General Synthesis of: 5-Substituted-3-acyl-4-carbethoxypyrazoles 3,6-Substituted-5-carbethoxy-4(1*H*)pyridazinones and 3,7-Substituted-pyrazolo[3,4-*d*]pyridazine-4(5*H*)ones *via* Reactions between 2-Hydroxy, Methoxy, and Acetoxy-3(2*H*)furanones and Hydrazine

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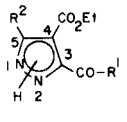
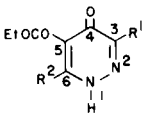
Synthesis of substituted 3-acyl-4-carbethoxypyrazoles, 5-carbethoxy-4(1*H*)pyridazinones and pyrazolo[3,4-*d*]pyridazine-4(5*H*)ones is described. They involve the reaction of the 2,5-substituted-4-carbethoxy-2-hydroxy, methoxy and acetoxy-3(2*H*)furanones with hydrazine hydrate. The reaction was found to be dependent on the hydroxy, methoxy or acetoxy substituents of these furanones and proceeds with ring opening followed by cyclisation. Pyrazoles were formed with hydroxy or methoxy substituents while pyridazinones are afforded with acetoxy group. The pyrazoles so formed were readily converted to pyrazolo[3,4-*d*]pyridazinones by condensation with excess hydrazine.

J. Heterocyclic Chem., 14, 75 (1977).

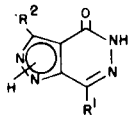
Previous and current work in this laboratory with the reactivity of 3(2*H*)furanones revealed this family of compounds interesting as intermediates in heterocyclic synthesis with nucleophilic reagents (1-4). In this paper we wish to report a new general route to unknown 3-acyl-5-alkyl(or aryl)-4-carbethoxypyrazoles (**5**), 3,6-dialkyl(or aryl)-5-carbethoxy-4(1*H*)pyridazinones (**6**) and 3,7-dialkyl-(or aryl)[3,4-*d*]pyridazine-4(5*H*)ones (**7**).



5a,b,c,d,e,f



6a,b,c,d,e,f



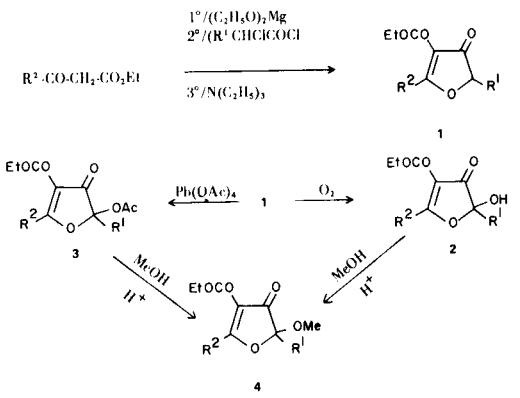
7a,b,c,d,e,f,g

	a	b	c	d	e	f	g
R^1	Me	Me	Me	Me	Me	C_6H_5	C_6H_5
R^2	Me	*n*-Pr	C_6H_5	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	Me	C_6H_5

These syntheses involve the condensation of hydrazine hydrate with 2,5-substituted-4-carbethoxy-2-hydroxy, methoxy, or acetoxy(2*H*)furanones (**2**) (**4**) (**3**). The preparation of **2**, **3**, **4** has been described in a recent publication (5) as shown in scheme 1.

Literature preparations of some vicinal carbethoxy and acylpyrazoles are based on the reaction of hydrazine with β-ethoxy-α-ethylenicketones first reported by Jones (6-8)

Scheme 1



or on addition of diazomethane upon acetylenic compounds (9). A method for the synthesis of 4(1*H*)-pyridazinones has been recently reported (10). The pyrazolo[3,4-*d*]pyridazines has been most frequently obtained with diacyl pyrazoles (9,11,13); 2-ethoxy-2-methyl-4-carbethoxy-3(2*H*)furanone has been shown to react with hydrazine to give 3-acetyl-4-carbethoxy-pyrazole, 3-methyl-5-carbethoxy-4(1*H*)pyridazinone and 7-methylpyrazolo[3,4-*d*]pyridazine-4(5*H*)ones (14). No investigation appears to have been carried out to introduce various substituents in these compounds. The substituted

products described here are interesting for pharmacologic studies (15,16).

