Reactivity of 3*H*-Pyrimido[5,4-*c*] [1,2,5]oxadiazin-3-one towards Carbanions: Synthesis of Pteridine-2,4-diones

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The reaction of 3*H*-pyrimido[5,4-*c*] [1,2,5]oxadiazin-3-one (**5**) with carbanions prepared *in situ* from compounds containing an activated methylene group afforded 6,7-disubstituted pteridine-2,4-diones **7a-m** in good yields. The reaction mechanism, involving the initial attack by carbanion at oxadiazinone nitrogen atom bonded to oxygen, is proposed and discussed.

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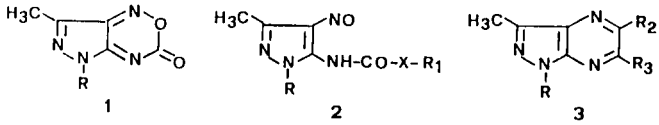
As a part of our program investigating the reactivity of fused heterocycles, we reported that pyrazolo[4,3-*c*] [1,2,5]-oxadiazin-3(5*H*)-ones **1** undergo easy attack by a variety of nucleophiles. In particular, we showed that amines and alcohols react with **1** to give ring opened products **2** [1-4] while carbanions lead to pyrazolo[3,4-*b*]pyrazines **3** [5] (Scheme 1).

Scheme 1



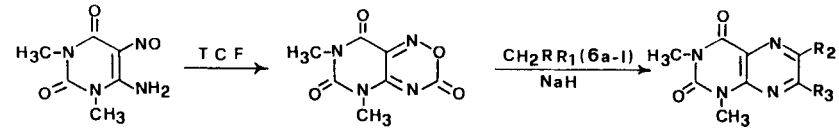
R, a =phenyl, b = methyl

X =NH or O

In order to explain these different results, we suggested that **2** are derived from the attack of amines and alcohols at carbonyl sp² carbon of oxadiazinone ring while **3** are generated by the attack of carbanions at 1-nitrogen atom bonded to oxygen. Considerating the synthetic potential of the above described reactions, we have extended our work to the study of analogs of **1**; in the present paper we report on the results obtained by reacting 3,6,8-trioxo-5,7-dimethyl-5,6,7,8-tetrahydro-3*H*-pyrimido[5,4-*c*] [1,2,5]oxadiazine (**5**) [6] with carbanions. The choice of **5** was made with the aim of achieving a new route to pteridine-2,4-diones or lumazines, a class of compounds possessing a wide range of biological activity [7].

The starting material **5** had been previously synthesized by condensation of 1,3-dimethyl-4-amino-5-nitrosouracil (**4**) with fosgene [6]; we have found that the synthesis of **5** could be accomplished with very high yield by reacting **4** with trichloromethyl chloroformate (TCF), that resulted easier to handle than phosgene. Carbanions were generated *in situ* through the action of a strong base on compounds containing an activated methylene group such as β-diketones **6a-c**, β-diesters **6d,e**, malononitrile (**6f**), β-ketoamides **6g,h** and β-ketoesters **6i,l** (Scheme 2).

Scheme 2



6

	R	R_1
a	$COCH_3$	$COCH_3$
b	COC_6H_5	COC_6H_5
c	$COCH_3$	COC_6H_5
d	$COOCH_3$	$COOCH_3$
e	$COOC_2H_5$	$COOC_2H_5$
f	CN	CN
g	$COCH_3$	$CONHC_6H_5$
h	$COCH_3$	$CONHCH_2C_6H_5$
i	$COCH_3$	$COOCH_3$
l	$COCH_3$	$COOC_2H_5$
m	-	-

7

R_2	R_3
$COCH_3$	CH_3
COC_6H_5	C_6H_5
COC_6H_5	CH_3
$COOCH_3$	OH
$COOC_2H_5$	OH
CN	NH_2
$CONHC_6H_5$	CH_3
$CONHCH_2C_6H_5$	CH_3
$COOCH_3$	CH_3
$COOC_2H_5$	CH_3
$COCH_3$	OH

