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Synthesis of 4-(2,4-Dioxo-5-pyrimidyl)-1,4-dihydropyridine Derivatives

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Abstract□Hantzsch synthesis of 5-formyluracil (**1**), methyl acetoacetate (**2**) and methyl 3-aminocrotonate (**3**) gave 2,6-dimethyl-4-(2,4-dioxo-5-pyrimidyl)-1, 4-dihydropyridine-3, 5-dicarboxylic acid dimethylester (**4a**) in 54.6% yield. As the same procedure, 1,3-dimethyl-5-formyl-uracil (**6**) gave 2,6-dimethyl-4-(1,3-dimethyl-2,4-dioxo-5-pyrimidyl)-1, 4-dihydropyridine-3, 5-dicarboxylic acid dimethyl ester (**7a**) in 52.2% yield. **4a** was methylated to afford **7a** also in 52% yield.

Keywords□1,4-Dihydropyridines, nifedipine, Hantzsch synthesis, 4-(2,4-dioxo-5-pyrimidyl)-1, 4-dihydropyridine.

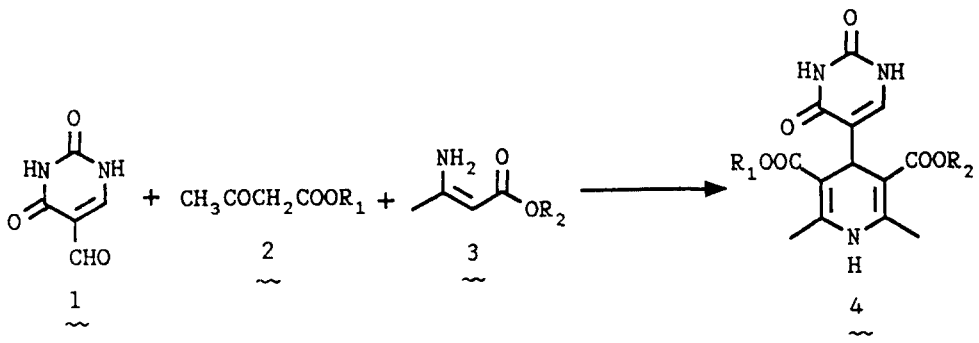
Since nifedipine[1,2] was introduced for the treatment of angina pectoris and hypertension, a number of symmetrically and asymmetrically substituted ester derivatives of 1,4-dihydropyridines have been synthesized and developed for cardiovascular agents[3-6]. These compounds are usually obtained by the various modification of Hantzsch synthesis[7,8]. Most of these 1,4-dihydropyridines have a substituted phenyl group at position 4. In recent years, substitution of heterocycles such as benzoxadiazole[9], pyridyl[10] and isoxazole[11] derivatives have been reported and claimed to be useful as antihypertensive agents.

Thus, as a part of ou. continuing effort to develop novel 1,4-dihydropyridines having specificity, we tried to substitute uracil moiety (2,4-dioxo-5-pyrimidyl) in the position 4 of 1,4-dihyropyridine ring.

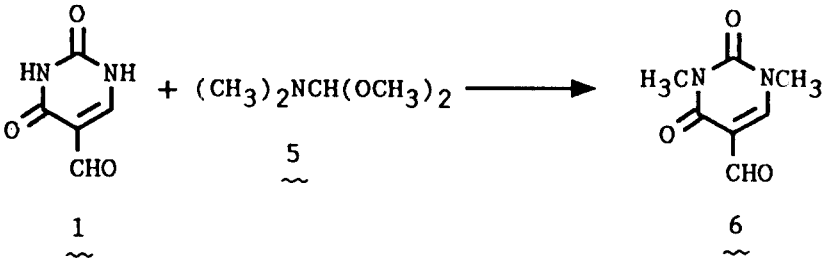
5-Formyluracil (**1**) was heated with methyl acetoacetate (**2a**) and methyl 3-aminocrotonate (**3a**) in isopropanol for 24 hours. After the reaction mixture was cooled, the precipitate was filtered and washed with isopropanol and ether to give 2,6-dimethyl-4-(2,4-dioxo-5-pyrimidyl)-1,4-dihydro-pyridine-3,5-dicarboxylic acid dimethyl ester (**4a**) in 54.6% yield. As the same synthetic procedure of **4a**, diethyl ester (**4b**) and methyl ethyl ester (**4c**) were also obtained in 52.5% and 49% yield, respectively (Scheme 1).

