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A series of two *N*-substituted-3(5)acyl-4-ethoxycarbonyl-5(3)substituted isomeric pyrazoles underwent ring closure with hydrazine and methylhydrazine to give the new anticipated *N*(1)- or *N*(2)alkyl-3,7-disubstituted pyrazolopyridazin-4(5*H*)ones. The purpose of this study was to determine distinguishing criteria between the two isomers. From the comparative ^{1}H- and ^{13}C-nmr spectra, sufficiently significant differences were observed. Uv and ir spectra showed no significant differences.

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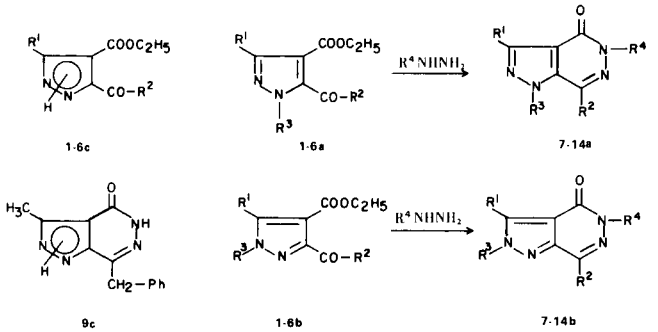
The conversion of 3(5)acyl-4-ethoxycarbonylpyrazole derivatives to pyrazolo[3,4-*d*]pyridazines has been recently described (1,2). The behavior of these purine isosteres toward alkylating agents is interesting, but a source of difficulty is inherent in assigning *N*(1)- or *N*(2)alkyl isomers. This topic apparently has not been studied. This paper deals with the conversion of *N*-alkylpyrazole isomers **1-6a** and **1-6b** to *N*(1)- or *N*(2)alkylpyrazolopyridazines (**7-14a** and **7-14b**). The structural assignment of compounds **1-6a,b** carried out in this laboratory (3) has been accomplished on the basis of the ^{1}H- and ^{13}C-nmr by comparison with appropriate structural models which have been reported recently in the pyrazole literature (4-8). The present work is concerned with the problem of finding spectral properties as a means for the characterization of the *N*-alkylated pyrazolopyridazin-4(5*H*)ones obtained in alternate synthesis.

The action of hydrazine hydrate on compounds **1-6a,b** produced the isomeric 1*H*- and 2*H*-*N*-alkylpyrazolo[3,4-*d*]pyridazin-4(5*H*)ones (**7-10a,b** and **12-13a,b**). The compounds **3,5a,b** were converted to 1*H*-, 2*H*-1,5- and 2,5-*N*-dialkylated pyrazolo[3,4-*d*]pyridazin-4(5*H*)ones (**11**, **14a,b**) by action of methylhydrazine. Their structures were provided by their pyrazole precursors. The pyrazolopyridazines thus prepared were studied by spectroscopic methods. A comparative compilation of spectroscopic data is summarized in Tables I-III.



1-6c 1-6a 7-14a

9c 1-6b 7-14b

	R^1	R^2	R^3		R^1	R^2	R^3	R^4
1	CH_3	CH_3	CH_3	7	CH_3	CH_3	CH_3	H
2	CH_3	CH_3	$CH_2C_6H_5$	8	CH_3	CH_3	$CH_2C_6H_5$	H
3	CH_3	$CH_2C_6H_5$	CH_3	9	CH_3	$CH_2C_6H_5$	CH_3	H
4	CH_3	$CH_2C_6H_5$	$CH_2C_6H_5$	10	CH_3	$CH_2C_6H_5$	$CH_2C_6H_5$	H
5	C_6H_5	CH_3	CH_3	11	CH_3	$CH_2C_6H_5$	CH_3	CH_3
6	C_6H_5	CH_3	$CH_2C_6H_5$	12	C_6H_5	CH_3	CH_3	H
				13	C_6H_5	CH_3	$CH_2C_6H_5$	H
				14	C_6H_5	CH_3	CH_3	CH_3

By comparing these data for compounds **11a,b** and **14a,b** with those of **9a,b** and **12a,b**, respectively, one can conclude that the latter heterocycles exist only in lactam tautomeric forms (9) (Table I).

The ultraviolet and infrared spectra data (Table I) cannot successfully differentiate between the *N*(1)- and *N*(2)alkyl isomers, because the observed values are nearly identical. An analysis of the ^{1}H-nmr spectra of the pyrazolopyridazin-4(5*H*)one derivatives (Table II) shows that the most interesting difference for these compounds is that the chemical values for the 3-methyl are deshielded from the *N*(1)- to the *N*(2)isomers. The methyl or the methylene groups at C-7 show instead a diamagnetic displacement. It is conceivable that these chemical shifts may vary with the position of the double bond in the two cycles. A deshielding shift can be expected when the methyl (or the methylene) groups are attached to a double bond conjugated with the carbonyl group C-3 for the *N*(2) isomers or C-7 for the *N*(1) isomers. The methyl group signals on C-3 of compounds **7-8a,b** were assigned by comparison with those of **9-11a,b**.

