SYNTHESIS OF SOME 2*H*-PYRONE AND FERROCENE CONTAINING HETEROCYCLIC SYSTEMS

Samila Malzogu, Ivana Sušnik*, Jasna Vorkapić-Furač, Vladimir Rapić, and Veronika Kovač

Faculty of Food Technology and Biotechnology, Zagreb, Croatia

Abstract

Reactions of ethyl 2-hydroxy-4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-4-oxobut-2-enoate (**1**) with *o*-phenylenediamines gave mixtures of the corresponding tetrahydroquinoxalinones, anil, 1,5-benzodiazepines, and pyrano[4,3-*b*][1,5]benzodiazepines. Action of *o*-phenylenediamine on ethyl 4-ferrocenyl-1,4-dioxobutanoate (**8**) gave a mixture of the corresponding quinoxalin-2-one and 1,5-benzodiazepine.

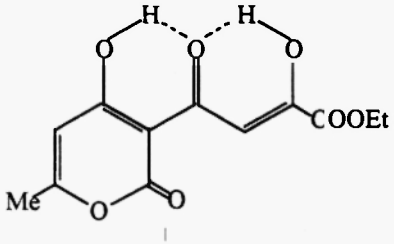
The 2*H*-pyrane polyoxo derivative **1** (1) has been reported to react with various cations giving chelate complexes, which have found application as analytical reagents (2, 3). In addition, a lot of Schiff bases, prepared by condensation of **1** with various nitrogen containing nucleophiles have been studied as potentially di-, tri- or polydentate ligands. In all these reactions the nucleophilic attack occured either at 4-position of 2*H*-pyran-2-one ring or at the carbonyl of the side chain attached at 3-position of this ring, as well as simultaneously on both fragments (3-5).

In connection with the mentioned studies we have planned to investigate the reactivity of polyoxo compound **1** towards 4,5-disubstituted *o*-phenylenediamines and 3-amino-1-phenyl-2-pyrazolin-5-one in order to obtain some novel heterocyclic compounds with potential cytostatic activity, as well as complexing ability (6, 7).

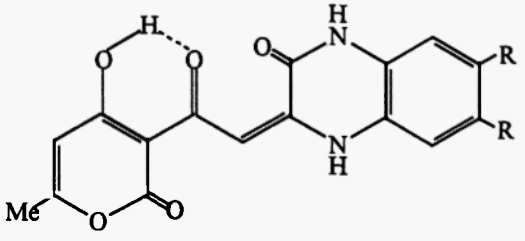
Some ferrocene derivatives exhibit interesting biological properties and they find application in biochemistry, microbiology and medicine, for example as radiotherapeutical agents, enzyme inhibitors, and anti-tumor agents (8). In our present research we are studying antiproliferant ability of some ferrocene chalcones for malignant cell line (9). Having in mind potential biological activity of benzodiazepine, quinoxaline, and pyrazolopyridine systems, we undertook a study of ferrocene derivatives of these heterocycles, obtained starting from ethyl 4-ferrocenyl-1,4-dioxobutanoate (10) in a similar way as above described for synthesis of pyrane containing heterocyclic systems.

Treatment of ethyl 2-hydroxy-4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-4-oxobut-2-enoate (**1**) with *o*-phenylenediamines afforded mixtures of several structurally different heterocyclic compounds:

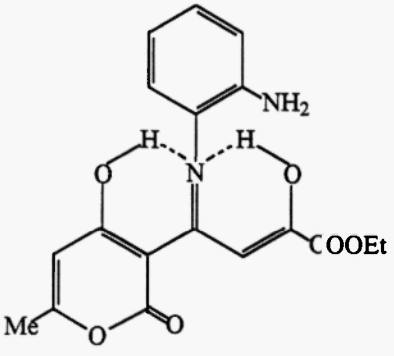
tetrahydroquinoxalinones (**2a-c**), anil (**3**) and 1,5-benzodiazepines (**4a-c** and **5a-c**). The compounds **2-4** are the products of nucleophilic attack at the side chain carbonyl carbons of aliphatic moiety, while compounds **5** were formed by nuchleophilic attack at 4-position of 2*H*-pyran-2-one ring and side chain α-carbonyl carbon at the same time. Considering the ambident electrophilic character of pyrane **1** in its reactions with *o*-phenylenediamines, one could expect formation of quinoxalinones or/and several isomeric 1,5-diazepine derivatives in accordance with the ratio of tautomeric forms of this compound (3) (Scheme 1).