Table 1

Analytical Data of 1,3-Dimethylpteridine-2,4-diones **7a-m**

Compound	Yield %	Mp. °C	[c]	Formula	Analysis % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
7a	83	169-170	a	$C_{11}H_{12}N_4O_3$	53.22	4.87	22.56	53.25	4.88	22.60
7b	91	202-204	b	$C_{21}H_{16}N_4O_3$	67.73	4.33	15.04	67.71	4.29	15.00
7c	98	195-196	a	$C_{16}H_{14}N_4O_3$	61.93	4.54	18.05	61.86	4.52	17.99
7d	68	252	c	$C_{10}H_{10}N_4O_5$	45.11	3.78	21.04	45.15	3.74	21.07
7e	70	170-172	c	$C_{11}H_{12}N_4O_5$	47.14	4.31	19.99	47.20	4.42	20.03
7f	95	>350 [b]	b	$C_9H_8N_6O_2$	46.55	3.47	36.19	46.35	3.42	36.23
7g	97	230-231	a	$C_{16}H_{15}N_5O_3$	59.07	4.64	21.52	59.33	4.66	21.52
7h	84	216-217	a	$C_{17}H_{17}N_5O_3$	60.16	5.05	20.63	60.15	5.04	20.59
7i	54	187-190	b	$C_{11}H_{12}N_4O_4$	49.99	4.57	21.20	50.02	4.59	21.23
7l	56	143-145	b	$C_{12}H_{14}N_4O_4$	51.79	5.07	20.30	51.83	5.05	20.22
7m	38 [a]	197-199	b	$C_{10}H_{10}N_4O_4$	48.00	4.02	22.30	47.83	3.99	22.32

[a] The yield is referred to the reaction of **5** with methyl acetoacetate (**6i**); with ethyl acetoacetate (**6l**) the yield of **7m** was 34%. [b] At about 275°, the colourless product changed into yellow crystals unmelting within 350°. [c] Crystallisation solvent: a = ethyl acetate, b = ethanol, c = dioxane.

Table 2

IR, ^{1}H-NMR Spectral Data of Compounds **7a-m**

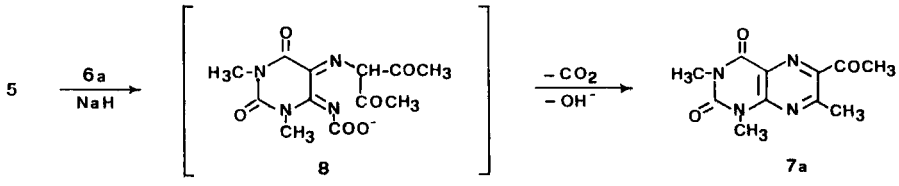
Compound	IR (cm^{-1}) [a]	^{1}H-NMR (δ) [b]
7a	1725, 1700, 1680, 1550	2.75 (s, 3H, CH_3CO), 2.90 (s, 3H, CH_3), 3.50 (s, 3H, CH_3N), 3.70 (s, 3H, CH_3N)
7b	1720, 1680, 1550	3.50 (s, 3H, CH_3N), 3.70 (s, 3H, CH_3N), 7.2-8.0 (m, 10H, 2ArH)
7c	1730, 1710, 1680, 1540	2.77 (s, 3H, CH_3), 3.52 (s, 3H, CH_3N), 3.72 (s, 3H, CH_3N), 7.4-7.8 (m, 5H, ArH)
7d	3420, 1725, 1700, 1660, 1560	3.47 (s, 3H, CH_3N), 3.65 (s, 3H, CH_3N), 4.07 (s, 3H, CH_3O), 11-13 (br, 1H, OH, deuterium oxide exchangeable)
7e	3400, 1715, 1685, 1660, 1565	1.45 (t, J = 8 Hz, 3H, CH_3), 3.5 (s, 3H, CH_3N), 3.65 (s, 3H, CH_3N), 4.55 (q, J = 8 Hz, 2H, CH_2), (OH signal undetected)
7f	3340, 3240, 2240, 1730, 1670, 1550	3.47 (s, 3H, CH_3N), 3.57 (s, 3H, CH_3N), 5.75 (br, 2H, NH_2, deuterium oxide exchangeable)
7g	3450, 3250, 1720, 1670, 1555, 1540	(hexadeuteriodimethylsulfoxide) 2.85 (s, 3H, CH_3), 3.38 (s, 3H, CH_3N), 3.60 (s, 3H, CH_3N), 7.2-8.0 (m, 5H, ArH), 10.5 (br, 1H, NH, deuterium oxide exchangeable)
7h	3400, 1720, 1680, 1660, 1550	(deuteriochloroform-hexadeuteriodimethylsulfoxide 1:1) 2.93 (s, 3H, CH_3), 3.40 (s, 3H, CH_3N), 3.65 (s, 3H, CH_3N), 4.57 (d, J = 7 Hz, 2H, CH_2), 7.35 (m, 5H, ArH), 9.0 (br, 1H, NH, deuterium oxide exchangeable)
7i	1725, 1685, 1560, 1550	2.92 (s, 3H, CH_3), 3.51 (s, 3H, CH_3N), 3.71 (s, 3H, CH_3N), 3.98 (s, 3H, CH_3O)
7l	1720, 1680, 1560	1.45 (t, J = 7Hz, 3H, CH_3CH_2), 2.92 (s, 3H, CH_3), 3.54 (s, 3H, CH_3N), 3.74 (s, 3H, CH_3N), 4.5 (q, J = 7 Hz, 2H, CH_2CH_3)
7m	3000 (br), 1725, 1680, 1650, 1565, 1545	2.88 (s, 3H, CH_3), 3.53 (s, 3H, CH_3N), 3.70 (s, 3H, CH_3N), 13.25 (br, 1H, OH, deuterium oxide exchangeable)

