Studies on Pyridazine Derivatives. IV (1). Mesylation Reaction of Pyridazinylpyrazoles

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On mesylation, 1-pyridazinylpyrazoles (**1**), give, depending on the substituents and reaction conditions, *O*-mesylpyrazoles (**2**) and *O*-mesyl-4-*N*-mesyl-1,4-dihydro-4-pyridyl-pyrazole derivatives (**3**). The structures of these compounds were confirmed by ir and ^{1}H nmr spectral data.

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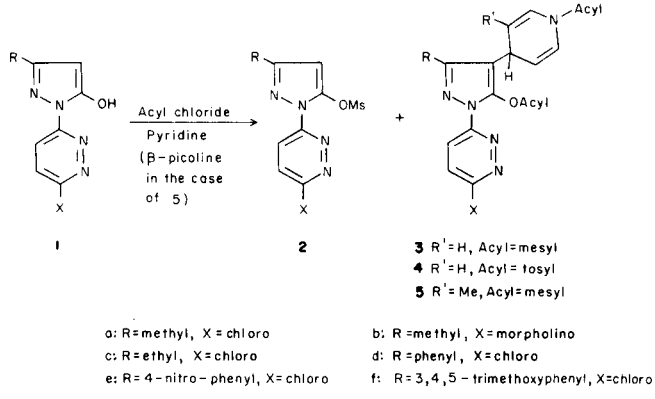
It has already been established that ring substituted 1-phenyl- and 1-benzyl-3-methyl-2-pyrazolin-5-ones can be acylated in high yields by alkyl- and arylsulphonyl chlorides (using benzene as a solvent in the presence of either potassium carbonate or pyridine) to give the respective *O*-sulphonyl derivatives (2,3).

Acylation of pyridazinylpyrazoles **1a-f** (4,5) with mesyl chloride in pyridine at room temperature gave the expected *O*-monomesyl derivatives (**2d,e,f**) only in case of compounds **1d,e** and **f** (6), while the analogues **1a,b** and **c** were converted into the dimesyl compounds **3a-c**, depending on the mole ratio of the reactants. The monomesyl compounds **2a-c** were formed in only minor quantities (7,8). The solvent plays an important role in the reaction. In tetrahydrofuran, in the presence of equimolar amounts of pyridine, **1a** is acylated by mesyl chloride to the monomesyl derivative **2a** as the major product at mole ratios of 1:1 and 1:2, respectively. Considering the electron distribution of *N*-acylpyridinium compounds (electrophilic centres (9)), the formation of 2-pyridyl derivatives may also be expected. However, compounds of this type were not found.

The structures of compounds **3a-c**, **4** and **5** were proved by ^{1}H nmr spectral data (see Table 1). As in the case of the monoacyl analogues **2**, the signals for the pyrazole ring substituents in positions 1 and 2, as well as the methyl singlet for the mesyl group in the case of compound **4**, and for the tosyl group in compound **5**, were observed. However, the signal of the pyrazole proton in position 4 disappeared, and the characteristic multiplets of the 1,4-dihydropyridine moiety were found at 4.3, 4.9 and 6.6 ppm (1:2:2 intensity), and were assigned to the protons in positions 4, 3, and 2, respectively. Since the multiplets in the spectra of **3a-c** and **4** were symmetric at their centres, the protons of the dihydropyridine moiety formed an AA'BXX' spin system, the 1,4-dihydro structure was proved (the theoretically possible 2-pyridyl, *i.e.*, 1,2-dihydro structure, could be ruled out).

The assumed structure of type **3** was also confirmed by synthesis.

Mesylation of compound **1a** in 2- and 4-picoline, respectively, yielded the monomesyl derivative **2a**, while in



3-picoline, the dimesyl analogue **5a** was also formed as a by-product.

In the spectrum of compound **5a**, the respective multiplets are asymmetric; the middle peak at about 4.9 ppm, originating from the proton in the β-5-position, corresponds to an intensity of 1H. The double doublet structure shows that the H-2, -6, -5 and -4 atoms represent an ABMX spin system ($\delta_A > \delta_B > \delta_M > \delta_X$), where $J_{AM} = J_{2,5} = J_{\alpha,\beta} < 1$ Hz, thus causing no significant splitting. The singlet of the 3-methyl group appears at 1.60 ppm. All these data confirm structure **5a**, as well as the analog structures **3a-c**, and **4**.

In the literature, only a few compounds of type **3** have been described. A similar type of reaction has been published for indole (10); the postulated reaction mechanism (11) may also be valid for compounds **3a-e**.

On the basis of structure **3**, the influence of the pyrazole substituent R on the product ratio for the reaction becomes apparent, *i.e.*, with increasing bulkiness of R the amount of derivatives of type **3** diminishes.

