1-Aryl-6-azauracils, XXXVI[1]:

Synthesis of 6-Azauracil Derivatives of Phenazone

1-Aryl-6-azauracile, 36. Mitt.: Synthese einiger 6-Azauracilphenazon-Derivate

Jan Slouka and Miloslav Hejsek

Institute of Analytical and Organic Chemistry, Palacky University, 771 46 Olomouc, CSFR

Received December 27, 1990

In spite of the fact that a great number of several 4-substituted derivatives of phenazone has already been prepared, the only derivative with 6-azauracile cycle up to now is 4-(2-thio-6-azauracil-5-yl)-phenazone, prepared by *Schmidt*[2].

This communication describes the synthesis of several further derivatives, in which, however, the rest of phenazone is joined at position 1 of the 6-azauracile cycle.

By diazotization of 4-aminoantipyrine and by coupling the formed diazonium salt with ethyl cyanoacetylcarbamate, ethyl 1-phenyl-2,3-dimethyl-5-oxo-2,5-dihydropyrazol-4-ylhydrazono-cyanoacetylcarbamate (**1**) was obtained in good yield, which was transformed both by alkaline and thermal cyclization to 1-(1-phenyl-2,3-dimethyl-5-oxo-2,5-dihydropyrazol-4-yl)-6-azauracil-5-carbonitrile (**2a**). This compound served as a starting material for the synthesis of other functional derivatives such as thioamide **2b**, amidoxime **2c**, 5-methyl-1,2,4-oxadiazol-3-yl-derivative **2d** and acid **2e**. By decarboxylation of this acid 1-(1-phenyl-2,3-dimethyl-5-oxo-2,5-dihydropyrazol-4-yl)-6-azauracil (**2f**) was obtained.

Experimental Part

Melting points: Boetius block, uncorrected.- IR-spectra: IR-75 spectrometer (Carl Zeiss, Jena), KBr.

Ethyl 1-phenyl-2,3-dimethyl-5-oxo-2,5-dihydropyrazol-4-ylhydrazono-cyanoacetylcarbamate (1)

A solution of 4.10 g (20.17 mmol)of 4-aminoantipyrine in 50 ml water and 10 ml 37% HCl was cooled to 0°C and diazotized with 1.38 g (20.00 mmol) $NaNO_2$ in 8 ml ice water. The mixture was left for 1 h at 0°C with intermittent stirring and then it was added with stirring to a mixture prepared from 4.20 g (26.90 mmol) ethyl cyanoacetylcarbamate dissolved in 900 ml hot water, cooled to 0°C and treated with 20 g sodium acetate. The mixture was set aside at 0-5°C for 5 d with intermittent stirring. The separated yellow crystals were collected, washed with water and dried: 6.35 g (95%). After recrystallization from ethanol m.p. 183-185°C (at rapid heating).- $C_{17}H_{18}N_6O_4$ (370.4) Calcd. C 55.1 H 4.90 N 22.7 Found C 55.1 H 4.82 N 22.7.- IR (KBr): 1676; 1772 (CO); 2194 (CN) cm^{-1}.

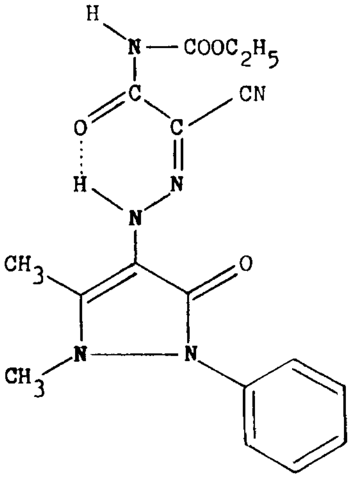
1-(1-Phenyl-2,3-dimethyl-5-oxo-2,5-dihydropyrazol-4-yl)-6-azauracil-5-carbonitrile (2a)

a) The mixture of 1.12 g (3.02 mmol) of hydrazone **1** and 70 ml xylene was refluxed 18 h and cooled. After 24 h the solid was collected, washed with hexane and dried: 825mg (84%). After recrystallization from water m.p. 317-319°C.