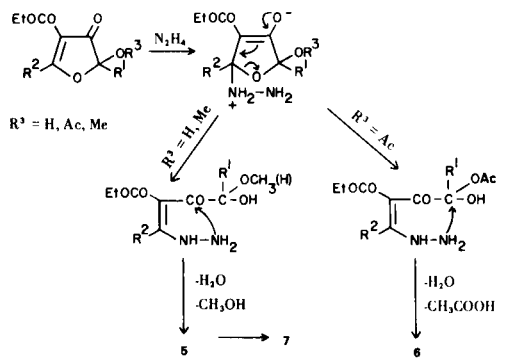
Results and Discussion.

The 2-hydroxy or 2-methoxy-3(2*H*)furanones **2** and **4** readily react with hydrazine hydrate in equimolar amount leading to pyrazoles **5** with a small quantity of **7** and to pyrazolo[3,4-*d*]pyridazines **7** with an excess of this reagent.

The 2-acetoxy-3(2*H*)furanones **3** afford the pyridazinones **6** with an excess of hydrazine in good yields if R^2 = aryl. Only in the case of **3a,b,f** (R^2 = alkyl) **6a,b,f** were accompanied by small amounts of **7a,b,f**.

The formation of these compounds can be explained by a nucleophilic attack at the 5 position followed by ring opening of furan ring, then cyclisation as previously reported with 2-arylidene-5-carbethoxy-3(2*H*)furanones (4). The reaction is linked with the presence of the leaving group; hydroxy, methoxy or acetoxy. The nature of the leaving group, in part, directs the course of the cyclisation towards C-2 to give **6**. The reaction path is shown in scheme 2.

Scheme 2



The structure of compounds are consistent with the nmr spectra, ir data and elemental analysis (see Tables) and are in good agreement with those further reported (4,14). The pyrazoles **5** and pyridazinones **6**, isomeres are readily distinguished because **5** was converted to **7** by condensation with hydrazine while no reaction was observed when **6** was treated, under the same conditions, with hydrazine. The mass spectrum of **6a**, showed principal ions at m/e: 196 (M^+, 79%), 150, 127 (base), 109, 81, 68, 42 and the lowering of the infrared carbonyl-stretching frequency previously reported (10,17) confirmed this structure.

Our results have shown that the furanones, **2**, **3**, **4** are useful intermediates for the preparation of substituted heterocycles **5**, **6**, **7**. Studies involving the reactions with other nitrogen nucleophiles are in progress in this laboratory.

EXPERIMENTAL

All melting and boiling points are uncorrected. The ir and uv spectra were taken with a Beckman Model Acculab 2 and DB spectrophotometers. The nmr spectra were measured using tetramethylsilane as the internal standard, with a Varian A-60 spectrometer. The mass spectrometric analyses were determined with Varian Mat CH5. Microanalyses were performed by Microanalytical Laboratory, Centre National de la Recherche Scientifique, Villeurbanne, France.

3-(2*H*)Furanones **2c,d,e,f,g**, **3a,b,c,d,e,f**, **4a,b,c,d,e,f,g** were prepared as previously described (4).

General Procedure for 5-Substituted-3-acyl-4-carbethoxypyrazoles (**5**).

A solution of **2** or **4** (0.04 mole) in 50 ml. of acetonitrile was cooled to -5° with stirring and 2 g. (0.04 mole) of hydrazine hydrate was added dropwise. The temperature was kept at 0° during the addition. After an additional 30 minutes of stirring under the same conditions and then for about 15 minutes at room temperature, the mixture was poured into 80 ml. of 5% aqueous sodium hydroxyde and extracted with ether. The aqueous layer was acidified with 6 *N* hydrochloric acid (*p*H 4) and extracted with methylene chloride. After drying and evaporation of the solvent, the residue was distilled *in vacuo* or recrystallized from water/ethanol (70/30). (Tables 1 and 4).

General Procedure for 3,6-Disubstituted-5-carbethoxy-4(1*H*)-pyridazinones (**6**).

Compounds **6a,b,f**: To a solution of **3** (0.01 mole) in 20 ml. of ethanol cooled to -5° was added a solution of hydrazine hydrate in ethanol (1.5 g. in 10 ml.) at such a rate that the reaction mixture stayed under 0°. After standing in the cold for 1 hour, ethanol was evaporated. The residue was extracted with methylene chloride. The mixture was filtered to remove **7**. The filtrate was evaporated *in vacuo* and the remaining solid was recrystallized from ethyl acetate. (Tables 2 and 4).

Compounds **6c,d,e**: To a suspension of **3c,d,e** (0.01 mole) in 5 ml. of ethanol was added at room temperature 1.5 g. (0.03 mole) of hydrazine hydrate and the homogeneous mixture was allowed to stand for 24 hours. The resulting precipitate was collected by filtration and recrystallized from ethyl acetate. (Tables 2 and 4).