In order to prepare 1,3-dimethyl compound, 5-formyl-uracil (**1**) was methylated by dimethylformamide-dimethylacetal (**5**) to give 1,3-dimethyl-5-formyluracil (**6**) in 57.2% yield (Scheme 2). 1,3-Dimethyl-5-formyluracil (**6**) was reacted with **2** and in isopropanol to give 2,6-dimethyl-4-(1,3-dimethyl-2,4-dioxo-5-pyrimidyl)-1,4-dihydropyridine-3,5-dicarboxylic acid dimethyl ester (**7a**) in 52.5% yield (Scheme 3, method A).

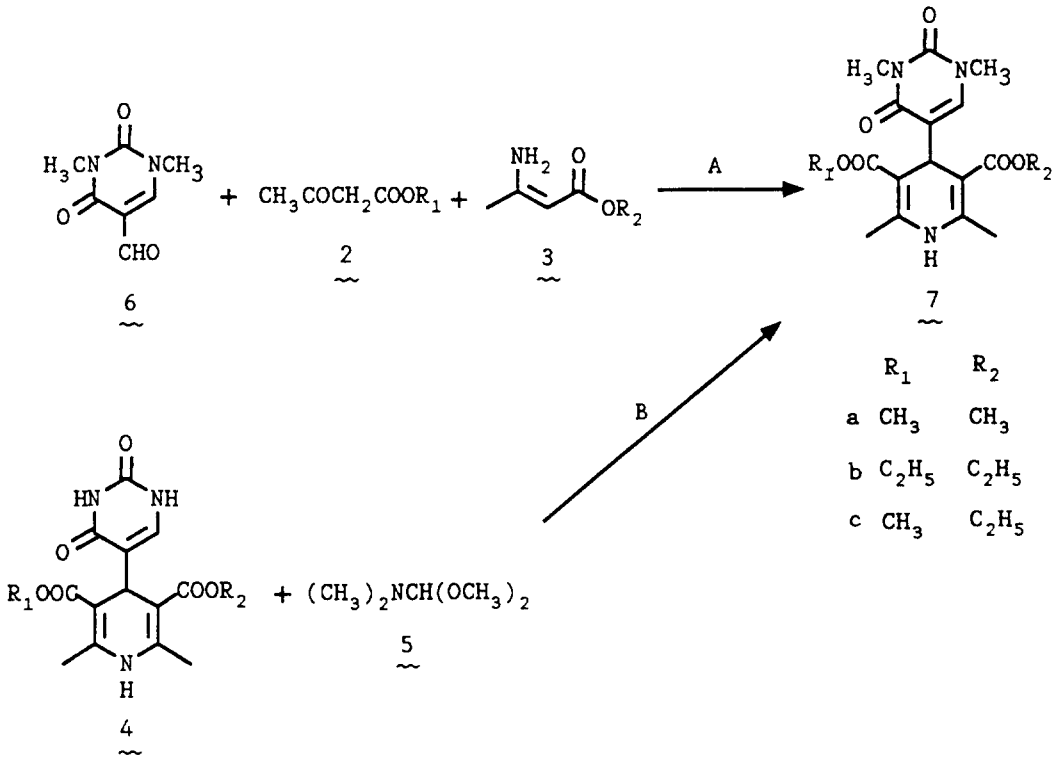
On the other hand, **4a** was methylated by dimethyl-



Sheme 1



Scheme 2



Scheme 3

formamide-dimethylacetal to give **7a** in 52% yield (method B). As the same synthetic procedure, **4b** gave **7b** in 49% and **4c** gave **7c** in 40% yield (Scheme 3, method B).

None of the six 1,4-dihydropyridine compounds showed significant vasodilating activities on the vascular smooth muscles in *in vitro* preparations of experimental animals.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Capillary melting point apparatus and are uncorrected. The pmr spectra were recorded on a Varian VXR-5200 (200 MHz). Chemical shifts are reported in ppm with tetramethylsilane as the internal standard. The IR spectra were recorded with a Shimazu IR-435 spectrometer. The elemental analysis (C, H, N) were carried out with a Carlo Erba 1106 elemental Analyzer.

5-Formyluracil (1)[12-14]

5-Formyluracil was prepared by the method of Ressner and co-workers. Yield: 44.3%; mp: 305-306°C (ref. 300-306°C); IR (KBr) cm^{-1}: 3493 (NH), 1719 (C=O), 1686 (C=O); NMR (DMSO-d_6): δ 8.1 (s, 1H, =CH), 9.8 (s, 1H, CHO), 11.5 (s, 1H, NH), 11.9

(s, 1H, NH).

