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Tricyclic Heteroaromatic Ring Systems III[1]. Synthesis of 1*H*,6*H*-Dipyrazolo[3,4—*b*:3′,4′—*d*]pyridin-3-ones

Short Communication

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The reaction of hydrazines with substituted ethyl 4-chloro-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxylates leads to the formation of 1*H*,6*H*-dipyrazolo[3,4—*b*:3′,4′—*d*]pyridin-3-ones.

(Keywords: Pyrazolo[3,4—b]pyridines; Ring closures)

Tricyclische heteroaromatische Ringsysteme, III. Synthese von 1H,6H-Dipyrazolo[3,4—b:3′,4′—d]pyridin-3-onen (Kurze Mitteilung)

Die im Titel genannten Verbindungen wurden durch die Reaktion von Hydrazinen mit substituierten Ethyl-4-chlor-1*H*-pyrazolo[3,4—*b*]pyridin-3-carboxylaten dargestellt.

Introduction

Whereas the linear dipyrazolo[3,4—*b*:3′,4′—*e*]pyridine ring system (**1**) has been known for some time[3], the corresponding angular dipyrazolo[3,4—*b*:3′,4′—*d*]pyridine ring system (**2**) has only recently been reported and some of its derivatives shown to act as tranquilizing and antiinflammatory agents[4]. During our studies on pyrazolo[3,4—*b*]pyridines[5] we obtained a number of compounds which were transformed into derivatives of **2**.

Results and Discussion

The pyrazolo[3,4—*b*]pyridines (**3**–**6**) used in this work were obtained by "chloro-cyclization"[6] of the corresponding ethyl α-carbethoxy-β-(pyrazol-5-ylamino)acrylates which in turn were obtained from the reaction of 5-aminopyrazoles with diethyl ethoxymethylenemalonate.

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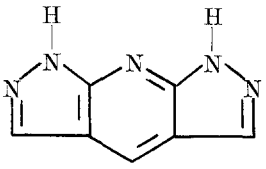

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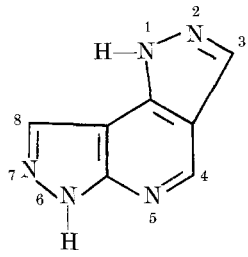

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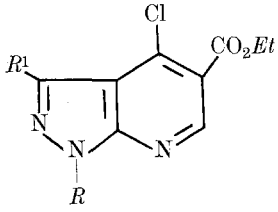
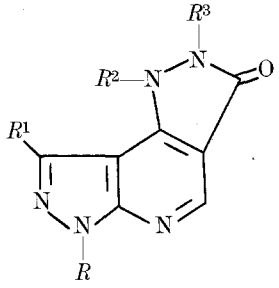
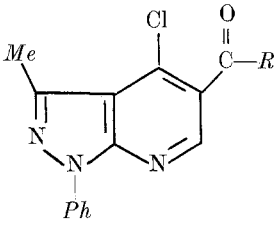




3 $R = R^1 = Me$
4 $R = Me$, $R^1 = Ph$
5 $R = R^1 = Ph$
6 $R = Ph$, $R^1 = Me$

7 $R = R^1 = Me$, $R^2 = R^3 = H$
8 $R = Me$, $R^1 = Ph$, $R^2 = R^3 = H$
9 $R = R^1 = Ph$, $R^2 = R^3 = H$
10 $R = Ph$, $R^1 = Me$, $R^2 = R^3 = H$
11 $R = R^1 = R^2 = Me$, $R^3 = H$
12 $R = R^2 = Me$, $R^1 = Ph$, $R^3 = H$
13 $R = R^1 = Ph$, $R^2 = Me$, $R^3 = H$
14 $R = Ph$, $R^1 = R^2 = Me$, $R^3 = H$
15 $R = Ph$, $R^1 = R^3 = H$, $R^2 = Me$
16 $R = R^3 = Ph$, $R^1 = Me$, $R^2 = H$
17 $R = R^2 = Ph$, $R^1 = Me$, $R^3 = H$



18 $R = OH$
19 $R = Cl$

The reaction of **3**-**6** with hydrazine and methylhydrazine leads to the desired tricyclic compounds **7**–**15**. From the reaction of **6** with phenylhydrazine an open chain derivative was formed which on treatment with acetic acid ringclosed to **16** with the phenyl ring on N-2. The isomeric compound **17** having the phenyl ring on N-1 was obtained indirectly. The chloroester (**6**) was hydrolyzed to the corresponding acid

(**18**) and then transformed into its acid chloride (**19**) which on reaction with phenylhydrazine at room temperature followed by heating in dioxan gave the isomeric tricyclic compound **17**. The data of these dipyrazolopyridines are presented in Table 1.