EXPERIMENTAL

Melting points were determined in a Boetius apparatus and are uncorrected. Ir spectra were recorded in potassium bromide pellets on a Perkin-Elmer 557 spectrometer; the nmr spectra were recorded on a JEOL 60 HL at 60 MHz, at room temperature, using TMS as internal standard. The compounds prepared in this study are summarized in Table 2.

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Table 1

Characteristic Ir and ^{1}H Nmr Data for Compounds **1a-f**, **2a,b,d-f**, **3a-c**, **4a** and **5a**

Compound Number	Ir Data Potassium Bromide (cm^{-1}) Characteristic Bands	^{1}H Nmr Data in DMSO-d_6 Solution (δ TMS = 0 ppm) (u) δ CH_3 (R) s 3H	δ CH_3 *N*-Ms s 3H	δ CH_3 *O*-Ms s 3H	δ H-γ DHPy m (b) 1H	δ H-β DHPy m (b) 2H	δ H-α DHPy m (b) 2H	β H-4 Pyrazole s 1H	δ H-4' Pyridazine 1H	δ H-5' Pyridazine 1H	Other Signals
1a	ν NH: 3300-2400; amide-I,II: 1640, 1415	2.30	—	—	—	—	—	5.25	8.72 (j)	7.98 (j)	—
1b	ν NH: 3300-2700; amide-I,II: 1635, 1445: ν C-O morpholine: 1120	2.25	—	—	—	—	—	5.25	8.23 (j)	7.47 (j)	3.7 (c) 8H
1c	ν NH: 3300-2500; amide-I,II: 1635, 1420	1.15 (h)	—	—	—	—	—	? (i)	8.65 (j)	7.65 (j)	—
1d (a)	ν NH: -; amide-I,II: -; phenyl: 760,690	—	—	—	—	—	—	6.00	8.20 (j)	7.75 (d,j)	435-455 m (k) 3H 460-475 m (k) 2 + 1H (d)
1e	ν NH: -; amide-I: -; nitro: 1570, 1335, 850	—	—	—	—	—	—	? (i)	8.62 (j)	7.83 (j)	8.02 (m) 2H 8.20 (m) 2H
1f	ν NH: -; amide-I: -; methoxy: 2820, 1120	3.75 (f) 3.90 (f)	—	—	—	—	—	6.10	8.48 (j)	7.95 (j)	7.20 s 2H (g)
2a	sulphone: 1375, 1190	2.35	—	3.60	—	—	—	6.50	8.10 s 2H		—
2b (a)	sulphone: 1370-1350, 1195; ν C-O morpholine: 1115	2.30	—	3.40	—	—	—	6.15	7.00 (j)	7.65 (j)	3.75 (c) 8H
2d (a)	sulphone: 1380-1365, 1190; phenyl: 775, 700	—	—	3.50	—	—	—	6.70	7.45 (j)	8.07 (j)	430-450 m (k) 3H 455-470 m (k) 2H
2e	sulphone: 1370-1350, 1200-1190; nitro: 1520, 1350, 835	—	—	3.70	—	—	—	7.40	8.30 s 6H (n)		—
2f	sulphone: 1375, 1190; methoxy: 2840, 1130	3.80 (f) 3.95 (f)	—	3.70	—	—	—	7.25 (d)	8.30 (j)	8.10 (j)	7.30 s 2 + 1H (d,g)
3a	sulphone: 1380-1370, 1180-1165; DHPy: 1680	2.35	3.30	3.70	4.35	4.95	6.70	—	8.15 s 2H		—
3b	sulphone: 1375-1360, 1185-1165; ν C-O morpholine: 1120; DHPy: 1680	2.25	3.20	3.50	4.30	4.90	6.45	—	7.67 (j)	7.43 (j)	3.65 (c) 8H
3c	sulphone: 1375-1365, 1185-1370; DHPy: 1680	1.30 (h)	3.25	3.65	4.40	4.95	6.65	—	8.10 s 2H		—
4a	sulphone: 1390-1375, 1195-1175; *p*-disubstituted phenyl: 815-810; DHPy: 1680	1.95	2.40 (p)	2.45 (p)	4.30	4.85	6.65	—	420-70 m 10H (o)		—
5a	sulphone: 1390-1370, 1185-1165; DHPy: 1690	2.30	3.25	3.70	4.30	4.90 (e,s)	6.6 (e)	—	8.15 (s)	2H	1.6 s (t) 3H