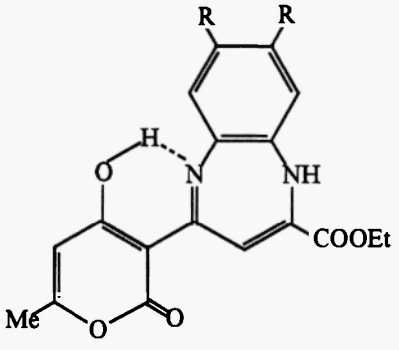
1



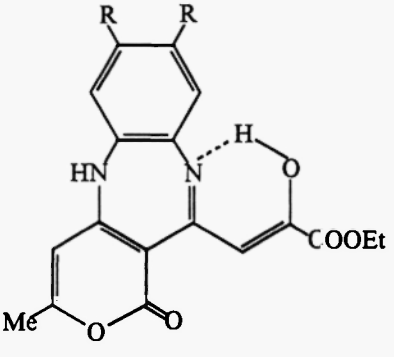
2a - c



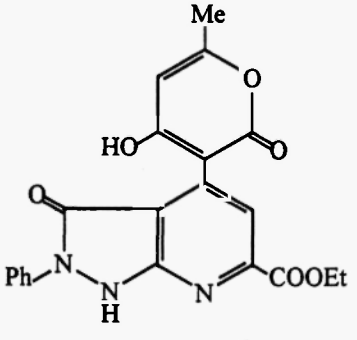
3



4a - c



5a – c

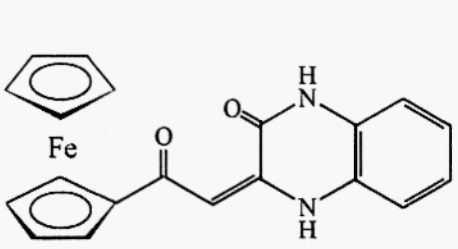


6

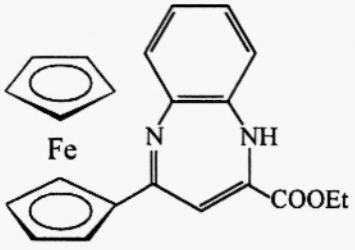
(**a**, R = H ; **b**, R = Me ; **c**, R = Cl)

Scheme 1

Refluxing of an ethanolic solution of equimolar amounts of ethyl 4-ferrocenyl-1,4-dioxobutanoate (8) and *o*-phenylenediamine gave a mixture of 57.9 % of 3-(2-ferrocenyl-2-oxoethylidene)-1,2,3,4-tetrahydroquinoxalin-2-one (9) and 36.0 % of ethyl 4-ferrocenyl-1,5-benzodiazepine-2-carboxylate (10) (Scheme 2).



9



10

Scheme 2

Ethyl 2-hydroxy-4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-4-oxobut-2-enoate (m.p. 139-141 °C) (1) and ethyl 4-ferrocenyl-1,4-dioxobutanoate (8) were prepared from dehydroacetic acid or acetylferrocene and diethyl oxalate according to procedures (5) and (10).

Reactions of Ethyl 2-hydroxy-4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-4-oxobut-2-enoate (1) with *o*-Phenylenediamine, 3,4-Dimethyl-, and 3,4-Dichloro-*o*-phenylenediamine (*General Procedure*)

The solution of appropriate *o*-phenylenediamine (2 mmol) in ethanol (30 ml) was added to a boiling solution of 1 (2 mmol) in ethanol (70 ml) and the reaction mixture refluxed for 2 hrs. After cooling, the resulting solid was collected by filtration, recrystallized from DMF, washed with ethanol and dried affording the tetrahydroquinoxalin-2-one derivatives 2a-c. The filtrate was evaporated to dryness and the residue suspended in ethanol. The insoluble part was identified as anil 3 (obtained only with R=H), while 1,5-benzodiazepines 4a-c and 5a-c and were obtained from the mother liquor by fractional crystallization.

