A New Synthesis of Pyrazolo[1,5-*d*][1,2,4]triazines from Pyrazolecarboxylic Acid Hydrazides and Carbonyl Compounds. I

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Pyrazolo[1,5-*d*][1,2,4]triazines were synthesized from pyrazolecarboxylic acid hydrazides and carbonyl compounds. Pyrazolecarboxylic acid *N'*-phenylhydrazide (**1c**) and formaldehyde gave not only the expected **4h** but **5**, respectively. The methyl substituted hydrazides with acetone afforded hydrazones, pyrazolotriazines or **13** depending on the position of the substituents. The reduction of both products yielded pyrazolecarboxylic acid hydrazides.

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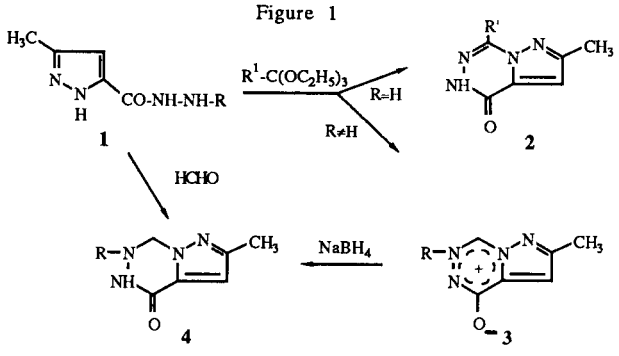
Introduction and Synthesis.

Ainsworth was the first to report on the reaction of pyrazolecarboxylic acid hydrazides **1**, unsubstituted both in the ring and at the hydrazide nitrogens, with orthoesters and he isolated 2-methylpyrazolo[1,5-*d*][1,2,4]triazin-4(5H)-one **2** as the member of a new ring system [1]. During our work the mezomeric betaine form **3** of the above condensed system was prepared in a similar reaction by condensing *N'*-substituted pyrazolecarboxylic acid hyrazides with orthoesters [2] (Figure 1).

Figure 1



1 2 4 3

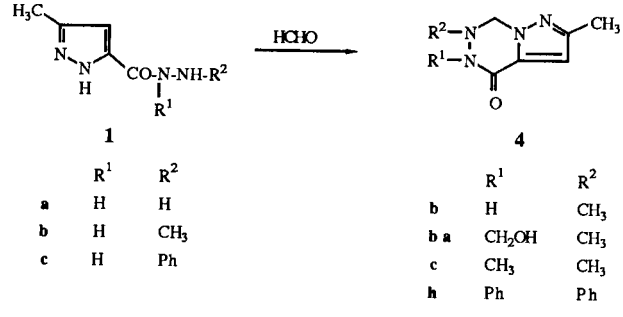
Other authors have proposed various methods to obtain pyrazolo[1,5-*d*][1,2,4]triazines [3-12] but surprisingly no carbonyl compounds were used for the ring closure.

We successfully applied formaldehyde to prepare some 6,7-dihydropyrazolotriazines **4** providing thereby synthetic evidence for the mesomeric betaine structures [2,13].

In this paper mainly the reactions of pyrazolecarboxylic acid hydrazides bearing various substituents with formaldehyde as well as with acetone will be discussed.

Reactions of *N'*-monoalkyl and *N,N'*-dialkyl substituted carboxylic acid hydrazides with formaldehyde and aliphatic aldehydes usually afforded the expected condensed ring systems (Figure 2). Treatment of **1b** (R_1 = H, R_2 = CH_3) with at least two equivalents of formaldehyde, beyond the ring closure, N-5 substitution, (CH_2OH) also occurred. Compound **4c** could be prepared also by methylation of **4b**. Reacting an *N'*-phenylhydrazide with formaldehyde in alcoholic solution afforded **4h**, however, a by-product was also isolated. When running the reaction in dioxane, this compound was the main product. Upon heating in dimethyl sulphoxide it was converted to **4h**, suggesting structure **5**. Other structures like **6** or similar cyclic dimers can be excluded on the basis of the OH-band in the ir spectrum (Figure 3). Using aliphatic aldehydes as reagents yielded compounds **4i-h**.