(a) ^{1}H Nmr data measured in deuteriochloroform. (b) Symmetric multiplet at the centre. (c) Centre of the AA'BB' multiplet of morpholine. (d) Overlapped signals. (e) For 2xd, $J_{\alpha,\beta} \approx J_{5,6} = 4$ Hz; $J_{\beta,\gamma} \approx J_{4,5} = 9$ Hz. (f) Methoxy signals of 9H intensity. (g) Signal of the aromatic protons. (h) For t, J = 7 Hz, 3H ethyl group. The methylene quartet appears at 2.40 (**1c**) and 2.75 (**3c**) ppm, respectively. (i) Insignificant signal because of fast hydrogen-deuterium exchange rate processes in solution. (j) A or B part of an AB quartet, $J_{AB} = 9$ Hz. (k) The multiplets (in Hz) of *meta*, *para* and *ortho* protons of the phenyl ring. (l) Overlapped, asymmetric multiplets of the α-protons (in position 2 and 6, respectively). (m) The chemical shifts of the 2,6- and 3,5 protons of the *p*-disubstituted phenyl ring, calculated by the AB-approximation from the AA'BB' multiplet, $J_{Ab} = 9$ Hz. (n) The singlet of H-4',5' overlapped with the singlet (as the AA'BB' multiplet approximates the A_4-limiting case) of the *p*-disubstituted aromatic ring. (o) The overlapped AA'BB' multiplets of the two tosyl rings and the AB quartet of the pyridazine protons. (p) Methyl groups of the tosyl substituents. (s) Asymmetric multiplet of the β- and γ-protons (in positions 5 and 4, respectively) of 1-1 H intensity. (t) Methyl group of the β-picolyl substituent. (u) Abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet; Ms, mesyl; DHPy, 1,4-dihydropyridine ring.

General Procedure for the Synthesis of **1a-f** (4).

A mixture of 3-hydrazino-6-X-pyridazine (for X = chloro see reference 12 and for X = morpholino see reference 13) (10 mmoles), the appropriate β-oxo ethyl ester (10 mmoles) and ethanol (10 ml.) was heated under reflux for 3 hours. The mixture was then cooled and 1 ml. of concentrated aqueous ammonia was added. Stirring was continued for 4 hours at room temperature and the mixture was allowed to stand overnight. The crystals which precipitated were collected by filtration, dried and recrystallized.

Preparation of *O*-Methylsulphonyl Compounds.

The *O*-methylsulphonyl compounds were prepared by either of the following two methods.

Method A.

This method was used for the preparation of compounds **2d-f**, **3a-c**, **4a** and **5a**. Mesyl chloride (tosyl chloride in the case of **4a**) (6 mmoles) was added to **1a-f** (5 mmoles) in pyridine (3-picoline in the case of **5a**) (15 ml.) at 0-5° and stirring was continued for 4 hours at room temperature. The solution was subsequently poured onto ice, the resulting precipitate filtered and the crude product recrystallized.

Method B.

This method was used for the preparation of compounds **2a,b**. Mesyl chloride (5.5 mmoles) was added dropwise at 0-5° to **1a,b** (2.5 mmoles) dissolved in a mixture of pyridine (5.5 mmoles) and tetrahydrofuran (7 ml.), and stirring was continued for 5 hours at room temperature. The solution was left to stand for 12 hours, then the solvent was evaporated *in vacuo* and the residue was recrystallized.

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REFERENCES AND NOTES

(1) Part III, G. Szilágyi, E. Kasztreiner, L. Tardos, L. Jaszlits, E. Kósa, Gy. Cseh, P. Tolnay and I. Kovács-Szabó, *Eur. J. Med. Chem.*, **14**, 439 (1979).