[a] Potassium bromide. [b] Deuteriochloroform was used as the solvent, unless otherwise noted.

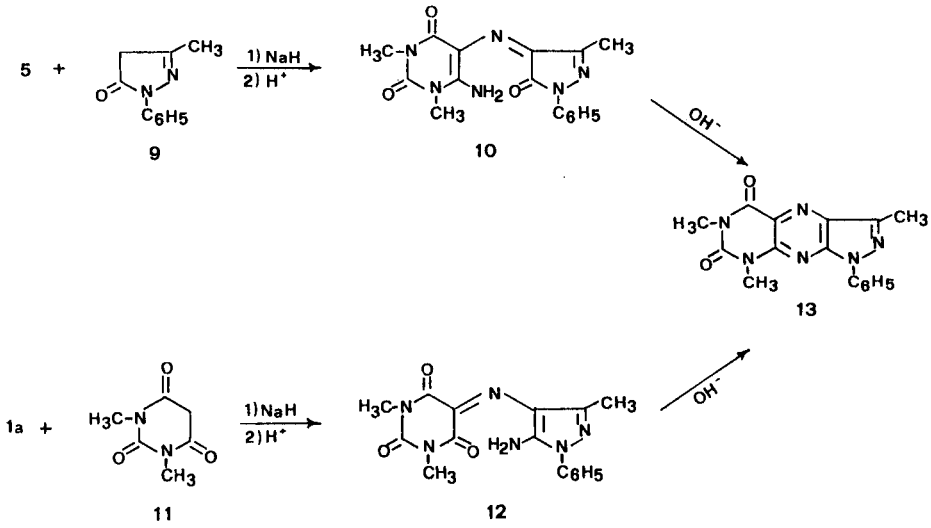
As a first attempt, a solution of **5** in anhydrous tetrahydrofuran, kept under stirring at room temperature, was treated with acetylacetone (**6a**) in the presence of sodium hydride. Within 30 minutes **5** was completely converted into 1,3,7-trimethyl-6-acetylpteridinedione (**7a**); during this time carbon dioxide continuously evolved from the reaction mixture. The structure of **7a** was inferred from analytical and spectral data; moreover this compound resulted identical with a sample of **7a** prepared by the known methods [8,9]. Following the above described procedure, **5** was reacted with the series of compounds **6a-l** and in all cases high yields of pteridinediones **7a-m** were recovered as final products (Tables 1, 2).

