1560, 1535, 1500, 1470, 1380, 1310, 1170, 1160, 1100, 790, 780, 775, 770, 730, 710, 700	8.2-7.3 (15H, m), 6.65 (1H, s), 5.65 (1H, s), 3.45 (3H, s)	399 (17), 397 (50), 396 (100), 381 (5), 368 (20), 354 (6), 277 (53), 257 (23), 243 (18), 242 (11), 241 (12), 215 (21), 202 (18), 141 (15), 139 (50), 111 (47), 77 (49)
2j	3060, 1630, 1520, 1495, 1475, 1380, 1305, 1250, 1225, 1170, 1100, 1070, 1030, 835, 820, 810, 780, 775, 765, 715	8.1-7.2 (15H, m), 6.7 (1H, s), 5.7 (1H, s), 3.82 (3H, s), 3.4 (3H, s)	

Table 3

2,3-Diaryl-5,7-diphenylindazolines **3**

Compound No.	R	Ar	Yield (%)	Mp (°C)	Molecular Formula	Analysis % Calcd./Found C	H	N
3a	C_6H_5	C_6H_5	92	160	$C_{32}H_{23}N$	91.18	5.50	3.32
					(421.5)	91.25	5.65	3.30
3b	C_6H_5	4-Br-C_6H_4	80	182	$C_{32}H_{22}BrN$	76.80	4.43	2.80
					(500.4)	76.98	4.40	2.70
3c	4-Cl-C_6H_4	C_6H_5	72	217	$C_{32}H_{22}ClN$	84.29	4.86	3.07
					(455.99)	84.35	4.72	3.02
3d	4-Cl-C_6H_4	4-Br-C_6H_4	79	213	$C_{32}H_{21}BrClN$	71.85	3.96	2.26
					(534.89)	71.82	3.73	2.50
3e	4-CH_3-C_6H_4	C_6H_5	82	213	$C_{32}H_{25}N$	91.00	5.79	3.22
					(435.6)	90.93	5.64	3.10
3f	4-CH_3-C_6H_4	4-Br-C_6H_4	86	204	$C_{33}H_{24}BrN$	77.04	4.70	2.72
					(514.47)	77.01	4.58	2.73

Table 3 (Continuation)

Compound No.	IR (ν cm^{-1}) (Nujol)	MS m/e (%)
3a	1600, 1460, 1380, 1320, 1295, 1165, 1130, 1070, 1030, 870, 865, 775, 765, 760, 705, 700, 690	421 (81), 420 (38), 344 (13), 202 (43), 195 (23), 191 (10), 190 (12), 189 (30), 178 (5), 171 (100), 115 (18), 113 (8), 105 (26), 102 (10), 91 (12), 77 (50)
3b	1605, 1500, 1465, 1390, 1325, 1180, 1145, 1080, 1020, 895, 850, 790, 770, 715	501 (100), 499 (100), 420 (8), 343 (13), 341 (11), 211 (45), 210 (55), 202 (69), 195 (31), 190 (16), 189 (50), 177 (7), 176 (10), 170 (77), 157 (17), 156 (16), 155 (8), 115 (10), 77 (41)
3c	1600, 1500, 1470, 1370, 1320, 1170, 1130, 1095, 1030, 1020, 870, 860, 835, 820, 770, 705	457 (35), 455 (100), 454 (47), 378 (10), 344 (5), 208 (12), 202 (23), 201 (12), 189 (18), 190 (5), 171 (25), 170 (16), 77 (20)
3d	1600, 1510, 1500, 1460, 1580, 1520, 1170, 1135, 1095, 1020, 1015, 860, 835, 775, 705	537 (28), 536 (38), 535 (100), 534 (58), 533 (58), 532 (27), 456 (5), 454 (7), 453 (7), 421 (4), 378 (4), 377 (6), 211 (14), 210 (17), 209 (32), 208 (34), 207 (20), 202 (34), 201 (19), 189 (18), 188 (11), 170 (33), 169 (18), 77 (20)
3e	1600, 1400, 1381, 1319, 1116, 1132, 1070, 1024, 877, 803, 707, 696	435 (98), 434 (45), 343 (17), 217 (28), 209 (23), 208 (27), 203 (38), 202 (83), 201 (30), 195 (26), 189 (47), 188 (17), 178 (20), 176 (20), 170 (26), 139 (17), 115 (22), 102 (21), 92 (68), 91 (46), 77 (100)
3f	1600, 1463, 1377, 1317, 1303, 1284, 1164, 1124, 1071, 1011, 759, 699	515 (100), 514 (70), 513 (99), 512 (40), 209 (17), 208 (20), 207 (11), 202 (32), 170 (15), 92 (13), 91 (14), 77 (17)