Figure 2



1

	R^1	R^2
a	H	H
b	H	CH_3
c	H	Ph

4

	R^1	R^2
b	H	CH_3
b a	CH_2OH	CH_3
c	CH_3	CH_3
h	Ph	Ph

Figure 3

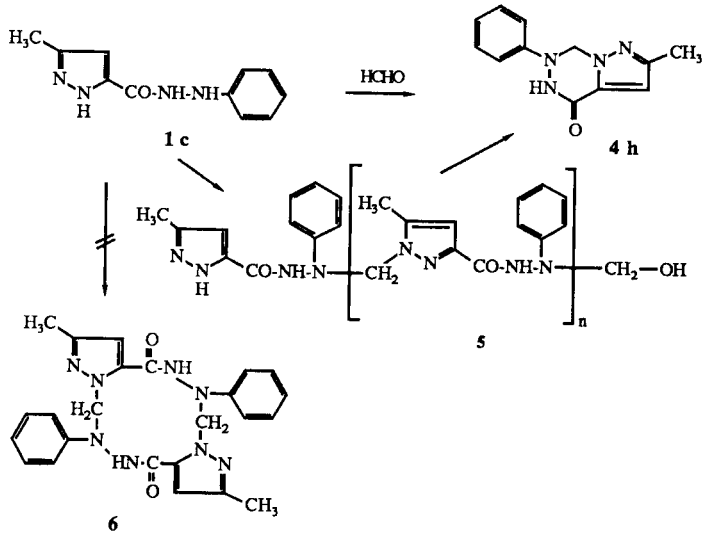
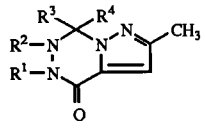


Table I

Characteristics for Compounds **4a-k** and **9a-e**



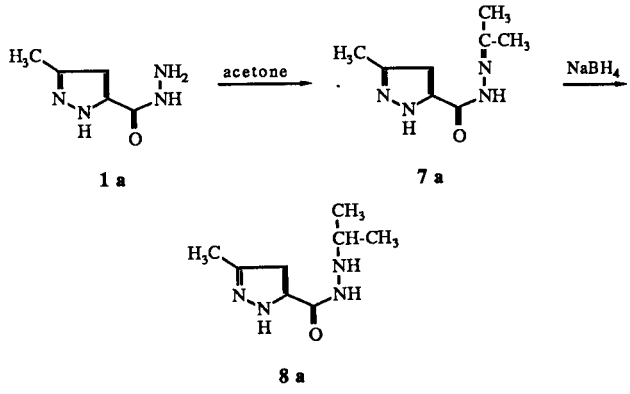
Compound	R^1	R^2	R^3	R^4	Yield (%)	Mp °C (solvent)	Formula
4a	CH_3	H	H	H	49	126 (N)	$C_7H_{10}N_4O$
4b	H	CH_3	H	H	31	177 (N)	$C_7H_{10}N_4O$
4ba	CH_2OH	CH_3	H	H	74	139 (N)	$C_8H_{12}N_4O_2$
4c	CH_3	CH_3	H	H	61	101 (B/P)	$C_8H_{12}N_4O$
4d	H	$CH(CH_3)_2$	H	H	91	192 (B)	$C_9H_{14}N_4O$
4e	H	cC_6H_{11}	H	H	85	194 (B)	$C_{12}H_{18}N_4O$
4f	H	CH_2-Ph	H	H	64	182 (B)	$C_{13}H_{14}N_4O$
4g	H	2,6-di-Cl-Ph	H	H	66	224 (B)	$C_{13}H_{12}Cl_2N_4O$
4h	H	Ph	H	H	87	183 (iP)	$C_{12}H_{12}N_4O$
4i	CH_3	H	H	CH_3	93	99 (N)	$C_8H_{12}N_4O$
4j	H	CH_3	H	CH_3	56	142 (B)	$C_8H_{12}N_4O$
4k	H	CH_3	H	C_2H_5	60	133 (B/P)	$C_9H_{14}N_4O$
9a	CH_3	H	CH_3	CH_3	90	92 (H)	$C_9H_{14}N_4O$
9b	H	CH_3	CH_3	CH_3	72	163 (B)	$C_9H_{14}N_4O$
9c	CH_3	CH_3	CH_3	CH_3	59	141 (B/P)	$C_{10}H_{16}N_4O$
9d	H	$CH(CH_3)_2$	CH_3	CH_3	68	185 (E)	$C_{14}H_{22}N_4O$
9e	H	cC_6H_{11}	CH_3	CH_3	49	192 (B/P)	$C_{11}H_{18}N_4O$