Compounds **6a-h** gave rise to a single reaction product. In particular, β-diketones **6a-c** afforded 6-acylpteridinediones **7a-c**; β-diesters **6d,e** produced 6-alkoxycarbonyl-7-hydroxypteridinediones **7d,e**, malononitrile (**6f**) provided 6-cyano-7-aminopteridinedione (**7f**); β-ketoamides **6g,h** yielded *N*-substituted-6-carboxamido-7- methylpteridinediones **7g,h** respectively. Two reaction products were recovered in the reaction of **5** with β-ketoesters: methyl acetoacetate (**6i**) gave a mixture of 6-methoxycarbonyl-7-methylpteridinedione (**7i**) and 6-acetyl-7-hydroxypteridinedione (**7m**); ethyl acetoacetate (**6l**) afforded an analogous mixture of compound **7m** and of 6-ethoxycarbonyl-7-methylpteridinedione (**7l**). In both reactions product **7m** was

Scheme 3



Scheme 4



the minor component of the mixture.

The analogy of structure and of chemical behaviour of **5** with pyrazolooxadiazinone **1** suggested a parallel reaction mechanism (Scheme 3).

The first step would consist in the attack of carbanion, for example the anion derived from acetylacetone (**6a**), at 1-nitrogen atom of **5** with cleavage of the N-O bond and formation of the unstable ring opened intermediate **8**.

Successively the intramolecular nucleophilic attack by the carboxyimine nitrogen at carbonyl group would lead to cyclic **7a** with loss of carbon dioxide. This mechanism explains the formation of one or two reaction products depending on the kind of carbanion. Symmetrical carbanions must necessarily give a single product, as found for β-diketones **6a,b**, β-diesters **6d,e** and malononitrile (**6f**), while unsymmetrical carbanions provide intermediates that cyclize by the attack of carboxyimine nitrogen at more electrophilic center. Accordingly, benzoylacetone (**6c**) and β-ketoamides **6g,h**, bearing a more electrophilic keto group, gave a single reaction product; β-ketoesters **6i,l** containing two competitive electrophilic centers afforded two kinds of products, one deriving from the attack at keto group (compounds **7i** and **7l**) the second (compound **7m**), from the attack at ester function with displacement of the alkoxy group. The lower yield of the latter product **7m** compared to that of **7i** and **7l** is due to the lower electrophilicity of the ester group.

Any attempt to isolate the key intermediates for the cyclisation process was unsuccessful, probably because of their high instability. An indirect evidence for the proposed mechanism was gained from the isolation of a weakly stable intermediate **10** prepared by reacting **5** with 1-phenyl-3-methyl-5-pyrazolone (**9**) under the usual conditions (Scheme 4).

The structure of **10** was supported by analytical and spectral data; moreover it was confirmed by the base-catalyzed conversion of **10** into the known 1-phenyl-3,6,8-trimethylpyrazolo[4,3-*g*]pteridine-5,7-dione (**13**) [10,11]. This product was alternatively prepared by reacting pyrazolooxadiazinone (**1a**) with 1,3-dimethylbarbituric acid (**11**)

through the intermediate **12**, isolated as a red stable product.

In conclusion, pyrimidooxadiazinone (**5**) presents a reactivity towards carbanions strictly similar to that observed for pyrazolooxadiazinones **1**. The N-O group of **5** behaves as a highly active nitroso function in which the nitrogen atom became the preferential center of attack by the negatively charged carbanions. The results obtained indicate that system **5** provides a new interesting entry to a variety of 6,7-disubstituted pteridine-2,4-diones.

EXPERIMENTAL

Melting points were determined using a Büchi capillary apparatus and are uncorrected. The ir spectra were recorded from potassium bromide discs on a Hitachi-Perkin 157G spectrometer. The ^{1}H-nmr spectra were recorded on a Perkin-Elmer R32 (90 MHz) and on a Bruker WP80 spectrometers; chemical shifts (δ) are given in parts per million (ppm) relative to tetramethylsilane as internal standard. Thin layer chromatography was performed on pre-coated silica gel 60 F-254 plates manufactured by Merck, Darmstad, Germany. Column chromatography was carried out using Merck 7734 silica gel.

3,6,8-Trioxo-5,7-dimethyl-5,6,7,8-tetrahydro-3*H*-pyrimido[5,4-*c*][1,2,5]-oxadiazine (**5**).