Table 4

Compounds **4** and **5** Prepared

Compound No.	R	Ar	Ar'	Yield (%)	Mp (°C)	Molecular Formula	Analysis % Calcd./Found C	H	N
4a	C_6H_5	C_6H_5	C_6H_5	82	127	$C_{39}H_{30}ClNO_2$	80.75	5.21	2.41
						(580.13)	80.62	5.13	2.34
4b	C_6H_5	C_6H_5	4-Br-C_6H_4	79	130	$C_{39}H_{29}BrClNO_2$	71.08	4.44	2.13
						(659.03)	71.15	4.31	2.12
4c	C_6H_5	4-CH_3-C_6H_4	C_6H_5	70	165	$C_{40}H_{32}ClNO_2$	80.86	5.43	2.36
						(594.15)	80.83	5.51	2.43
5a	C_6H_5	C_6H_5	C_6H_5	65	235	$C_{39}H_{27}NO$	89.11	5.18	2.66
						(525.7)	89.19	5.15	2.53
5b	C_6H_5	C_6H_5	4-Br-C_6H_4	62	187	$C_{39}H_{26}BrNO$	77.48	4.34	2.32
						(604.55)	77.36	4.42	2.30
5c	C_6H_5	4-CH_3-C_6H_4	C_6H_5	60	218	$C_{40}H_{29}NO$	89.02	5.42	2.60
						(539.7)	89.12	5.33	2.39

Table 4 (Continuation)

Compound No.	IR (ν cm^{-1}) (Nujol)	MS m/e (%)
4a	1739, 1620, 1597, 1552, 1495, 1455, 1415, 1376, 1240, 1177, 1161, 1081, 1064, 1025, 1002, 894, 849, 770, 713, 696	
4b	1735, 1650, 1615, 1595, 1550, 1485, 1460, 1450, 1415, 1380, 1240, 1170, 1080, 1065, 1115, 1005, 890, 840, 825, 770, 725, 710	
4c	1728, 1649, 1562, 1456, 1377, 1244, 1184, 1084, 770, 756, 730, 691	
5a	1631, 1602, 1506, 1483, 1467, 1376, 1217, 1161, 1127, 1076, 1025, 934, 906, 764, 696	525 (100), 524 (12), 449 (10), 448 (27), 420 (21), 262 (40), 208 (10), 202 (16), 105 (34), 77 (43)
5b	1631, 1622, 1507, 1474, 1458, 1376, 1072, 916, 760, 695	605 (100), 604 (49), 603 (100), 449 (24), 448 (64), 421 (30), 420 (65), 302 (52), 301 (50), 240 (15), 215 (18), 202 (34), 185 (60), 183 (60), 157 (40), 155 (40), 103 (18), 77 (56)
5c	1630, 1619, 1602, 1579, 1506, 1483, 1460, 1449, 1376, 1217, 1155, 1121, 1075, 1024, 905, 758, 696	539 (100), 538 (12), 462 (22), 434 (15), 269 (25), 202 (10), 105 (28), 77 (41)

Table 5

Compound **7** and **8** Prepared

Compound No.	Ar	Yield (%)	Mp (°C)	Molecular Formula	Analysis % Calcd./Found C	H	N
7a	C_6H_5	88	174	$C_{27}H_{16}N_3$ (385.47)	84.13 84.28	4.97 4.71	10.90 10.89
7b	4-CH_3-C_6H_4	85	177	$C_{28}H_{21}N_3$ (399.5)	84.18 84.02	5.30 5.25	10.52 10.68
7c	4-Cl-C_6H_4	83	171	$C_{27}H_{18}ClN_3$ (419.91)	77.23 76.94	4.32 4.17	10.00 9.78
8a	C_6H_5	75	115	$C_{27}H_{19}N_3$ (385.47)	84.13 83.95	4.97 5.06	10.90 10.85
8b	4-CH_3-C_6H_4	77	192	$C_{28}H_{21}N_3$ (399.5)	84.18 84.06	5.30 5.12	10.52 10.31
8c	4-Cl-C_6H_4	80	183	$C_{27}H_{18}ClN_3$ (410.91)	77.23 77.10	4.32 4.54	10.00 9.84