Abbreviations: B = benzene, E = ethanol, H = *n*-hexane, iP = 2-propanol, N = no recrystallization, P = petroleum ether.

The reaction of pyrazolecarboxylic hydrazides, substituted with one or more methyl groups, with acetone afforded various products depending on the substitution.

As it is known, unsubstituted (both in the ring and at the hydrazide nitrogen) **1a** reacts with acetone to give **7a** [14] (Figure 4). Reduction of **7a** with sodium borohydride lead to the isopropylhydrazide **8a**. According to our observations the *N'*-methylhydrazide **1b** cyclized to **9b** under similar conditions, in boiling acetone. The *N*-methylhydrazides similarly afforded the corresponding pyrazolotriazinone **9a** instead of **7b**. This can be explained by the most probable route of dehydratation of intermediate **10**. (Deprotonation of the ring nitrogen is the most likely route

Figure 4



1 a **7 a** **8 a**

and thus, after elimination of water, cyclization occurs) (Figure 5).

Reduction of both **9a** and **9b** with borohydride lead to ring opening. In the case of **9a** the carbonyl group was also reduced.

This phenomenon can be explained by the electron releasing effect of the *N*-methyl group adjacent to the ring carbonyl. In the latter case, **9a**, the sequence of the two reduction steps could also be assumed. Namely, under analogous conditions, the carbonyl group of the *N*-methylhydrazide **1e** could not be reduced, consequently the reduction of the carbonyl group, **11**, had to preceed the ring opening.

Reaction of **9b** with methyl *p*-toluenesulphonate in the presence of sodium methoxide afforded **9c**. Under similar conditions **9a** could not be converted to **9c**. The cyclic structures **9c-b** gave the corresponding hydrazides upon

Table II

Selected Spectral Data of **4**, **7**, **8**, **9**, **12**, **13**, and **19**

4b: δ (DMSO-d_6): 2.27 (s 3H, C_2-CH_3), 2.55 (s, 3H, N_6-CH_3), 5.2 (s 2H, CH_2), 6.6 (s 1H, C_3-H), 9.8 (b 1H, NH); ν: 1660, CO

7c: δ (DMSO-d_6): 1.95 (s 3H and 2.0 s 3H, =C(CH_3), 2.2 (s 3H, C_3-CH_3), 4.0 (s 3H, N_1-CH_3), 6.7 (s, 1H, C_4-H), 10.4 (b 1H, NH); ν: 3170, NH; 1650, CO

8b: δ (DMSO-d_6): 1.05 [d 6H, CH(CH_3)$_2$], 2.03 (s, 3H, C_3-CH_3), 2.6 (s 3H, N-CH_3), 3.0 (sp 1H, CH), 6.45 (s 1H, C_4-H), 8.6 (b 1H, CO-NH), 12.9 (b 1H, ring NH); ν: 1655, CO

8d: δ (deuteriochloroform): 2.25 (s, 3H, C_3-CH_3), 4.1 (s 3H, N-CH_3), 4.9 (B 1H, NH), 6.45 (S 1H, C_4-H), 8.7 (b 1H, CO-NH); ν: 3300, 3240, NH; 1635 CO