General Procedure for 3,7-Disubstituted[3,4-*d*]pyridazine-4(5*H*)-ones (**7**).

A mixture of **2** or **4** (0.01 mole), 10 ml. of ethanol and 1.5 g. (0.03 mole) of hydrazine hydrate was refluxed for 30 minutes. After cooling, the resulting crystals were collected, washed with ether and purified by sublimation at 200-230°/1 mm Hg (Tables 3 and 4).

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Table 1

Physical Data for Compounds **5**

Compound	Yield %	B.p. °C nm	M.p. °C	Molecular Formula	Analyses Calcd. % / Found %			Uv in Ethanol λ max (nm) ε		Ir (cm^{-1}, Carbon tetrachloride	
					C	H	N			ν NH	ν C=O
5a	35	165_1	74	$C_9H_{12}O_3N_2$	55.09	6.17	14.28	210	7400	3450	1735
					55.00	6.26	14.24	242	5450	3260	1690
5b	30	175_1		$C_{11}H_{16}O_3N_2$	58.91	7.19	12.49	210	7400	3450	1735
					58.88	7.36	12.43	242	4900	3270	1690
5c	50	195_1	38	$C_{14}H_{14}O_3N_2$	65.11	5.46	10.85	210	14400	3450	1735
					65.10	5.62	11.09	236	18200	3260	1700
5d	55	200_1		$C_{15}H_{16}O_3N_2$	66.16	5.92	10.29	212	15700	3450	1735
					65.59	6.08	9.23	242	17750	3280	1700
5e	62	215_1		$C_{15}H_{16}O_4N_2$	62.49	5.59	9.72	210	14400	3450	1735
					62.33	5.70	9.33	239	14900	3280	1700
								306	5600		
5f	50		67	$C_{14}H_{14}O_3N_2$	65.11	5.46	10.85	210	13550	3480	1700
					65.02	5.19	10.83	252	12450	3420	
										3260	1680

Table 2

Physical Data for Compounds **6**

Compound	Yield	M.p. °C	Molecular Formula	Analyses Calcd. % / Found %			Uv in Ethanol λ max (nm) ε		Ir (cm^{-1}, chloroform)		
				C	H	N			νNH		νC=O
6a	35	165	$C_9H_{12}O_3N_2$	55.09	6.17	14.28	211	5300	3420	3150	1735
				55.35	6.19	14.40	266	11200	3250		1610
6b	25	136	$C_{11}H_{16}O_3N_2$	58.91	7.19	12.49	208	7750	3420	3150	1735
				58.36	7.27	12.91	266	11350	3250		1610
6c	85	195	$C_{14}H_{14}O_3N_2$	65.11	5.42	10.82	208	13600	3420	3150	1735
				65.32	5.41	10.99	238	13700	3250		1610
							275	13600			
6d	70	200	$C_{15}H_{16}O_3N_2$	66.16	5.92	10.29	208	13200	3420	3150	1735
				66.10	5.83	10.28	246	16700	3250		1610
							270	15000			
6e	85	213	$C_{15}H_{16}O_4N_2$	62.49	5.59	9.72	210	12000	3420	3150	1735
				62.74	5.59	9.72	268	22400	3250		1610
							290	15300			
6f	20	168	$C_{14}H_{14}O_3N_2$	65.11	5.46	10.85	205	14550	3420	3100	1730
				65.11	5.41	10.81	247	14200	3250		1605
							322	6500			

Table 3

Physical Data for Compounds **7**

Compound	Yield %	M.p. °C	Molecular Formula	Analyses Calcd. / Found % C	H	N	Uv in Ethanol λ max (nm) ε		Ir (cm^{-1}, Potassium bromide	
7a	85	350	$C_7H_8ON_4$	51.21	4.91	34.13	270	4500	3270	1650
				50.99	4.85	33.97			3260	1620
7b	85	283	$C_9H_{12}ON_4$	56.23	6.29	29.15	272	4680	3275	1660
				56.03	6.32	29.17			3200	1620
7c	90	350	$C_{12}H_{10}ON_4$	63.70	4.46	24.77	210	14800	3270	1650
				63.88	4.39	24.69	256	16300	3200	1620
7d	75	350	$C_{13}H_{12}ON_4$	64.98	5.03	23.32	211	32600	3280	1650
				65.03	5.25	23.45	263	28000	3200	1620
7e	75	345	$C_{13}H_{12}O_2N_4$	60.93	4.72	21.87	210	21600	3280	1655
				59.85	4.74	21.96	274	18700	3220	1620
7f	75	330	$C_{12}H_{10}ON_4$	63.70	4.46	24.77	228	16600	3240	1650
				63.54	4.78	24.93	290	10620	3180	1610
7g	72	345	$C_{17}H_{12}ON_4$	70.17	4.27	18.82	210	40500	3240	1650
				70.82	4.20	19.44	238	35600	3190	1620
							292	25000		