Table 2

Analytical Data for Compounds **1a-f, 2a,b,d-f, 3a-c, 4a** and **5a**

Compound No.	M.p. °C (Solvent)	Yield %	Formula	Analysis % Calculated C	H	N	S	Found C	H	N	S
1a	234-237 (Ethanol) (a)	86	$C_8H_7ClN_4O$	45.62	3.35	26.60	—	34.32	3.57	26.42	—
1b	215-217 (Ethanol)	55	$C_{12}H_{15}N_5O_2$	55.16	5.78	26.81	—	55.32	5.91	26.85	—
1c	200-202 (Methanol)	64	$C_9H_9ClN_4O$	48.11	4.04	24.94	—	47.88	4.32	24.74	—
1d	162-164 (Isopropanol)	73	$C_{13}H_9ClN_4O$	55.21	6.77	19.81	—	55.49	6.85	19.68	—
1e	222-223 (Ethanol)	93	$C_{13}H_8ClN_5O_3$	49.15	2.54	22.05	—	49.01	2.65	21.80	—
1f	209-211 (Ethanol)	57	$C_{16}H_{15}ClN_4O_4$	52.97	4.17	15.45	—	53.09	4.32	15.22	—
2a	144-145 (Ethanol)	49	$C_9H_9ClN_4O_3S$	37.44	3.14	19.41	11.11	37.22	3.35	19.22	11.01
2b	155-157 (Ethanol)	40	$C_{13}H_{17}N_5O_4S$	46.00	5.05	20.64	9.45	45.74	5.36	20.30	9.83
2d	125-127 (Isopropanol)	77	$C_{14}H_{11}ClN_4O_3S$	47.93	3.16	15.97	9.14	47.95	3.38	15.55	9.11
2e	204-205 (Ethanol)	43	$C_{14}H_{10}ClN_5O_5S$	42.48	2.55	17.70	8.10	42.41	2.71	17.31	7.75
2f	206-208 (Ethanol)	66	$C_{17}H_{17}ClN_4O_6S$	46.31	3.89	12.71	7.27	46.65	4.05	12.59	7.42
3a	196-197 (Ethanol)	40	$C_{15}H_{16}ClN_5O_5S_2$	40.40	3.62	15.71	14.38	40.80	3.60	15.30	14.20
3b	188-190 (Ethanol)	26	$C_{19}H_{24}N_6O_6S_2$	45.95	4.87	16.93	12.91	46.11	4.81	16.72	12.63
3c	158-159 (Ethanol)	29	$C_{16}H_{18}ClN_5O_5S_2$	41.78	3.94	15.23	13.94	41.61	4.11	15.02	13.51
4a	170-173 (Ethanol)	25	$C_{27}H_{24}ClN_5O_5S_2$	54.22	4.04	11.72	10.72	54.01	4.01	11.59	10.61
5a	194-196 (Ethanol) (b)	6	$C_{16}H_{18}ClN_5O_5S_2$	41.78	3.94	15.23	13.94	41.61	3.98	15.11	13.69

(a) F. Kuhelj, B. Stanovnik and M. Tisler, *Croat. Chim. Acta,* **38**, 299 (1966); *Chem. Abstr.,* **66**, 55458y (1967), report m.p. 232-233°. (b) **1a**:mesyl chloride = 1:2.

(2) G. A. Galoyan, S. G. Agbalyan and G. T. Esayan, *Arm. Khim. Zh.,* **22**, (5), 430 (1969); *Chem. Abstr.,* **71**, 70535t (1969).

(3) *Belgian Patent* 823,507 (1975).

(4) Hungarian Patent Application GO-1381 (1977); *Belgian Patent* 868,987 (1978).

(5) Theoretically, compounds **1** may exist in the aromatic hydroxypyrazole (see Formula) or in the 4,5- and 2,5-dihydropyrazol-5-one structure, *i.e.* 2- and 3-pyrazoline forms, respectively. The NH and amide-I bands in the ir spectra (see Table 1) show that in the solid phase, compounds **1a-c** are in the 2,5-dihydropyrazole form, while **1d-1f**, devoid of these bands, exist presumably as hydroxypyrazoles. In the ^{1}H nmr spectra of **1a, 1b, 1d** and **1f**, the H-4 signals have chemical shifts characteristic for olefinic protons. Thus, in solution, the 4,5-dihydropyrazole structure can also be excluded.

(6) The *O*-mesyl structure of compounds **2** is confirmed by both the lack of the amide-I ir band and the chemical shift of the methyl signal in the ^{1}H nmr spectra. This shift would be much smaller in the case of *N*-substituted analogues of the 2,5-dihydropyrazole tautomer (see the chemical shift of the *N*- and *O*-mesyl signals for compounds **3a-c**),

(7) Tosylation of **1a** yielded the ditosyl derivative **4a**, analogous to **3a**.

(8) With a ratio of **1a** to mesyl chloride of 1:1 or 1:2, respectively, the yield of **3a** is 40 and 48%, respectively.

(9) R. A. Abramovich, "Pyridine and its Derivatives, The Chemistry of Heterocyclic Compounds", Vol. 14, Supplement, Part I, John Wiley and Sons, Inc., New York, N.Y., 1974, p. 376.

(10) H. von Dobeneck and W. Goltzsche, *Chem. Ber.,* **95**, 1484 (1962).

(11) J. Bergman, *J. Heterocyclic Chem.,* **7**, 1071 (1970).

(12) N. Takahayashi, *Yakugaku Zasshi,* **75**, 778 (1955); *Chem. Abstr.,* **50**, 4970b (1956).

(13) E. Bellasio, F. Parravicini and E. Testa, *Farmaco, Ed. Sci.,* **24**, 919 (1969); *Chem. Abstr.,* **72**, 121471z (1970).