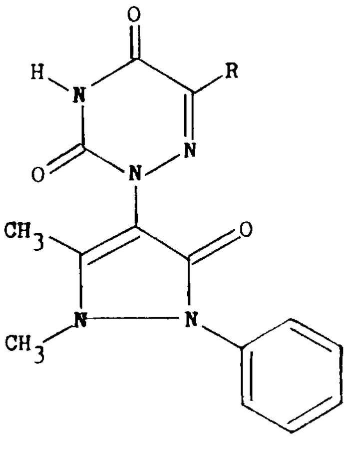
b) The mixture of 1.12 g (3.02 mmol) of hydrazone **1**, 700 mg Na_2CO_3 and 30 ml water was heated for 30 min on a boiling water bath, cooled and acidified to pH 2. After several h the separated solid was collected, washed with water and dried: 880 mg (90%), m.p. 317-319°C (water).- $C_{15}H_{12}N_6O_3$ (324.3) Calcd. C 55.5 H 3.73 N 25.92 Found C 55.5 H 3.75 N 26.1.- IR (KBr): 1703; 1731; 1746 (CO); 2235 (CN) cm^{-1}.

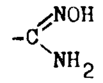
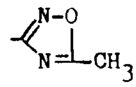
1-(1-Phenyl-2,3-dimethyl-5-oxo-2,5-dihydropyrazol-4-yl)-6-azauracil-5-carbothioamide (2b)

The solution of 325 mg (1.00 mmol) nitrile **2a** in 20 ml water and 3.0 ml 25% NH_3 was saturated with H_2S, allowed to stand in a stoppered flask at room temp. for 48 h and evaporated *in vacuo*. The residue was dissolved in a small amount of 1% aqueous ammonia. After addition of a little bit of charcoal the solution was filtered and the filtrate acidified with acetic acid. Next day, the crystals were collected, washed with water and dried in the



1



2	R
a	-CN
b	$-CSNH_2$
c	
d	
e	-COOH
f	-H

2

open air at room temp., yield of the monohydrate: 320 mg (85%). After recrystallization from water m.p. 253-255°C (decomp.).- $C_{15}H_{14}N_6O_3S\cdot H_2O$ (376.3) Calcd. C 47.9 H 4.29 N 22.3 Found C 48.1 H 4.05 N 22.1.- IR (KBr): 1702; 1739 (CO) cm^{-1}.

Amidoxime of 1-(1-phenyl-2,3-dimethyl-5-oxo-2,5-dihydropyrazol-4-yl)-6-azauracil-5-carboxylic acid (**2c**)

Hydroxylamine hydrochloride (100 mg) was added to a solution of 325 mg (1.00 mmol) of nitrile **2a** in 10 ml of 7% aqueous ammonia. After standing for 10 days in a stoppered flask at room temp., the mixture was evaporated *in vacuo* and the residue was mixed with a small volume of water and several drops of acetic acid. Next day, the crystals were collected, washed with a little water and dried, yield of the dihydrate: 293 mg (74%), m.p. 248-250°C (decomp.).- $C_{15}H_{15}N_7O_4\cdot 2H_2O$ (393.4) Calcd. C 45.8 H 5.80 N 24.9 Found C 45.6 H 5.55 N 24.8.- IR (KBr): 1695; 1720 (CO) cm^{-1}.

1-(1-Phenyl-2,3-dimethyl-5-oxo-2,5-dihydropyrazol-4-yl)-5-(5-methyl-1,2,4-oxadiazol-3-yl)-6-azauracil (**2d**)

A mixture of 200 mg (0.51 mmol) amidoxime **2c**, 25 ml acetic acid and 8 ml acetanhydride was refluxed 5 h, the mixture was evaporated *in vacuo* and the residue was mixed with 1 ml of water. Next day, the crystals were collected, washed with water and dried, yield of the monohydrate: 195mg (96%), m.p. 318-320°C.- $C_{17}H_{15}N_7O_4\cdot H_2O$ (399.4) Calcd. C 51.1 H 4.29 N 24.6 Found C 50.9 H 4.08 N 24.8.- IR (KBr): 1638; 1713; 1735 (CO) cm^{-1}.