9a: δ (deuteriochloroform): 1.6 (s, 6H, C(CH_3)$_2$], 2.25 (s, 3H, C_3-CH_3), 3.2 (s, 3H, N-CH_3), 4.95 (b, 1H, NH), 6.5 (s, 1H, C_4-H), ν: 3220, NH; 1640, CO

9b: δ (DMSO-d_6): 1.65 [s, 6H, C(CH_3)$_2$], 2.5 (s, 1H, N-CH_3), 9.75 (b, 1H, NH); ν: 3300-3000, NH; 1670, CO

9d: δ (deuteriochloroform): 0.85 [d, 6H, CH(CH_3)$_2$], 1.75 [s, 6H, C(CH_3)$_2$], 2.25 (s, 3H, C_2-CH), 3.5 (sp, 1H, CH), 6.5 (s, 1H, C_3-H), 8.0 (b, 1H, NH); ν: 1700, CO

12: δ (deuteriochloroform): 1.0 [d, 6H, CH(CH_3)$_2$], 2.25 (s, 3H, C_3-CH_3), 2.4 (s, 3H, N-CH_3), 2.9 (sp, 1H, CH), 3.7 (d, 2H, CH_2), 5.95 (s, 1H, C_4-H); ν: 3200, NH

13: δ_H (deuteriochloroform): 1.32 and 1.40 [s, 6H, C(CH_3)$_2$], 1.8 (s, 3H, pyrazolidine C-CH_3), 2.29 (s, 6H, 2 x C_3-CH_3), 2.15 and 2.3 (s, 2H, CH_2), 2.56 (s, 3H, N-CH_3), 2.7 (s, 3H, pyrazolidine N-CH_3) 4.12 and 4.14 (s, 6H, 2 x pyrazole N1-CH3), 6.57 and 6.91 (s, 2 x 3H, 2 x C_4-H);

δ_C (deuteriochloroform): 158.3 and 160.8, CO; pyrazole: 13.3, (C_3)-CH_3; 38.8 and 39.7, N_1-CH_3; 135.1 and 135.4, C_5; 146.4 and 146.9, C_3; 105.7 and 109.1, C_4; pyrazolidine: 23.2 and 25.9, (C_3)(CH_3)$_2$; 28.8, (C_5)-CH_3; 42.1, N-CH_3; 50.0, C_4; 61.5, C_3; 90.0, C_5; ν: 3270, NH; 1665, CO; ms: M^+ 416 (0.2%), m/z (%): 193 (100), 123 (100), 249 (61), 20 (32.5), 125 (30.5), 209 (17.5), 168 (10.5), 57 (9.2)

19: δ_H (deuteriochloroform): 1.15 (d, 3H, C-CH_3), 1.22 and 1.19 [s, 2 x 3H, C(CH_3)$_2$], 2.20 (s, 6H, 2 x C_3-CH_3), 2.56 and 2.64 (s, 2 x 1H, 2 x N-CH_3), 4.06 (s, 6H, 2 x ring N_1-CH_3), 6.53 and 6.68 (s, 2 x 1H, 2 x 1H, 2 x C_4-H), 8.18 and 9.34 (b, 2 x 1H, NH);

δ_C (deuteriochloroform): 14.9, (CH)-CH_3; 23.8 and 26.2 (C)-(CH_3)$_2$; 41.6, N-CH_3; 57.2, CH; 159.5. and 159.7, CO; pyrazole: 13.2, C_3-CH_3; 38.7, N-CH_3; 134.9 and 135.8, C_5; 146.6 and 146.9, C_3; 105.8, C_4; ν: 3260 and 3180, NH; 1665 and 1645, CO; ms: M^+ 418 (8%), m/z (%): 209 (100), 195 (48), 127 (22.5), 123 (20), 280 (17), 112 (16), 83 (9)