The ^{1}H-nmr spectra of the isomeric 3-phenylpyrazolopyridazinones (**12,13,14**) show a downfield shift for the *ortho* protons in the phenyl ring for the *N*(1) isomers (**a**) which was not found for the *N*(2) isomers (**b**). These findings reflect the coplanarity or non-coplanarity of the phenyl and heteroaromatic rings. The introduction of an *N*-alkyl group into the 2 position interacts sterically with a reduction in resonance. This steric *ortho* effect is characteristic of *ortho*-substituted biphenyls and analogous heterocyclic compounds (4,10).

We have also investigated the ^{13}C-nmr. Unfortunately the compounds are not very soluble in DMSO-d_6. The spectra have been determined only for the most soluble compounds (**9a,b**). The assignment of the lines are determined by application of the usual shift parameters δ 158.5, 159 C=O (lactam) (8,11), from the obtained signal multiplicities in the off resonance spectrum (substituents at C-3, C-7 and at the nitrogen atoms). The remaining carbons resonance in the molecules can be assigned because it is known that the carbon resonance

Table I

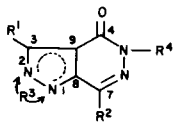
Physical, Analytical and Spectroscopic Data for Compounds **7-14**

Compound	M.p. °C (a)	Yield %	Empirical Formula	Elemental Analysis Calcd. % C	H	N	Found % C	H	N	Uv in Ethanol λ nm (ε x 10^{-3})	Ir (cm^{-1}) (b)
7a	(c)	85	$C_8H_{10}N_4O$	53.92	5.66	31.45	54.38	5.65	31.73	217 (14), 227 (6.4), 278 (5.2)	3400 1685 (d)
7b	(c)						53.60	5.52	31.31	216 (12.4), 276 (5.8)	
8a	216	88	$C_{14}H_{14}N_4O$	66.12	5.55	22.04	65.94	5.55	22.19	216 (18.9), 280 (6.1)	3400 1685 (d)
8b	212 (AE)						65.98	5.52	22.07	215 (16.1), 277 (6.1)	3410 1685 (d)
9a	264	95	$C_{14}H_{14}N_4O$	66.12	5.55	22.04	66.23	5.56	22.01	215 (20.6), 280 (5.7)	3200 1690
9b	208	92					66.07	5.34	21.78	216 (12.6), 278 (5.0)	3170 1690
10a	209	98	$C_{20}H_{18}N_4O$	72.70	5.49	16.96	72.49	5.62	17.10	218 (21.4), 282 (6.5)	3170 1685
10b	174						72.54	5.36	16.90	218 (20.3), 280 (7.5)	3160 1660
11a	152	75	$C_{15}H_{16}N_4O$	67.14	6.01	20.88	67.06	6.17	21.03	216 (21.9), 286 (7.0)	1675
11b	111 (AH)	73					66.97	6.07	20.99	217 (15.5), 284 (6.3)	1675
12a	278	65	$C_{13}H_{12}N_4O$	64.98	5.03	23.32	64.86	5.06	23.44	214 (10.3), 260 (14.4)	3170 1670
12b	262	60					64.92	5.01	23.18	214 (13.5), 253 (12.5), 268 (10.5)	3400 1680 (d)
13a	208	95	$C_{19}H_{16}N_4O$	72.13	5.10	17.71	72.14	4.91	17.96	213 (16.3), 260 (14.9)	3400 1690 (d)
13b	259	90					71.65	5.24	17.76	217 (17.1), 250 (11.3)	3420 1690 (d)
14a	184	80	$C_{14}H_{14}N_4O$	66.12	5.55	22.04	65.87	5.56	22.08	214 (12.9), 261 (14.0)	1670
14b	158	75					66.12	5.46	21.13	216 (15.8), 254 (12.1), 272 (9.6)	1660 (d)

(a) Solvent of crystallization: ethanol if not otherwise stated; (AE) ethyl acetate; (AH) ethyl acetate/hexane 50:50. (b) In potassium bromide if not otherwise stated. (c) Sublimation takes place at atmospheric pressure (220°). (d) In chloroform.

Table II

^{1}H-Nmr Data for Compounds **7-14**
Chemical Shifts in δ (a)