Trichloromethyl chloroformate (2.64 ml, 22 mmoles) was added to a suspension of 1,3-dimethyl-4-amino-5-nitrosouracil (**4**) (3.68 g, 20 mmoles) in anhydrous tetrahydrofuran (100 ml). The reaction mixture was stirred at room temperature for 3 hours, the solvent was evaporated *in vacuo* and the residue was crystallized from methanol to give 3.65 g (87%) of **5**, mp 217-219°, lit [6] 218-220°; ir (potassium bromide): 1780, 1740, 1685, 1625, 1570 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 3.25 (s, 3H, CH_3), 3.90 (s, 3H, CH_3).

General Procedure for Pteridine-2,4-diones **7a-h**.

A 55% sodium hydride dispersion (0.5 g, 11 mmoles) was added to a solution of **5** (2.10 g, 10 mmoles) and of the pertinent reactant **6a-h** (11 mmoles) in anhydrous tetrahydrofuran (60 ml). The mixture was stirred at room temperature until **5** was completely reacted (within 30-60 minutes, as ascertained by tlc). The solvent was evaporated *in vacuo*, the residue was poured into water (50 ml) and acidified with hydrochloric acid. The resulting precipitate was collected and washed with water; it appeared to be pure tlc. Analytical and spectral data are recorded in Tables 1,2.

Reaction of **5** with Ketoesters: Synthesis of Compounds **7i**, **7m**.

A solution of methyl acetoacetate (**6i**) (1.08 ml, 10 mmoles) in anhydrous tetrahydrofuran (20 ml) was treated with a 55% sodium hydride dispersion (0.5 g, 11 mmoles) and then added dropwise to a stirred solution of **5** (2.10 g, 10 mmoles) in anhydrous tetrahydrofuran (60 ml), kept under a nitrogen atmosphere. Upon completation of the addition (1.5 hours), the solvent was removed *in vacuo* and the residue was poured into water (50 ml). The resulting suspension was extracted with chloroform (3 x 20 ml), the extracts were dried (magnesium sulfate) and evaporated to give 1.43 g (54%) of **7i**, mp 188-190° (ethanol); ir (potassium bromide): 1725, 1685, 1560, 1550 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.92 (s, 3H, CH_3), 3.51 (s, 3H, CH_3N), 3.71 (s, 3H, CH_3N), 3.98 (s, 3H, CH_3O). The aqueous solution was acidified with hydrochloric acid and extracted with chloroform (3 x 20 ml). After being dried (magnesium sulfate), the extracts were evaporated *in vacuo* to give 0.95 g (38%) of **7m**, mp 197-199° (ethanol); ir (potassium bromide): 3000, 1725, 1680, 1650, 1565, 1560 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.88 (s, 3H, CH_3), 3.53 (s, 3H, CH_3N), 3.70 (s, 3H, CH_3N), 13.25 (br, 1H, OH, deuterium oxide exchangeable).

Following the above described procedure, ethyl acetoacetate (**6l**) was reacted with **5** to give a mixture of compounds **7l** and **7m** that were analogously separated (analytical and spectral data are recorded in Tables 1,2).

Synthesis of Compound **10**.

A 55% sodium hydride dispersion (0.5 g, 11 mmoles) was added to a solution of **5** (2.10 g, 10 mmoles) and **9** (1.76 g, 10 mmoles) in anhydrous tetrahydrofuran (50 ml). After being stirred for 20 minutes, the suspension was acidified with acetic acid and the solvents were removed *in vacuo*. The violet residue was purified by passage through a silica column (eluting system: methylene chloride-methanol-acetic acid 80:20:1.2) to yield 3.23 g (95%) of **10**, mp was undetermined because heating of the product led to its conversion into **13**; ir (potassium bromide): 3360, 3280, 3200, 1720, 1675, 1610, 1570, 1535, 1485 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.27 (s, 3H, CH_3), 3.42 (s, 3H, CH_3N), 3.5 (s, 3H, CH_3N), 6.0 (br, 2H, NH_2, deuterium oxide exchangeable), 7.2-7.4 (m, 3H, aromatic), 7.85-7.95 (m, 2H, aromatic).

Anal. Calcd. for $C_{16}H_{16}N_6O_3$: C, 56.46; H, 4.74; N, 24.69. Found: C, 56.40; H, 4.68; N, 24.70.

Synthesis of Compound **12**.