Analytical Data

Compound	Calculated(%) C	H	N	Found(%) C	H	N
4a	50.59	6.07	33.71	50.67	6.28	33.53
4b	50.59	6.07	33.71	50.68	6.27	33.68
4ba	48.97	6.16	28.56	48.82	6.19	28.36
4c	53.32	6.71	31.09	53.29	6.59	31.19
4d	55.65	7.27	28.85	55.75	7.39	28.88
4e	61.52	7.74	23.91	61.55	7.55	23.42
4f	64.45	5.82	23.13	64.51	5.90	23.00
4g	50.18	3.89	18.01	50.08	3.87	17.93
4h	63.15	5.30	24.55	62.97	5.18	24.37
4i	53.32	6.71	31.09	53.17	6.58	30.98
4j	53.32	6.71	31.09	53.29	6.84	31.15
4k	55.65	7.27	28.85	55.62	7.47	28.91
5	60.75	5.52	23.61	61.20	5.57	23.30
7c	55.65	7.26	28.85	55.70	7.41	29.21
8b	55.08	8.22	28.54	55.08	8.44	28.33
8c	49.99	7.19	33.31	50.37	7.38	33.31
8d	55.08	8.22	28.55	55.22	8.26	28.44
89a	55.65	7.27	28.85	55.65	7.32	28.77
9b	55.65	7.27	28.85	55.46	7.17	28.87
9c	57.67	7.74	26.90	57.81	7.53	27.11
9d	64.09	8.45	21.36	64.21	8.37	21.21
9e	59.44	8.16	25.20	59.27	8.02	24.98
12	59.31	9.95	30.74	59.02	9.76	30.51
13	57.67	7.75	26.90	58.32	8.06	26.50
19	57.38	8.19	26.77	57.81	8.59	26.50