Table 5 (Continuation)

Compound No.	IR (ν cm^{-1}) (Nujol)	^{1}H-NMR δ (ppm) (Deuteriochloroform)	MS m/e (%)
7a	2197, 2174, 1625, 1500, 1455, 1376, 1348, 1278, 1144, 1058, 1030, 968, 889, 849, 775, 764, 730, 696	8-6.8 (17H, m), 5.75 (2H, s)	385 (22), 359 (17), 294 (10), 241 (7), 231 (7), 202 (10), 164 (8), 91 (100)
7b	2191, 2174, 1631, 1580, 1540, 1500, 1461, 1376, 1347, 1325, 1280, 1149, 1064, 968, 928, 917, 868, 856, 851, 795, 767, 700	7.92-6.83 (16H, m), 5.75 (2H, s), 3.06 (3H, s)	399 (5), 384 (5), 373 (10), 360 (5), 334 (6), 308 (6), 230 (12), 105 (100), 91 (10), 77 (20)
7c	2193, 2172, 1630, 1599, 1547, 1504, 1493, 1477, 1460, 1448, 1418, 1377, 1335, 1286, 1138, 1097, 1061, 1030, 1012, 866, 850, 802, 769, 762, 702, 688	7.75-7.15 (16H, m), 5.72 (2H, s)	421 (18), 419 (56), 394 (10), 308 (15), 295 (35), 232 (100), 103 (40), 164 (37), 128 (20), 126 (58)
8a	3466, 3374, 3328, 2214, 1631, 1597, 1545, 1489, 1461, 1387, 1376, 1223, 1127, 1081, 1030, 849, 753, 702		385 (100), 384 (77), 368 (11), 308 (16), 307 (15), 202 (15), 178 (17), 177 (15), 165 (25), 154 (54), 151 (17), 140 (21), 127 (25), 104 (20), 77 (89)
8b	3477, 3364, 3222, 3202, 1631, 1546, 1517, 1500, 1461, 1393, 1376, 1325, 1217, 1121, 1030, 849, 820, 764, 753, 696, 679		399 (100), 398 (75), 382 (10), 322 (10), 307 (10), 202 (5), 191 (5), 179 (5), 164 (4), 115 (5), 91 (10), 77 (14)
8c	3449, 3347, 3199, 2203, 1636, 1614, 1597, 1546, 1489, 1461, 1381, 1127, 1093, 1013, 860, 832, 758, 696		421 (34), 419 (100), 418 (73), 385 (19), 384 (20), 307 (20), 270 (33), 263 (28), 203 (20), 202 (35), 191 (23), 177 (23), 165 (19), 153 (34), 140 (20), 139 (35), 127 (30), 125 (17), 111 (24), 102 (28), 91 (20), 77 (70)

[9], react with malononitrile in the presence of triethylamine to give the corresponding 1-arylmethyl-2-dicyanomethylene-1,2-dihydropyridines **7** in very good yields. The reaction can be performed in ethanolic solution at reflux temperature for 14 hours. Support for the formulation of **7** is clearly provided by their spectral data. The ir spectra of **7** show two strong absorption bands at 2170 and 2190 cm^{-1} respectively, attributable to the cyano groups stretching; the proton nmr spectra show among others a singlet at δ 5.75 ppm corresponding to the N-CH_2- group. Mass spectra show the expected molecular ion peak and the fragmentation pattern are in accord with the proposed structure.

Metallation of **7** with lithium diisopropylamide at −78° lead to the corresponding 2-amino-1-cyano-3-aryl indolizines **8**, which are isolated as yellow crystals in good yields (Table 5). The ir spectra of **8** show absorption bands near 3300 and 3400 cm^{-1} due to the amino group and at 2200 cm^{-1} due to the cyano group. Mass spectra are in accord with the proposed structure.