3-[2-(4-Hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxoethylidene]-1,2,3,4-tetrahydroquinoxalin-2-one (2a) Yield: 0.123 g (20%), m.p. 295 °C from DMF. IR (KBr): 3195, 3140 (N–H, O–H), 1720 (pyrone C=O), 1680 (lactam C=O), 1605 (chelat. C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ=2.43 (s, 3H, CH_3), 6.09 (s, 1H, pyrone), 7.14 (s, 1H, =CH–), 7.05-7.57 (m, 4H, benzene), 11.94 (broad s, 1H, NH), 12.45 (broad s, 1H, NH), 16.39 (broad s, 1H, OH). MS(EI): m/z (%)=312 (M^+, 100), 269 (30), 187 (64), 159 (30), 131 (24), 153 (28), 85 (18), 69 (16), 43 (40). $C_{16}H_{12}N_2O_5$ (312.27): calcd. C 61.54, H 3.87, N 8.97; found C 61.41, H 4.13, N 9.13.

3-[2-(4-Hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxoethylidene]-6,7-dimethyl-1,2,3,4-tetrahydroquinoxalin-2-one (2b) Yield: 0.142 g (22%), m.p. 268 °C (decomp.) from DMF. IR (KBr): 3180, 3140 (N–H, O–H), 1710 (pyrone C=O), 1670 (lactam C=O), 1610 (chelat. C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ=2.48 (m, 9H, CH_3), 6.09 (s, 1H, pyrone), 6.94 (s, 1H, =CH–), 7.44 (d, *J*=10 Hz, 2H, benzene), 11.84 (broad s, 1H, NH),

12.87 (broad s, 1H, NH), 16.59 (broad s, 1H, OH). MS(EI): m/z (%)=340 (M^+, 100), 297 (30), 215 (53), 187 (70), 159 (22), 85 (15), 69 (13), 43 (57). $C_{18}H_{16}N_2O_5$ (340.32): calcd. C 63.52, H 4.74, N 8.23; found C 63.57, H 4.68, N 8.41.

6,7-Dichloro-3-[2-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxoethylidene]-1,2,3,4-tetrahydroquinoxalin-2-one (2c) Yield: 0.152 g (21%), m.p. 310-312 °C from DMF. IR (KBr): 3181, 3140 (N–H, O–H), 1718 (pyrone C=O), 1685 (lactam C=O), 1622 (chelat. C=O) cm^{-1}. MS(EI): m/z (%)=380 (M^+, 15), 337 (11), 255 (100), 227 (31), 199 (23), 153 (17), 125 (17), 85 (11), 69 (72), 43 (62). $C_{16}H_{10}Cl_2N_2O_5$ (381.16): calcd. C 50.41, H 2.64, N 7.35, Cl 18.60; found C 63.57, H 4.68, N 8.41, Cl 18.28.

Ethyl 4-(*o*-aminophenylimino)-2-hydroxy-4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-but-2-enoate (3) Yield: 0.046 g (6%), m.p. 218-219 °C. IR (KBr): 3430, 3330, 3240 (N–H), 1740 (pyrone C=O), 1690 (ester C=O), 1640 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.37 (t, *J*=7 Hz, 3H, CH_2CH_3), 2.13 (s, 3H, CH_3), 4.10 (broad s, 2H, NH_2), 4.40 (q, *J*=7 Hz, 2H, $-CH_2CH_3$), 5.7 (s, 1H, enole =CH–), 6.25 (s, 1H, pyrone), 6.60-7.00 (m, 4H, benzene), 14.90 (broad s, 1H, OH), 16.12 (broad s, 1H, OH). MS(EI): m/z (%)=358 (13), 343 (13), 285 (100), 211 (48), 183 (53), 133 (73), 92 (27), 65 (20). $C_{18}H_{18}N_2O_6$ (358.34): calcd. C 60.34, H 5.03, N 7.82; found C 60.44, H 4.58, N 7.73.