Figure 5

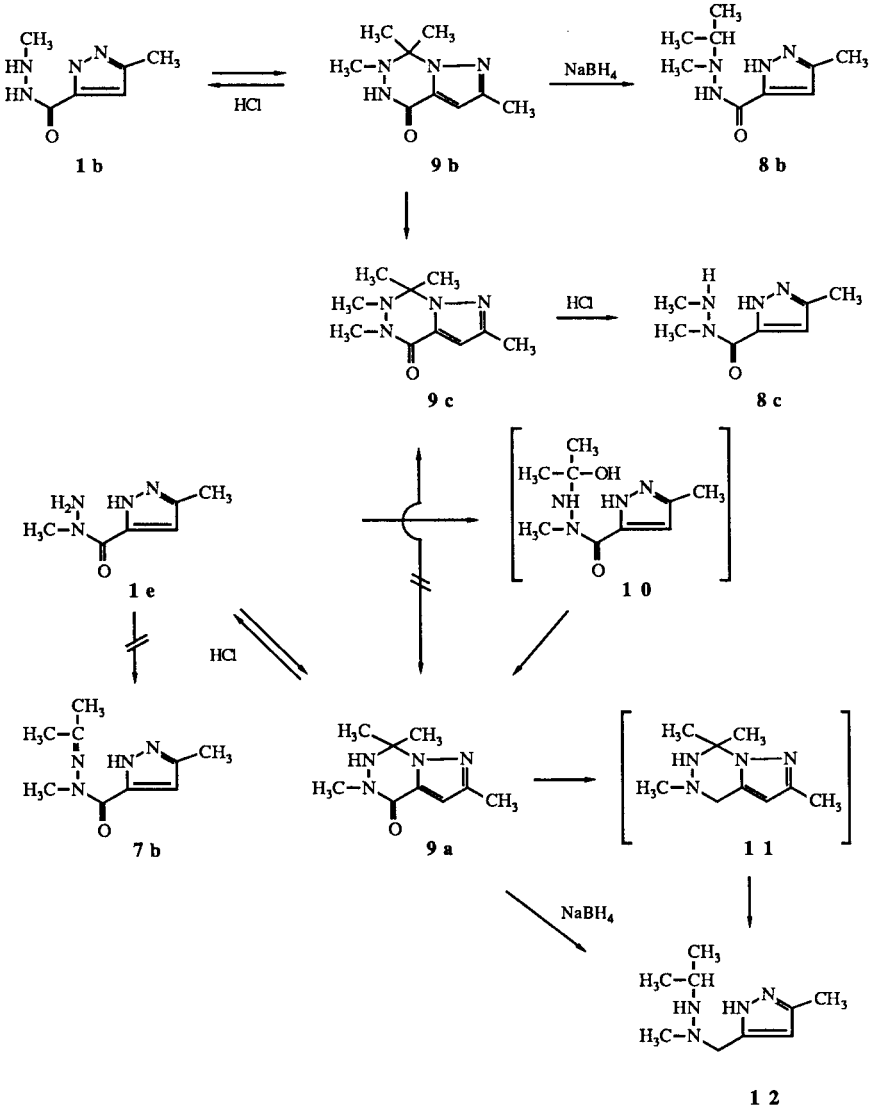
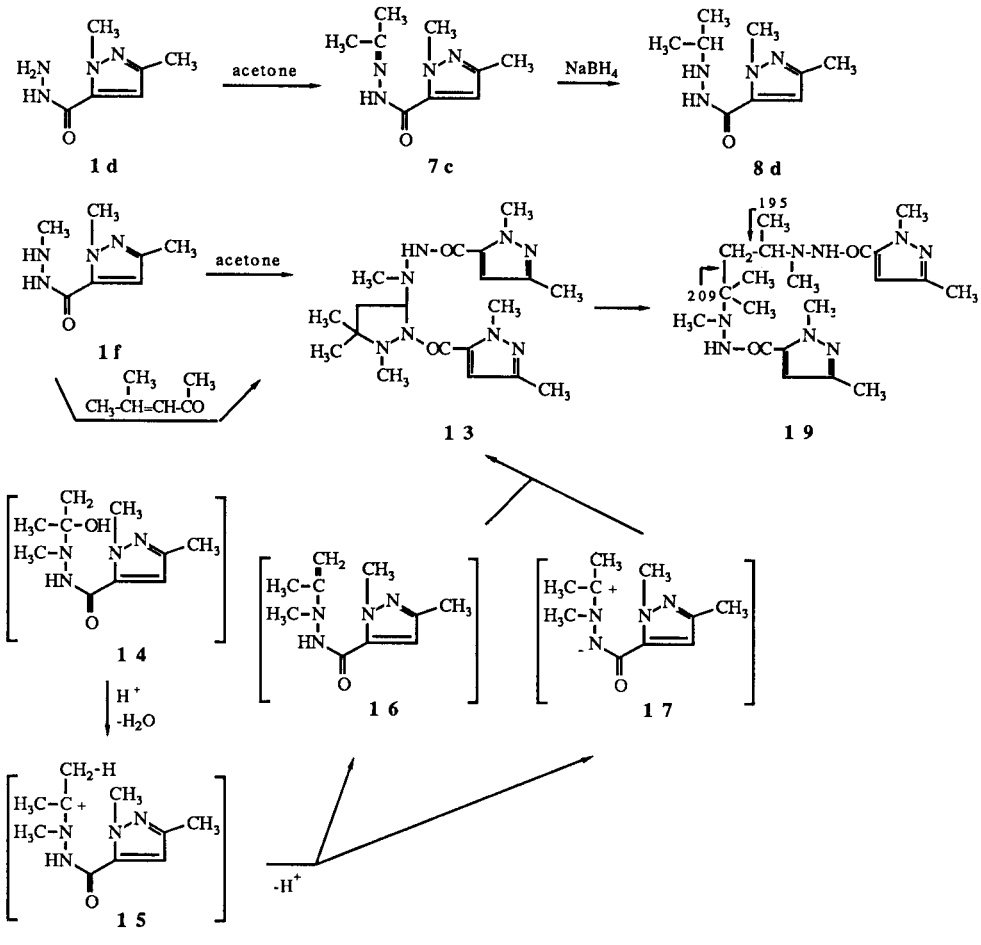


Figure 6

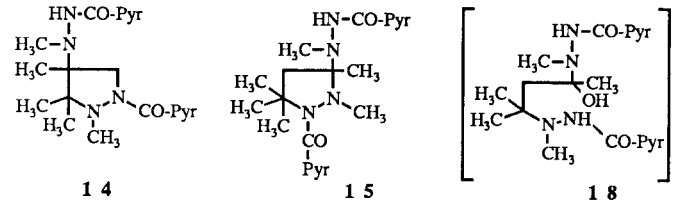


treatment with hydrochloric acid in methanol/water. In this manner *N,N'*-dimethylhydrazide **8c** can easily be prepared (Figure 5).