Compound	R^1	R^2	R^3	R^4	Solvent	R^1	R^2	R^3	R^4
7a	CH_3	CH_3	CH_3	H	DMSO-d_6	2.52	2.65	4.18	12.2 (br)
7b	CH_3	CH_3	CH_3	H		2.66	2.38	4.0	11.9 (br)
9a	CH_3	CH_2Ph	CH_3	H	DMSO-d_6	2.53	4.45; 7.3-7.5 (m)	3.95	12.2 (br)
9b	CH_3	CH_2Ph	CH_3	H		2.65	4.15; 7.3-7.5 (m)	4.0	12.1 (br)
11a	CH_3	CH_2Ph	CH_3	CH_3	DMSO-d_6	2.55	4.48; 7.3-7.6 (m)	3.92	3.75
11b	CH_3	CH_2Ph	CH_3	CH_3		2.68	4.17; 7.3-7.6 (m)	4.02	3.68
12a	Ph	CH_3	CH_3	H	DMSO-d_6	7.60 (b); 8.50 (c)	2.68	4.33	12.5 (br)
12b	Ph	CH_3	CH_3	H		7.55-8.0 (m)	2.50	4.11	12.0 (br)
14a	Ph	CH_3	CH_3	CH_3	deuteriochloroform	7.60 (b); 8.53 (c)	2.63	4.16	3.81
14b	Ph	CH_3	CH_3	CH_3		7.65	2.60	4.08	3.75
8a	CH_3	CH_3	CH_2Ph	H	DMSO-d_6	2.50	2.61	5.86; 7.1-7.6 (m)	12.4 (br)
8b	CH_3	CH_3	CH_2Ph	H		2.70	2.45	5.70; 7.2-7.6 (m)	12.0 (br)
10a	CH_3	CH_2Ph	CH_2Ph	H	DMSO-d_6	2.57	4.27; 7.0-7.6 (m)	5.57; 7.0-7.6 (m)	12.8 (br)
10b	CH_3	CH_2Ph	CH_2Ph	H		2.70	4.23; 7.3-7.6 (m)	5.70; 7.3-7.6 (m)	12.1 (br)
13a	Ph	CH_3	CH_2Ph	H	DMSO-d_6	7.3 (b); 8.65 (c)	2.56	6.0; 7.1-7.5 (m)	12.7 (br)
13b	Ph	CH_3	CH_2Ph	H		7.65	2.50	5.66; 7.3-7.5 (m)	12.0 (br)

(a) Singlet if not otherwise stated; (m) multiplet; (br) broad. (b) 3*H* (m). (c) 2*H* (m).

Table III

^{13}C-Nmr Data for Compounds **9** (a)

Compound	C-3	C-4	C-7	C-8	C-9	CH_3 (C-3)	CH_2-C_6H_5 (b)	N CH_3
9a	144.7	158.5	137.2 (c)	137.6 (c)	114.0	12.2	37.3	38.2
9b	140.8 (c)	159.0	139.9 (c)	143.5	111.6	10.0	36.5	37
9c	(d)	159.3	(d)	(d)	111.5	11.1	36.5	

(a) All the spectra (δ values in parts per million from TMS) were recorded in DMSO-d_6. (b) The aromatic carbon absorptions are omitted. (c) Assignments may be interchanged. (d) Resonance could not be distinguished with base line noise in available spectra.

for a pyridine-like environment (-N=C-) occurs at lower field than for a pyrrole-like environment (-N-C=) (5-8,11); consequently, the C-3 and C-8 lines move in the opposite direction in going from the isomer **a** to the isomer **b**. Furthermore, in a pyrazole ring, the C-4 carbon atom reveals small differences between two isomeric compounds and occurs always at higher field than the other carbon atoms of the ring. Therefore, the lines at δ 144.7 and 143.5 are attributed to C-3 for **9a** and to C-8 for **9b**; the lines at δ 114 and 111.6 are assigned to C-9. No attempt was made to assign the resonances at C-7 and C-8 for **9a**, or C-3 and C-7 for **9b**.

The ^{13}C-nmr spectrum of the *N*-unsubstituted corresponding compound (**9c**) in tautomeric equilibrium *N*(1): *N*(2) shows that the chemical shift of the carbon methyl C-3 is useful in determining the structure of isomers **a** or **b** formed by methylation. The *N*(1) methylation causes a deshielding shift, while the *N*(2) methylation results in a highfield shift.

EXPERIMENTAL

Melting points were determined on a Kofler hot plate and boiling points are uncorrected. Infrared and ultraviolet spectra were obtained with a Beckman Model Acculab 2 and DB spectrophotometers. ^{1}H-Nmr spectra were taken on a Varian A-60; ^{13}C-nmr spectra were obtained with a Varian XL-100-12FT. The chemical shifts reported are in parts per million from internal TMS.

Elemental analysis were performed by Microanalytical Laboratory, Centre National de la Recherche Scientifique, Villeurbanne, France.

The pyrazoles **1-6a** or **b** may be prepared as major reaction products, respectively, by the action of methylhydrazine or benzylhydrazine on 3(2*H*)furanone derivatives, or by alkylation of unsubstituted pyrazoles **1-6c** (3). These compounds were obtained from the same 3(2*H*)furanone derivatives and hydrazine hydrate (1,2). The synthesis of compound **9c** has been described in reference 2.

N-Alkylpyrazolo[3,4-*d*]pyridazin-4(5*H*)one Derivatives (**7-14a,b**). General Procedure.

The appropriate compound (**1-6a,b**) (0.01 mole) and hydrazine hydrate or methyl hydrazine (0.02 mole) were allowed to react at room temperature for 12 hours. The resulting precipitated pyrazolopyridazinone was collected, washed with cold water and purified by recrystallization. Table I lists the compounds prepared and their physical properties, and ultraviolet and infrared data.

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