A 55% sodium hydride dispersion (0.25 g, 5.5 mmoles) was added to a stirred solution of pyrazolooxadiazinone (**1a**) (1.14 g, 5 mmoles) and 1,3-dimethylbarbituric acid (**11**) (0.86 g, 5.5 mmoles) in anydrous tetrahydrofuran (50 ml). After being stirred for 1.5 hours, the mixture was acidified with acetic acid and the solvents were removed under reduced pressure. The red residue was chromatographed on a silica column (eluting system: ethyl acetate-light petroleum 8:2) to yield 1.39 g (82%) of **12**, mp 191-193° (benzene); ir (potassium bromide): 3320, 1720, 1660, 1630, 1470 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.4 (s, 3H, CH_3), 3.45 (s, 6H, 2 CH_3N), 6.5 (br, 2H, NH_2, deuterium oxide exchangeable), 7.4-7.6 (m, 5H, aromatic).

Anal. Calcd. for $C_{16}H_{16}N_6O_3$: C, 56.46; H, 4.74; N, 24.69. Found: C, 56.44; H, 4.62; N, 24.50.

1-Phenyl-3,6,8-trimethylpyrazolo[4,3-*g*]pteridine-5,7-dione (**13**).

Method A (from **10**).

A solution of **10** (1.02 g, 3 mmoles) in 0.1*N* ethanolic potassium hydroxide (100 ml) was stirred at room temperature for 15 minutes. The solution turned from dark violet to yellow and gave a pale yellow precipitate. The solvent was reduced *in vacuo* to about 20 ml and the precipitate was collected and washed with water, yield 0.93 g (96%), mp 242° (ethanol), lit [10,11] 242°; ir (potassium bromide): 1720, 1670, 1600, 1530 1500 cm^{-1}; ^{1}H-nmr (trifluoroacetic acid): δ 2.95 (s, 3H, CH_3), 3.8 (s, 3H, CH_3N), 3.95 (s, 3H, CH_3N), 7.6-8.0 (m, 5H, aromatic).

Anal. Calcd. for $C_{16}H_{14}N_6O_2$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.44; H, 4.34; N, 26.20.

Method B (from **12**).

A solution of **12** (1.02 g, 3 mmoles) in 0.1*N* ethanolic potassium hydroxide (50 ml) was stirred at room temperature for 15 minutes. The solution turned from dark red to yellow; it was worked up as above to yield 0.91 g (94%) of a product identical with that obtained through the Method A and with a sample of **13** prepared by the known methods [10,11].

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REFERENCES AND NOTES

[1] M. Guarneri, R. Ferroni, P. Giori and C. A. Benassi, Chem. Biol. Pept., Proc. Am. Pept. Symp., J. Meienhofer, ed, Ann Arbor, MI, 1972, p 213.

[2] P. Giori, M. Guarneri, D. Mazzotta, C. B. Vicentini and C. A. Benassi, *Eur. J. Med. Chem.*, **10**, 428 (1975).

[3] R. Tomatis, R. Ferroni, M. Guarneri and C. A. Benassi, *Farmaco, Ed. Sci.*, **31**, 70 (1976).

[4] P. Giori, D. Mazzotta, G. Vertuani, M. Guarneri, D. Pancaldi and A. Brunelli, *Farmaco, Ed. Sci.*, **36**, 1019 (1981).

[5] P. Giori, A. C. Veronese, T. Poli, C. B. Vicentini, M. Manfrini and M. Guarneri, *J. Heterocyclic Chem.*, **23**, 585 (1986).

[6] W. Pfleiderer and F. E. Kempter, *Chem. Ber.*, **103**, 908 (1970).

[7] A. R. Katrizsky and W. Rees, "Comprehensive Heterocyclic Chemistry", Vol **3**, A. J. Boulton and A. McKillop, eds, Pergamon Press, Oxford, 1984, p 263.

[8] F. Sachs and G. Meyerheim, *Chem. Ber.*, **41**, 3957 (1908).

[9] R. Baur, E. Kleiner and W. Pfleiderer, *Ann. Chem.*, 1798 (1984).

[10] V. C. Barry, J. E. McCormick, G. Henseke, P. Brosche, J. Demuth, U. Müller, H. Engelmann and G. Cravack, *Ann. Chem.*, **648**, 96 (1961).

[11] M. Guarneri, R. Ferroni and F. Fiorini, *Ann. Chim.* (Rome), **58**, 684 (1968).