Ethyl 4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-5*H*-1,5-benzodiazepine-2-carboxylate (4a) Yield: 0.368 g (54%), m.p. 170-172 °C from ethanol. IR (KBr): 3320 (N–H, O–H), 1710 (pyrone C=O), 1690 (ester C=O), 1650 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.37 (t, *J*=6.9 Hz, 3H, CH_2CH_3), 2.13 (s, 3H, CH_3), 4.38 (q, *J*=7 Hz, 2H, CH_2CH_3), 5.71 (s, 1H, azepine =CH–), 6.44 (s, 1H, pyrone), 6.50-7.02 (m, 4H, benzene), 7.51 (broad s, 1H, NH), 15.10 (broad s, 1H, OH). ^{13}C NMR ($CDCl_3$): δ=162.1, 96.8, 170.0, 107.1, 163.0 (pyrone), 148.4, 101.1, 161.7 (diazepine), 139.9, 131.5, 125.9, 122.6 (benzene), 184.4 (CO), 62.8 (CH_2), 19.2 (CH_3). MS(EI): m/z (%)=340 (43), 267 (100), 182 (22), 154 (22), 117 (36). $C_{18}H_{16}N_2O_5$ (340.33): calcd. C 63.52, H 4.74, N 8.23; found C 63.42, H 5.00, N 8.34.

An ethanolic solution of sodium hydroxyde (*w*=0.5) was added into a stirred solution of ester 4a (0.108 g; 0.32 mmol) in ethanol (22 ml) till pH reached 9.5, and the reaction mixture refluxed with stirring for 1 hr. After cooling, hydrochloric acid (*w*=0.14) was dropped until the solution remained neutral. **4-(4-Hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-5*H*-1,5-benzodiazepine-2-carboxylic acid** obtained was washed with water, then ethanol and finally recrystallized from DMF/ ethanol (1:1). Yield: 0.048 g (48%), m.p. 238-240 °C from DMF. IR (KBr): 3330 (N–H, O–H), 3100-2700 (O–H, COOH), 1710 (pyrone C=O), 1680 (acid), 1640 (benzodiazepine C=N), 1600 (pyrone C=C) cm^{-1}. MS(EI): m/z (%)=312 (10), 268 (100), 183 (33), 155 (57), 118 (40). $C_{16}H_{12}N_2O_5$ (312.27): calcd. C 61.54, H 3.87, N 8.97; found C 61.57, H 4.12, N 9.17.

Ethyl 4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-7,8-dimethyl-5*H*-1,5-benzodiazepine-2-carboxylate (4b) Yield: 0.381 g (52%), m.p. 242-244 °C from ethanol. IR (KBr): 3340 (N–H, O–H), 1713 (pyrone C=O), 1690 (ester C=O), 1645 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.36 (t, *J*=7 Hz, 3H, CH_2CH_3), 2.05 (m, 9H, CH_3),

4.29 (q, *J*=6.9 Hz, 2H, CH_2CH_3), 5.68 (s, 1H, azepine =CH–), 6.13 (s, 1H, pyrone), 6.40 (s, 2H, benzene), 7.34 (broad s, 1H, NH), 14.90 (broad s, 1H, OH). ^{13}C NMR ($CDCl_3$): δ=162.1, 96.2, 169.13, 106.8 (pyrone), 147.9, 100.0, 161.9 (diazepine), 136.2, 133.4, 128.4, 123.6 (benzene), 183.8 (CO), 62.3 (CH_2), 18.7 (CH_3). MS(EI): m/z (%)=368 (33), 295 (100), 210 (9), 182 (7), 145 (22). $C_{20}H_{20}N_2O_5$ (368.38): calcd. C 65.21, H 5.47, N 7.61; found C 65.47, H 5.76, N 7.49.

Ethyl 7,8-dichloro 4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-5*H*-1,5-benzodiazepine-2-carboxylate (4c) Yield: 0.412 g (51%), m.p. 282-284 °C from $CHCl_3$/ EtOH (1:1). IR (KBr): 3340 (N–H, O–H), 1720 (pyrone C=O), 1695 (ester C=O), 1640 (C=N) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ=1.28 (t, *J*=7 Hz, 3H, CH_2CH_3), 2.08 (s, 3H, CH_3), 4.31 (q, *J*=6.9 Hz, 2H, CH_2CH_3), 5.73 (s, 1H, diazepine =CH–), 6.71 (s, 1H, pyrone), 7.13-7.20 (d, 2H, benzene), 7.77 (broad s, 1H, NH), 14.54 (broad s, 1H, OH). ^{13}C NMR (DMSO-d_6): δ=161.1, 99.4, 168.7, 106.7 (pyrone), 148.4, 100.0, 161.1, (diazepine), 139.4, 134.5, 124.7, 123.8 (benzene), 184.1 (CO), 62.5 (CH_2), 18.7 (CH_3) MS(EI): m/z (%)=408 (30), 335 (100), 250 (23), 222 (17), 185 (16). $C_{18}H_{14}Cl_2N_2O_5$ (409.21): calcd. C 52.83, H 3.45, N 6.85; found C 53.03, H 3.75, N 6.86.