2,6-Dimethyl-4-(2,4-dioxo-5-pyrimidyl)-1,4-dihydropyridine-3,5-dicarboxylic acid dimethyl ester (4a)

A mixture of 5-formyluracil (**1**, 1.4g), methyl 3-amino crotonate (**3**, 1.26g), methyl acetoacetate (**2**, 1.28g) and isopropanol (40 m*l*) was heated for 24 hours. After cooling, the precipitate was filtered and washed with isopropanol and ether, and recrystallized from CH_3OH. Yield: 1.83g (54.6%); mp: 298-301°C; IR (KBr) cm^{-1}: 3328 & 3200 (NH), 1714 & 1674 (C=O); NMR (DMSO-d_6): δ 2.2 (s, 6H, $CH_3 \times 2$), 3.56 (s, 6H, $OCH_3 \times 2$), 4.7 (s, 1H, C_4-H), 6.76 (s, 1H, =CH), 8.84 (s, 1H, NH), 10.5 (s, 1H, CONH) 10.84 (s, 1H, CONH); Anal. Cald. for $C_{15}H_{17}N_3O_6$: C, 53.73: H, 5.11; N, 12.53, Found: C, 53.82; H, 5.18; N, 12.16.

2,6-Dimethyl-4-(2,4-dioxo-5-pyrimidyl)-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester (4b)

Yield: 52.5%; mp: 286-288°C; IR (KBr) cm^{-1}: 3424 (NH), 3199 (NH), 1712, 1691 (C=O) NMR (DMSO-d_6): δ 1.2 (m, 6H, $-CH_2CH_3 \times 2$), 2.2. (s, 6H, $-CH_3 \times 2$), 3.9-4.2 (m, 4H, $-OCH_2 \times 2$), 4.6 (s, 1H, C_4-H), 6.8 (s, 1H, =CH), 8.8 (s, 1H, NH), 10.5 (s, 1H, NH), 10.8 (s, NH).

2,6-Dimethyl-4-(2,4-dioxo-5-pyrimidyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl 5-ethyl ester (4c)

Yield: 49%; mp: 260-261°C; IR (KBr) cm^{-1}: 3338 (NH), 3194 (NH), 1712 (C=O), 1687 (C=O); NMR (DMSO-d_6): δ 1-1.3 (m, 3H, $-CH_2CH_3$), 2.2 (s, 6H, $-CH_3 \times 2$), 3.6 (s, 3H, $-OCH_3$) 3.9-4.2 (m, 2H, $-OCH_2$), 4.6 (s, 1H, C_4-H), 6.8 (s, 1H, =CH), 8.8 (s, 1H, NH), 10.5 (s, 1H, NH), 10.8 (s, 1H, NH).

1,3-Dimethyl-5-formyluracil (6)[12,15]

A mixture of 5-formyluracil (**1**, 5g) and dimethylformamide-dimethylacetal (**5**, 25 m*l*) was heated to reflux for 1 hour. The reaction mixture was cooled and evaporated in vacuo. The residue was triturated with methanol and ether. The yellow precipitate was filtered and washed with methanol and ether. Yield: 3.45g (57.5%); mp: 123-124°C (ref. 125-126°C); IR (KBr) cm^{-1}: 1710 (C=O), 1690 (C=O); NMR ($CDCl_3$): δ 3.4 (s, 3H, N-CH_3), 3.58 (s, 3H, N-CH_3), 8.5 (s, 1H, =CH), 10.05 (s, 1H, CHO).

2,6-Dimethyl-4-(1,3-dimethyl-2,4-dioxo-5-pyrimidyl)-1,4-dihydropyridine-3,5-dicarboxylic acid dimethyl ester (7a)

Method A: A mixture of 1,3-dimethyl-5-formyluracil (**6**, 0.84g), methyl 3-aminocrotonate (**3**, 0.58g), methyl acetoacetate (**2**, 0.58g) and isopropanol (10 m*l*) was heated to reflux for 24 hours. After cooling, the precipitate was filtered and washed with isopropanol. Yield: 0.95g (52.2%); mp: 260-264°C; IR (KBr) cm^{-1}: 3348 (NH), 1688 & 1652 (C=O); NMR (DMSO-d_6): δ 2.2 (s, 6H, $CH_3 \times 2$), 3.1 (s, 3H, NCH_3), 3.33 (s, 3H, NCH_3), 8.84 (s, 1, NH); Anal. Calcd. for $C_{17}H_{21}N_3O_6$: C, 56.19; H, 5.83;N, 11.56, Found: C, 56.23; H, 5.89; N, 11.08.