The signals for the protons of N-methyl groups (at N-1 or N-6) are between δ 4.00 and 4.15 ppm and for the protons of the C-methyl group (at C-8) between 2.63 and 2.75 for the majority of the compounds. However, in **12** and **13** the N-methyl proton signals were observed at 3.32 and in **17** the C-methyl proton-signal at 1.75. These upfield shifts for the methyl protons are ascribed to the ring-current-shielding of the benzene ring on C-8 and N-1, respectively. These anisotropic shielding effects of phenyl groups have earlier been noticed in other tricyclic systems[7].

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Experimental

The proton magnetic resonance spectra (PMR) were obtained on a Hitachi Perkin-Elmer model R-20 B spectrometer operating at 60 Mc/s (tetramethylsilane as internal standard). The infrared (IR) absorption spectra were taken by the Perkin-Elmer model 727 spectrophotometer and were measured in potassium bromide disks. Melting points (mp) were determined with a Fisher-Johns apparatus and are uncorrected. Elemental analyses were determined on a Perkin-Elmer model 240.

Ethyl 4-chloro-1,3-dimethylpyrazolo[3,4—*b*]pyridine-5-carboxylate (**3**) mp 93-94°; ethyl 4-chloro-1-methyl-3-phenylpyrazolo[3,4—*b*]pyridine-5-carboxylate (**4**) mp 130-131°; ethyl 4-chloro-1,3-diphenyl-pyrazolo[3,4—*b*]pyridine-5-carboxylate (**5**) mp 162-163°; and ethyl 4-chloro-3-methyl-1-phenylpyrazolo[3,4—*b*]pyridine-5-carboxylate (**6**) mp 110° used in this work were all obtained by the chlorocyclization of the corresponding ethyl α-carbethoxy-β-(pyrazol-5-ylamino)acrylates[5].

1H,6H-Dipyrazolo[3,4—b:3',4'—d]pyridin-3-ones

General Method. An equimolar mixture of a chloroester (**3-6**) and hydrazine hydrate or methylhydrazine in 5-10 ml of ethanol was heated under reflux for 15 h (hydrazine hydrate) or 3 h (methylhydrazine). The reaction mixture was concentrated, diluted with water, filtered and washed with water. The cyclized product thus obtained was dried and crystallized from an appropriate solvent to give **7-15** (Table 1).

2,6-Diphenyl-8-methyldipyrazolo[3,4—b:3',4'—d]pyridin-3-one (**16**)

A mixture of 0.9 g of **6**, 0.3 g of phenylhydrazine in 10 ml of ethanol was heated under reflux to give 0.88 g (80%) of *N*-phenyl-*N'*-(5-carbethoxy-3-methyl-1-phenylpyrazolo[3,4-*b*]pyrid-4-yl)hydrazine as light brown crystals