Ethyl 2-hydroxy-3-[3-methyl-1-oxo-1*H*, 5*H*-pyrano[4,3-*b*][1,5]benzodiazepin-11-yl]prop-2-enoate (5a) Yield: 0.071 g (10%), m.p. 178-180 °C from $CHCl_3$/ EtOH (1:1). IR (KBr): 3320 (O–H), 1745 (pyrone C=O), 1680 (ester C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$/ CF_3COOH): δ=1.33 (t, *J*=7 Hz, 3H, CH_2CH_3), 2.33 (s, 3H, CH_3), 4.13 (q, *J*=6.9 Hz, 2H, CH_2CH_3), 6.30 (s, 1H, enol =CH–), 6.77 (s, 1H, pyrone), 7.10-7.73 (m, 4H, benzene), 7.92 (broad s, 1H, NH), 13.77 (broad s, 1H, enol OH). MS(EI): m/z (%)=340 (43), 267 (100), 225 (21), 182 (21), 154 (22), 141 (11). $C_{18}H_{16}N_2O_5$ (340.324): calcd. C 63.52, H 4.74, N 8.23; found C 63.65, H 4.71, N 8.48.

Ethyl 2-hydroxy-3-[3,7,8-trimethyl-1-oxo-1*H*, 5*H*-pyrano[4,3-*b*][1,5]benzodiazepin-11-yl]prop-2-enoate (5b) Yield: 0.083 g (11%), m.p. 216-219 °C from $CHCl_3$/ EtOH (1:1). IR (KBr): 3332 (O–H), 1715 (pyrone C–O), 1620 (lactam C–O), 1590 (benzodiazepine C=N) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ=1.22 (t, *J*=7 Hz, 3H, CH_2CH_3), 4.40 (q, *J*=6.9 Hz, 2H, CH_2CH_3), 5.47 (s, 1H, diazepine), 6.28 (s, 1H, pyrone), 7.11-7.30 (d, 2H, arom.), 7.54 (broad s, 1H, NH), 10.83 (broad s, 1H, OH). MS(EI): m/z (%)=368 (25), 295 (100), 253 (20), 210 (10), 182 (10), 169 (15). $C_{20}H_{20}N_2O_5$ (368.4): calcd. C 65.21, H 5.47, N 7.61; found C 64.85, H 5.98, N 7.56.

Ethyl 2-hydroxy-3-[7,8-dichloro-3-methyl-1-oxo-1*H*, 5*H*-pyrano[4,3-*b*][1,5]benzodiazepin-11-yl]prop-2-enoate (5c) Yield: 0.098 g (12%), m.p. 249-250 °C from $CHCl_3$/ EtOH (1:1). IR (KBr): 3290 (O–H), 1730 (pyrone C=O), 1675 (ester C=O), 1645 (lactam C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ=1.28 (t, *J*=7 Hz, 3H, CH_2CH_3), 2.36 (s, 3H, CH_3), 4.25 (q, *J*=6.9 Hz, 2H, CH_2CH_3), 6.15 (s, 1H, diazepine), 6.38 (s, 1H, pyrone), 6.67-6.70 (d, 2H, arom.), 7.92 (broad s, 1H, NH), 13.77 (broad s, 1H, OH). MS(EI): m/z (%)=409 (30), 335 (100), 293 (21), 250 (23), 222 (17), 209 (12). $C_{18}H_{14}N_2O_5$ (409.22): calcd. C 52.83, H 3.45, N 6.85, Cl 17.15; found C 52.43, H 3.50, N 6.57, Cl 17.42.