The reaction of structural isomer **1d**, also bearing two methyl substitutents, with acetone and subsequent reduction of the product **7c** to **8d** are chemically unambigous (Figure 6). It was somewhat surprising, however, that 1,3,-*N'*-trimethyl-1*H*-pyrazole-5-carboxylic hydrazide **1f** also reacted with acetone.

In the ^{1}H nmr spectrum of the product nine methyl groups, one methylene group, two pyrazole C-H and one acidic N-H could be identified. On the basis of the nmr and microanalytical data structures **13**, **14** and **15** (Figures 6 and 7) could be assumed, respectively. The formation of **13** from **1f** and acetone can be explained by cycloaddition of **16** and **17**. The latter compounds being generated by protonation, water elimination and subsequent deprotonation. Compound **14** might be formed similarly from **16** and **17** but with an opposite orientation, which seemed to be unlikely.

Figure 7



Additional data were acquired to exclude structure **14** by reducing the mentioned product with sodium borohydride. On the basis of the ^{1}H nmr data the reduced compound remained a "dimer" containing two pyrazole rings and nine methyl groups, but the isopropyl group which could be expected after cleavage of N_1-C_5 bond in the pyrazolidine ring of **14** was not observed.

On the basis of the ^{13}C nmr and mass spectroscopic data no decision could be made between the isomeric structures **13** and **15**.

Finally, structure **13** could unambigously be proved by reaction of the starting hydrazide **1f** with mesityl oxide,

providing the same product as the reaction with acetone, through **18** as an intermediate. There is no doubt that **18** is formed during the two-step nucleophilic addition of hydrazide **1f** to mesityl oxide. In the mass spectrum of the reduced material **19** the intensity ratio of the peaks m/z = 209 and m/z = 195 was 2:1 (100% and 48%, respectively) as expected, providing thus evidence for structure **19** and in an indirect manner for structure **13** as well.

Thus we can conclude, that in the reactions of acetone with pyrazolecarboxylic acid hydrazides substituted with one or more methyl groups, three kinds of products can be expected. Pyrazole derivatives substituted at the hydrazide group but unsubstituted at the ring nitrogen afford pyrazolotriazines. Under similar conditions the analogues unsubstituted at the hydrazide nitrogen are converted to hydrazones indepentently from the substitutions at the ring nitrogen. The reaction of 1,3,*N'*-trimethylpyrazolecarboxylic acid hydrazide with acetone lead to a dimeric compound containing two pyrazole rings and one pyrazolidine ring. The cyclic product formed in the condensation reactions undergo reductive ring opening upon treatment with sodium borohydride. In the next paper the reactions of pyrazolecarboxylic acid hydrazides with other carbonyl compounds will be discussed.

EXPERIMENTAL

All melting points are uncorrected and are within ± 1°, except as marked. The ir spectra were measured using a Perkin-Elmer 577 spectrometer, nmr spectra were obtained on a Varian XL-100 spectrometer (TMS as internal standard). Mass spectra were measured on a Varian MAT SM-1 instrument at 70 eV and R 1250.

Synthesis of **4a-h**.

Method A.

Twenty mmoles of hydrazide **1**, 8 ml of water and 2.3 ml of 37% formaldehyde solution were stirred at room temperature overnight. The crystals were filtered off, washed with water, dried and recrystallized.

Method B.

Five mmoles of hydrazide **1**, 10 mmoles of paraformaldehyde in 25 ml of ethanol were boiled for 4-12 hours. The solvent was evaporated, the residue was trituated with chloroform, the solution was washed with water, dried, the solvent was evaporated and the product was recrystallized.

Method C.