1-(Phenyl-2,3-dimethyl-5-oxo-2,5-dihydropyrazol-4-yl)-6-azauracil-5-carboxylic acid (**2e**)

A mixture of 330 mg (1.02 mmol) nitrile **2a** and 15 ml 20% HCl was refluxed for 4 h and then evaporated *in vacuo*. The residue was mixed with a small amount of water, the crystals were collected, washed with water and air-dried at room temp., yield of the monohydrate: 320 mg (87%). After recrystallization from water m.p. 245-247°C (decomp.).- $C_{15}H_{13}N_5O_5\cdot H_2O$ (361.3) Calcd. C 49.9 H 4.18 N 19.4 Found C 49.7 H 4.16 N 19.6.- IR (KBr): 1612; 1716; 1722 (CO) cm^{-1}.

1-Phenyl-2,3-dimethyl-4-(6-azauracil-1-yl)-2,5-dihydropyrazol-5-one(**2f**)

Acid **2e** (180 mg, 0.5 mmol) was heated at 245-250°C until decarboxylation had ceased. The residue was recrystallized from water with use of charcoal and the filtrate was concentrated to a small volume. Next day, the crystals were collected and air-dried at room temp., yield of dihydrate: 160 mg (96%), m.p. 140-142°C.- $C_{14}H_{13}N_5O_3\cdot 2H_2O$ (335.3) Calcd. C 50.1 H 5.11 N 20.9 Found C 50.0 H 5.18 N 20.7.- IR (KBr): 1645; 1701; 1724 (CO) cm^{-1}.

References

1 Part XXXV: J. Slouka, Coll. Czech. Chem. Commun. *55*, 2967 (1990).

2 F. Schmidt, Arch. Pharm. (Weinheim) *299*, 150 (1956).

[KPh555]

Verantwortlich für die Redaktion: Prof. Dr. W. Wiegrebe. Pharmazeutisches Institut der Universität Regensburg, Universitätsstraße 31, Postfach 397, D-8400 Regensburg. – Anzeigenleitung: R.J. Roth, D-6940 Weinheim – VCH Verlagsgesellschaft mbH (Geschäftsführer: Hans Dirk Köhler), Postfach 101161, D-6940 Weinheim – Alle Rechte, insbesondere die der Übersetzung in fremde Sprachen, vorbehalten. Kein Teil dieser Zeitschrift darf ohne schriftliche Genehmigung des Verlages in irgendeiner Form – durch Photokopie, Mikrofilm oder irgendein anderes Verfahren – reproduziert oder in eine von Maschinen, insbesondere von Datenverarbeitungsmaschinen verwendbare Sprache übertragen oder übersetzt werden. – All rights reserved (including those of translation into foreign languages). No part of this issue may be reproduced in any form – photoprint, microfilm, or any other means – nor transmitted or translated into a machine language without the permission in writing of the publishers. – Von einzelnen Beiträgen oder Teilen von ihnen dürfen nur einzelne Vervielfältigungsstücke für den persönlichen und sonstigen eigenen Gebrauch hergestellt werden. Die Weitergabe von Vervielfältigungen, gleichgültig zu welchem Zweck sie hergestellt werden, ist eine Urheberrechtsverletzung. Der Inhalt dieses Heftes wurde sorgfältig erarbeitet. Dennoch übernehmen Autoren, Herausgeber, Redaktion und Verlag für die Richtigkeit von Angaben, Hinweisen und Ratschlägen sowie für eventuelle Druckfehler keine Haftung. This journal was carefully produced in all its parts. Nevertheless, authors, editors and publishers do not warrant the information contained therein to be free of errors. Readers are advised to keep in mind that statements, data, illustrations, procedural details or other items may inadvertently be inaccurate. – Die Wiedergabe von Gebrauchsnamen, Handelsnamen, Warenbezeichnungen u. dgl. in dieser Zeitschrift berechtigt nicht zu der *Annahme, daß* solche Namen ohne weiteres von jedermann benutzt werden dürfen. Es handelt sich häufig um gesetzlich eingetragene Warenzeichen, auch wenn sie in dieser Zeitschrift nicht als solche gekennzeichnet sind. Texterfassung und EDV-Bearbeitung: Fa. Hellinger, D-6901 Heiligkreuzsteinach; Druck und Buchbinder: Rheinhessische Druckwerkstätte, D-6508 Alzey, – Unverlangt zur Rezension eingehende Bücher werden nicht zurückgesandt.

Printed on acid-free and low chlorine paper/Gedruckt auf säurefreiem und chlorarm gebleichtem Papier