EXPERIMENTAL

The melting points were determined with a Kofler hot stage microscope and were uncorrected. The ir spectra were recorded on mineral oil mulls with a Nicolet-FT 5DX instrument. The proton nmr spectra were recorded with a Varian EM-360 instrument with TMS as the internal

standard. Mass spectra were obtained with a Hewlett-Packard 5993C GC/MS system; compounds were introduced through the direct insertion probe. Microanalyses were performed with a Perkin-Elmer 240C instrument.

Reagents.

4,6-Diphenylpyran-2-thione was prepared from 4,6-diphenyl-2-pyrone and phosphorus pentasulfide [10]. 1-Substituted 4,6-diphenylpyridine-2-thiones were prepared from 4,6-diphenylpyran-2-thione and primary amines [11].

1-Substituted 4,6-Diphenyl-2-phenacylthiopyridinium Bromides **1**. General Procedure.

To a solution of 1-substituted-4,6-diphenylpyridine-2-thione (6 mmoles) in dry benzene (30 ml), the appropriate phenacyl bromide (6 mmoles) was added. The reaction mixture was stirred at room temperature for 5 hours. The resultant precipitated solid was collected by filtration and recrystallized from dichloromethane/ether (1:1) to give **1** (Table 1).

Thermolysis of Pyridinium Bromides **1**. Typical Procedure.

The pyridinium bromide **1a** (4 mmoles) was heated at a temperature slightly above its melting point (160°) under reduced pressure (1 torr). The distillate was collected in a cold trap (−36°). The product thus collected was benzyl bromide, proton nmr analysis of the product shows no impurities. The residue was treated with ether and the resulting solid recrystallized from methanol/chloroform to give 4,6-diphenyl-2-phenacylthiopyridine as white needles, mp 141-142°; ir (nujol): 3060, 2920, 1690 (s), 1590 (s), 1530 (s), 1490, 1440, 1385, 1270, 1225, 1220, 1150, 1070, 1060, 1030, 1000, 990, 860, 770, 750 (s), 690 (s), 650 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 8.07 (1H, s), 7.82 (1H, s), 7.63-7.36 (15H, m), 5.78 (2H, s); ^{13}C-nmr (deuteriochloroform): 192.6 (C=O), 43.62 ($-CH_2-$).

Anal. Calcd. for $C_{25}H_{19}NOS$: C, 78.72; H, 5.02; N, 3.67. Found: C, 78.56; H, 4.93; N, 3.71.

Reaction of Pyridinium Bromides **1** with Sodium Benzenethiolate. General Procedure.

To a solution of pyridinium bromide **1** (3 mmoles) in dry methanol (20 ml) an equimolecular amount of sodium benzenethiolate was added. The reaction mixture was refluxed for 2 hours. After cooling at room temperature, the corresponding *N*-substituted 4,6-diphenylpyridine-2-thione was separated and collected by filtration. To the filtrate the solvent was removed and the residue extracted with dichloromethane (2 × 10 ml). Elimination of the solvent from extracts leads to the crude α-phenylthioacetophenone which was purified by sublimation.

By the above procedure the following compounds were prepared: α-phenylthioacetophenone (60%); α-phenylthio-*p*-bromoacetophenone (72%); α-phenylthio-*p*-chloroacetophenone (65%); α-phenylthio-*p*-phenylacetophenone (80%); α-phenylthio-*p*-methoxyacetophenone (77%); and α-phenylthio-*p*-nitroacetophenone (75%).

Preparation of Anhydrobases **2**. General Procedure.

To a solution of pyridinium bromide **1** (3 mmoles) in ethanol (50 ml), triethylamine (4.5 mmoles) was added. The reaction mixture was refluxed for 15 minutes. After cooling, the red precipitated solid was collected by filtration and recrystallized from ethanol to give **2** (Table 2).

Preparation of 2,3-Diaryl-5,7-diphenylindazolines **3**. General Procedure.

A solution of diisopropyl amine (10 ml) in dry tetrahydrofuran (20 ml) was cooled at −78° and 1.6 molar *n*-butyllithium in hexane (0.78 ml, 8.5 mmoles) was added under nitrogen. The resultant solution was stirred for 30 minutes and the solution of the appropriate anhydrobase **2** (6 mmoles) in tetrahydrofuran (10 ml) was added. The reaction mixture was stirred for 1 hour and allowed to warm to room temperature for 12 hours. The solution was poured into an ammonium chloride solution and the organic layer washed with water (3 × 10 ml) and dried with anhydrous sodium sulfate. The solvent was removed to dryness and the residual material recrystallized from ethanol/benzene (2:1) gave **3** as yellow solids (Table 3).