Table 1. *1H,6H-Dipyrazolo[3,4—b:3',4'—d]pyridin-3-ones*

Compd. No.	Yield (%)	mp° (from)	Molecular formula[a]	IR (cm^{-1})	PMR (J in Hz)[b] (temp°)
7	84	258-259 (*Ac*OH)	$C_9H_9N_5O$	3250-2400 (NH); 1640 (C=O)	2.63 (3H, s, C-*Me*); 4.04 (3H, s, N-*Me*); 8.89 (1H, s, H-4); 9.10 (br., NH). (60)
8	89	278-279 (*Ac*OH)	$C_{14}H_{11}N_5O$	3300-2500 (NH) 1645 (C=O)	4.15 (3H, s, N-*Me*); 7.40-8.20 (5H, m, *Ph*); 8.81 (1H, s, H-4); 10.00 (br., NH). (80)
9	85	288-289 (*Ac*OH)	$C_{19}H_{13}N_5O$	3380-2500 (NH) 1640 (C=O)	3.35 (br., NH); 7.40-8.40 (10H, m, *Ph*); 8.90 (1H, s, H-4). (34)
10	86	278-279 (*Ac*OH)	$C_{14}H_{11}N_5O$	3300-2800 (NH) 1648 (C=O)	2.75 (3H, s, C-*Me*); 7.30-8.40 (5H, m, *Ph*); 8.87 (1H, s, H-4); 12.00 (br., NH). (34)
11	96	295-297 (*Et*OH)	$C_{10}H_{11}N_5O$	3250-2350 (NH) 1630 (C=O)	2.70 (3H, s, C-*Me*); 4.00 (3H, s, N-*Me*); 4.03 (3H, s, N-*Me*); 8.75 (1H, s, H-4). (100)
12	95	>300 (*Ac*OH)	$C_{15}H_{13}N_5O$	3200-2300 (NH) 1625 (C=O)	3.32 (s, N-1-*Me* + NH + H_2O); 4.15 (3H, s, N-6-*Me*); 7.58 (5H, s, *Ph*); 8.75 (1H, s, H-4). (34)
13	95	>300 (*Ac*OH)	$C_{20}H_{15}N_5O$	3250-2400 (NH) 1630 (C=O)	3.32 (3H, s, N-*Me*); 7.30-8.50 (10H, m, *Ph*); 8.84 (1H, s, H-4). (100)
14	77	>300 (*Et*OH)	$C_{15}H_{13}N_5O$	3300-2100 (NH) 1630 (C=O)	2.75 (3H, s, C-*Me*); 4.15 (3H, s, N-*Me*); 7.30-8.50 (5H, m, *Ph*); 8.68 (1H, s, H-4); 11.25 (br., NH). (34)
15	17	>300 (*Et*OH)	$C_{14}H_{11}N_5O$	3250-2100 (NH) 1645 (C=O)	3.30 (br., NH); 4.15 (3H, s, N-*Me*); 7.30-8.50 (5H, m, *Ph*); 8.64 (1H, s, H-8); 8.79 (1H, s, H-4). (50)
16	98	>300 (*Ac*OH)	$C_{20}H_{15}N_5O$	3200-2500 (NH) 1640 (C=O)	2.69 (3H, s, C-*Me*); 7.20-8.20 (10H, m, *Ph*); 8.61 (1H, s, H-4). (50)
17	86	>300 (*Ac*OH)	$C_{20}H_{15}N_5O$	3200-2300 (NH) 1625 (C=O)	1.75 (3H, s, C-*Me*); 7.50 (5H, s, *Ph*-1); 7.30-8.30 (5H, m, *Ph*-6); 8.89 (1H, s, H-4); 11.00-12.00 (br., NH). (80)

[a] Elemental analyses are in full agreement with the calculated values.
[b] Solvent *DMSO-d_6*.

mp 180-181° (ethanol). PMR ($CDCl_3$) δ: 1.35 (3H, t, $J = 7$ Hz, CH_3—CH_2—OCO); 3.48 (3H, s, *Me*-3); 4.30 (2H, q, $J = 7$ Hz, CH_3—CH_2—OCO—); 6.30 (1H, s, *Ph*—NH—N); 6.68—7.30 and 8.00-8.30 (10H, m, arom.); 8.89 (1H, s, H-6); 10.48 (1H, s, *Ph*—NH—NH—). IR cm^{-1}: 3260 and 3250-2800 (NH); 1680 (CO, ester).

On heating the hydrazine obtained above in 10 ml of acetic acid for 4 h. **16** was isolated from the reaction mixture on diluting with water and crystallization (Table 1).

1,6-Diphenyl-8-methyl-1H,6H-dipyrazolo[3,4—b:3',4'—d]pyridin-3-one (**17**)

A solution of 20 ml of acetic acid and hydrochloric acid and 0.95 g of (**16**) was heated under reflux for a period of 3 h and the product filtered off to give 0.81 g (94%) of 4-chloro-3-methyl-1-phenylpyrazolo[3,4—*b*]pyridine-5-carboxylic acid (**18**) as colorless crystals, mp 236-237° (*Ac*OH). PMR (*DMSO-d*$_6$) δ: 2.64 (3H, s, *Me*); 7.40-8.10 (5H, m, arom.); 8.58 (1H, s, H-6). IR cm^{-1}: 3300-2900 (OH); 1725 (CO, acid); 1600, 1498, 1190, 755, 690.

The acid **18** was converted into its acid chloride **19** by heating under reflux 0.5 g of **18** with 5 ml of thionyl chloride for 1 h and the excess thionyl chloride evaporated under reduced pressure. To the cooled residue 10 ml of dioxan and 0.2 g of phenylhydrazine was added and left at room temperature with stirring for 0.5 h and then heated under reflux for 4 h, diluted with water, filtered and purified to give **17** (Table 1).

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