Table 4

Proton Magnetic Resonance Parameters (a)

Compound	
5a	1.34 (t, 3H), 2.50 (s, 3H), 2.61 (s, 3H), 4.36 (q, 2H), 11.8 (1H) (b) (c)
5b	0.93 (t, 3H, J = 7 Hz), 1.32 (t, 3H), 1.56 (sext. 2H), 2.51 (s, 3H), 2.81 (t, 2H, J = 7 Hz), 4.25 (q, 2H), 10.9 (1H) (b) (c)
5c	1.21 (t, 3H), 2.58 (s, 3H), 4.29 (q, 2H), 7.33-7.86 (m, 5H), 11.1 (1H) (b) (d)
5d	1.21 (t, 3H), 2.25 (s, 3H), 2.46 (s, 3H), 4.16 (q, 2H), 6.9 (d, 2H), 7.23 (d, 2H), 10.5 (1H) (b) (d)
5e	1.19 (t, 3H), 2.50 (s, 3H), 3.70 (s, 3H), 4.16 (q, 2H), 6.88 (d, 2H), 7.40 (d, 2H), 13.5 (1H) (b) (d)
5f	0.91 (t, 3H), 2.50 (s, 3H), 3.96 (q, 2H), 7.24-8.01 (m, 5H), 13.6 (1H) (b) (d)
6a	1.35 (t, 3H), 2.25 (s, 3H), 2.38 (s, 3H), 4.33 (q, 2H), 13 (1H) (b) (c)
6b	1.00 (t, 3H, J = 7 Hz), 1.38 (t, 3H), 1.78 (sext., 2H), 2.40 (s, 3H), 2.88 (t, 2H, J = 7 Hz), 13.3 (1H) (b) (c)
6c	0.93 (t, 3H), 2.23 (s, 3H), 4.06 (q, 2H), 7.33-7.80 (m, 5H), 13.0 (1H) (b) (d)
6d	1.00 (t, 3H), 2.23 (s, 3H), 2.41 (s, 3H), 4.10 (q, 2H), 7.15-7.55 (m, 4H), 12.9 (1H) (b) (c)
6e	1.00 (t, eH), 2.20 (s, 3H), 3.83 (s, 3H), 4.08 (1, 2H), 7.1 (d, 2H), 7.5 (d, 2H), 13.3 (1H) (b) (d)
6f	1.31 (t, 3H), 2.41 (s, 3H), 4.40 (q, 2H), 7.28-7.66 (m, 3H), 7.91-8.23 (m, 2H), 12.9 (1H) (b) (c)
7a	2.45 (s, 3H), 2.61 (s, 3H), 11.9 (1H) (b), 13.8 (1H) (b) (d)
7b	0.92 (t, 3H, J = 7 Hz), 1.80 (m, 2H), 2.45 (s, 3H), 3.00 (t, 2H, J = 7 Hz), 10.0 (1H) (b), 12.5 (1H) (b) (d)
7c	2.50 (s, 3H), 7.28-7.72 (m, 3H), 8.22-8.62 (m, 2H), 12.2 (1H) (b), 14.3 (1H) (b) (d)
7d	2.40 (s, 3H), 2.51 (s, 3H), 7.33 (d, 2H), 8.42 (d, 2H), 12.1 (1H) (b), 14.1 (1H) (b) (d)
7e	2.48 (s, 3H), 3.83 (s, 3H), 7.05 (d, 2H), 8.40 (d, 2H), 10.2 (1H) (b), 13.8 (1H) (b) (d)
7f	2.75 (s, 3H), 7.50-7.73 (m, 3H), 8.17-8.63 (m, 2H), 12.0 (1H) (b), 12.3 (1H) (b) (d)
7g	7.27-7.78 (m, 6H), 8.03-8.58 (m, 4H), 11 (1H) (b), 12 (1H) (b) (d)

(a) Coupling constants carbethoxy group CH_3CH_2: J = 7 Hz. Coupling constants orthoaromatic ring protons: J = 8.5 Hz. (b) Broad. (c) In deuteriochloroform. (d) In DMSO-d_6.

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