Six mmoles of hydrazide **1** in 30 ml of ethanol was cooled to 0°, 7 mmoles of aldehyde was added to the solution and the mixture was stirred overnight. The solvent was removed *in vacuo* and the material was trituated with petroleum ether.

Synthesis of **5**.

Paraformaldehyde (1.53 g) and 10.8 g of 3(5)-methyl-1*H*-pyrazole-5(3)-carboxylic acid *N'*-phenylhydrazide in 250 ml of dioxane were heated under reflux and stirred for 5 hours. The crystals were filtered off and washed with dioxane, yield 5.39 g, mp 252-254°.

Synthesis of **4h** from **5**.

A mixture of 1 g of **5** in 5 ml of dimethyl sulphoxide was stirred in an oil bath (140°) for 2 hours. The solution was poured into 100 ml of water, the precipitate was filtered off and washed with water, yield 0.6 g.

Synthesis of **4ba**.

Hydrazide **1b** (3.08 g) and 5 ml of 37% formaldehyde solution were stirred at room temperature overnight. The crystals were filtered off and washed with water, yield 3.89 g (73%).

Synthesis of **9a-b** and **9d-e**.

One g of hydrazide **1**, 20 ml of acetone and 0.01 g of *p*-toluenesulphonic acid were refluxed for two hours. The acetone was distilled off and the crude product was purified by column chromatography over silica (eluent benzene:methanol 3:1), and/or recrystallized.

Reduction of **9a-b** with Sodium Borohydride.

One mmole of **9a-b** pyrazolo[1,5-*d*][1,2,4]triazine and 0.4 g of sodium borohydride were heated under reflux in 10 ml of 2-propanol for 1 hour. To the cooled reaction mixture 5 ml of water and 10 ml of methanol were added and stirred for 1 hour at room temperature. The solvent was evaporated and the evaporation was repeated three times with 15 ml of methanol. The material was treated with 10 ml of water and extracted with chloroform (4 x 10 ml). The organic layer was evaporated and the crude product was recrystallized.

Synthesis of **9c**.

Sodium (0.84 g) was dissolved in 30 ml of methanol, 7 g of methyl *p*-toluenesulphonate and 5.4 g of **9b** in 30 ml of methanol was added dropwise to the solution. The mixture was stirred overnight filtered and the solvent evaporated. The residue was dissolved in 50 ml of chloroform and 10 ml of water and the water layer was extracted four times with chloroform. The organic layer was evaporated and the crude product recrystallized from water, yield 3.1 g (54%), mp 147-148°.

Synthesis of **8c**.

A mixture of 6 g of **9c**, 60 ml of methanol and 6 ml of 37% aqueous hydrochloric acid solution were stirred for two days at room temperature and then concentrated. The hydrochloride salt was converted to the free base with aqueous sodium hydrogen carbonate and extracted with chloroform. The chloroform was evaporated and the residue was trituated with petroleum ether, yield 3.76 g (78%), mp 94-95°.

Synthesis of **13**.

Method A.

A mixture of 1 g of 1,3,*N'*-trimethyl-1*H*-pyrazole-5-carboxylic acid hydrazide and 2 ml of freshly distilled acetone was stirred overnight. The crystals were filtered off and washed with water, yield 0.46 g, mp 145-148° dec.

Method B.

A mixture of 4.5 g of 1,3,*N'*-trimethyl-1*H*-pyrazole-5-carboxylic acid hydrazide and 4.5 ml of mesityl oxide were stirred form two days at room temperature. The crystals were filtered of and washed with water, yield 2.96 g.

Synthesis of **19**.

Three g of **13** was dissolved in 20 ml of methanol and 3 g of sodium borohydride in 6 ml of 0.1 *N* sodium hydroxide was added slowly to the stirred solution. The mixture was stirred for additional two hours at room temperature and then concentrated. The residue was partitioned between water and chloroform and the water layer was extracted twice with chloroform. The organic layers were collected, evaporated and the material obtained was trituated with ether, filtered and washed with ether, yield 2.69 (89%), mp 136-138°.

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