Ethyl 2-phenyl-4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-3-oxo-3-pyrazolino[3,4-*b*]pyridine-6-carboxylate (6)

Piperidine (1ml) and 3-amino-1-phenyl-5-pyrazolone (0.350 g; 0.2 mmol) in ethanol (20 ml) were added to a stirred and boiling solution of **1** (0.536 g; 0.2 mmol) in ethanol (60 ml) and the reaction mixture refluxed for 2 hrs. After addition of water the precipitate obtained was recrystallized from chloroform/ ethanol (1:1). Yield: 0.477 g (59%), m.p. 262-263 °C. IR (KBr): 3140 (N–H), 3080 (O–H), 1700 (pyrone C=O), 1680 (ester C=O), 1660 (pyrazole C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 1.38 (t, *J*=7 Hz, 3H, CH_2CH_3), 2.25 (s, 3H, CH_3), 4.42 (q, *J*=7 Hz, 2H, CH_2CH_3), 6.14 (s, 1H, pyrone), 7.26-7.98 (m, 5H, C_6H_5), 8.37 (s, 1H, pyridine), 17.01 (broad s, 1H, NH), 18.19 (s, 1H, OH). MS(EI): m/z (%)=407 (100), 361 (20), 333 (50), 304 (40), 249 (20), 193 (15), 116 (12), 103 (19), 91 (16), 85 (26), 43 (30). $C_{21}H_{17}N_3O_6$ (407.37): calcd. C 62.06, H 3.97, N 10.34, found C 62.16, H 4.19, N 10.47.

Reactions of ethyl 4-ferrocenyl-1,4-dioxobutanoate (8) with *o*-phenylenediamine

In a similar way as described for ester **1** in reaction of **8** (0.328 g; 1 mmol) with an equimolar amount of *o*-phenylenediamine 0.210 g (57.9 %) of 3-(2-ferrocenyl-2-oxoethylidene)-1,2,3,4-tetrahydroquinoxalin-2-one (**9**) and 0.141 g (36.0 %) of ethyl 4-ferrocenyl-1,5-benzodiazepine-2-carboxylate (**10**) were obtained.
9 m.p. 169-170 °C from glacial acetic acid. IR (KBr): 3250 (N–H), 1685 (lactam C=O), 1651 (ferrocenoyl C=O), 1348 (quinoxaline) cm^{-1}. $C_{20}H_{16}FeN_2O_2$ (372.21): calcd. C 64.54, H 4.33, N 7.53; found C 64.65, H 4.21, N 7.80. **10** m.p. 132-133 °C from ethanol abs. IR(KBr): 3310 (N–H), 1693 (ester C=O), 1660 (C=N) cm^{-1}. $C_{22}H_{20}FeN_2O_2$ (400.27): calcd. C 66.02, H 5.04, N 7.00; found C 66.31, H 49.90, N 7.28.

References

(1) A. Brbot-Šaranović, B. Katušin-Ražem, I. Sušnik, Heterocycles 29, 1559 (1989).

(2) M. Lačan, S. Malazogu, H. Džanić, I. Sušnik-Rybarski, Bull. Soc. Chem. Technology, Sarajevo 21/22, 35 (1973/1974).

(3) V. Drevenkar, A. Deljac, Z. Štefanac, J. Seibl, Polyhedron 2, 447 (1983).

(4) I. Sušnik-Rybarski, N. Filipović-Marinić, D. Baturić, M. Lačan, Bull. Soc. Chim., Beograd 48, 489 (1983).

(5) V. Drenovački, N. Filipović-Marinić, J. Serb. Chem. Soc. 50, 217 (1985).

(6) I. Sušnik, J. Vorkapić-Furač, S. Durakovič, S. Koprivanac, J. Lasinger, Monatsh. Chem. 123, 817 (1992).

(7) I. Sušnik-Rybarski, H. Džanić, M. Lačan, V. Mesić, Liebigs Ann. Chem., 382 (1982).

(8) N. Motohashi, R. Meyer, S. R. Gollapudi, K. R. Bhattiprolu, J. Organomet. Chem. 398, 205 (1990).

(9) M. Poljak-Blaži, A. Ferle-Vidovič, V. Rapič, D. Škare, Antiproliferative Ability of Ferric-Sorbitol-Citrate and Ferrocenes for Malignant Cell Line, Hep2 and F10, 10th International Symposium on Trace Elements in Man and Animal, Evian, France, May 02-07 1999, Book of Abstracts, p. 256; A. Ferle–Vidovič, M. Poljak-Blaži, V. Rapič, D. Škare, Cancer Biotherapy & Radiopharmaceuticals, submitted.

(10) M. Lačan, V. Rapič, Croat. Chem. Acta 42, 411 (1970).

Received on August 7, 2000