Preparation of 1-Aroyl-2,3-diaryl-5,7-diphenylindolizines **5**. General Procedure.

To a solution of *N*-substituted-4,6-diphenyl-2-phenacylidene-1,2-dihydropyridine **2** (2 mmoles) in dry tetrahydrofuran (20 ml), the appropriate aroyl chloride (2.4 mmoles) was added. The reaction mixture was stirred at room temperature for 3 hours. The precipitated solid was collected by filtration and recrystallized from dichloromethane/ether gave **4** as a crystalline solid (Table 4).

To a solution of **4** (5 mmoles) in ethanol (20 ml), triethylamine (10 ml) was added. The reaction mixture was refluxed for 5 hours. After cooling, the red precipitated solid was filtered and recrystallized from ethanol/benzene (2:1) to give **5** (Table 4).

Préparation of 1-Arylmethyl-4,6-diphenyl-2-dicyanomethylene-1,2-dihydropyridine **7**. General Procedure.

To a solution of pyridinium iodide **6** (3 mmoles) in ethanol (20 ml), malononitrile (3.5 mmoles) and triethylamine (3.5 mmoles) were added. The reaction mixture was refluxed for 14 hours. After cooling, the separated solid was collected by filtration and recrystallized from ethanol to give **7** as crystalline solids in good yields (Table 5).

Preparation of 2-Amino-1-cyano-3-aryl-5,7-diphenylindolizines **8**. General Procedure.

A solution of diisopropylamine (10 mmoles) in dry tetrahydrofuran (20 ml) was cooled at −78° and 1.6 molar *n*-butyllithium in hexane (0.78 ml, 8.5 mmoles) was added under nitrogen. The resultant solution was stirred for 30 minutes and a solution of the appropriate 1-arylmethyl-2-dicyanomethylene-1,2-dihydropyridine **7** (6 mmoles) in tetrahydrofuran (10 ml) was added. The reaction mixture was stirred for 1 hour and allowed to warm to room temperature for 12 hours. The solution was poured into an ammonium chloride solution and the organic layer washed with water (3 × 10 ml) and dried with anhydrous sodium sulfate. The solvent was removed to dryness and the residual material recrystallized from ethanol/benzene (2:1) to give **8** (Table 5).

Acknowledgement.

The authors wish to thank the Comisión Asesora de Investigación Científica y Técnica for supporting this research.

REFERENCES AND NOTES

[1] F. J. Suinbourne, J. H. Hunt and G. Klinkert, "Advances in Heterocyclic Chemistry", Vol **23**, Academic Press, New York, 1978, p 103.

[2] T. Uchida and K. Matsumoto, *Synthesis*, 209 (1976).

[3] A. Oshawa, Y. Abe and H. Igeta, *Bull. Chem. Soc. Japan*, **53**, 3273 (1980).

[4] R. S. Sagitullin, S. P. Gromov and A. Y. Sergeikin, *Khim. Geterotsikl. Soedin.*, **5**, 702 (1981).

[5] T. Abe, A. Ahsawa and H. Igeta, *Chem. Pharm. Bull.*, **30**, 881 (1982).

[6] A. Kakehi, S. Ito, T. Maeda, R. Takeda, M. Nishimura, M. Tamashima and T. Yamaguchi, *J. Org. Chem.*, **43**, 4837 (1978).

[7] A. Kakehi, S. Ito, T. Ohizumi and M. Ito, *Bull. Chem. Soc. Japan*, **56**, 1219 (1983).

[8] H. Pauls and F. Kröhnke, *Chem. Ber.*, **110**, 1294 (1977).

[9] P. Molina, M. Alajarin, A. Ferao, M. J. Lidon, P. M. Fresneda and M. J. Vilaplana, *Synthesis*, 472 (1982) and references cited therein.

[10] E. I. Kholy, F. K. Rafla and M. M. Mishrikey, *J. Chem. Soc., (C)*, 1598 (1970).

[11] P. Molina, A. Lorenzo and M. J. Vilaplana, *Synthesis*, 853 (1980).