Method B: A mixture of 2,6-dimethyl-4-(2,4-dioxo-5-pyrimidyl)-1,4-dihydropyridine-3,5-dicarboxylic acid dimethyl ester (**4a**, 0.25g) and dimethylformamide-dimethylacetal (5 m*l*) was heated to reflux for 5 hours and cooled. The precipitate was filtered and washed with isopropanol. Yield: 0.14g (52%); recrystallized from isopropanol, mp; 256-258°C.

2,6-Dimethyl-4-(1, 3-dimethyl-2, 4-dioxo-5-pyrimidyl)-1, 4-dihydropyridine-3, 5-dicarboxylic acid diethyl ester (7b)

Method B: Yield, 49%; mp.: 214-216°C; IR (KBr) cm^{-1}: 3321 (NH), 1705 (C=O), 1690 (C=O); NMR (DMSO-d_6): δ 1-1.3 (m, 6H, $-CH_2CH_3 \times 2$), 2.2. (s, 6H, $-CH_3 \times 2$), 3.1 (s, 3H, NCH_3), 3.3 (s, 3H, NCH_3), 3.9-4.2 (m, 4H, $-OCH_2 \times 2$), 4.65 (s, 1H, C_4-H), 7.2 (s, 1H, =CH), 8.8 (s, 1H, NH).

2,6-Dimethyl-4-(1, 3-dimethyl-2, 4-dioxo-5-pyrimidyl)-1, 4-dihydropyridine-3, 5-dicarboxylic acid 3-methyl 5-ethyl ester (7c)

Method B: Yield: 40% mp.: 194-196°C; IR (KBr) cm^{-1}: 3324 (NH), 1712 (C=O), 1690 (C=O); NMR (DMSO-d_6): δ 1.3 (m, 3H, $-CH_2CH_3$), 2.2 (s, 6H, $-CH_3 \times 2$), 3.15 (s, 3H, NCH_3), 3.35 (s, 3H, NCH_3), 3.6 (s, 3H, $-OCH_3$), 3.9-4.2 (m, 2H, $-OCH_2$), 4.7 (s, 1H, C_4-H), 7.25 (s, 1H, =CH), 8.8 (s, 1H, NH).

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LITERATURE CITED

1. Grun, Von G. and Fleckenstein, A.: Die elektromechanische Entkoppelung der glatten Gafä β-muskulatur als Grund-prinzip der Coronardilatation durch 4-(2-Nitrophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-di-carbonsäure-dimethylester

(BAY a 1040, Nifedipine). *Arzneim. Forsch.* (-Drug Res.), **22**, 334 (1972).
2. Bossert, F. and Vater, W.: Dihydropyridine, eine Gruppe stark wirksamer Coronartherapeutika. *Naturwissenschaften*, **58**, 578 (1971).
3. Meyer, Von, H., Bossert, F., Wehinger, E., Stoepel. K. und Vater, W.: Synthese und Vergleichende pharmakoligische Untersuchungen von 1, 4-Dihydro-2,6-dimethyl-4-(3-nitro phenyl)pyridine-3,5-dicarbonsäure estern mit nichtidentischen Esterfunktione. *Arzneim. Forsch.* (Drug Res.), **31**, 407 (1981).
4. Iwanami M., Shibanuma, T., Fujimoto, M., Kawai, R., Tamazawa, K., Takenaka, T., Takahashi, K. and Murakami, M.: Synthesis of New Water-soluble Dihydropyridine Vasodilators. *Chem. Pharm. Bull.*, **27**, 1426 (1979).
5. Prous, J., Blancafort, P., Castaner, J., Serradell, M.N. and Mealy, N.: Biologically Active 1, 4-Dihydropyridine Derivatives. *Drugs of the Future*, **6**, 427 (1981).
6. Bossert, F., Meyer, H. and Wehinger, E.: 4-Aryldihydropyridines, a New Class of Highly Active Calcium Antagonists. *Angew. Chem. Int. Ed. Engl.*, **20**, 762 (1981).
7. Stout, D.M. and Meyers, A.I.: Recent Advances in the Chemistry of Dihydropyridines. *Chem. Rev.*, **82**, 223 (1982).
8. Sausins, A. and Duburs, G.: Synthesis of 1,4-Dihydropyridines by Cyclocondensation Reactions. *Heterocycles*, **27**, 269 (1988).
9. Prous, J.R.: Isradipine. *Drugs of the Future*, **10**, 747 (1985).
10. Prous, J.R.: 140-931. *Annual Drug Data Report*, **10**, 642 (1988).
11. Mekenna, J.L., Schlicksupp, L., Natale, N.R., Willett, R.D., Maryanoff, B.E. and Flaim, S.F.: Cardioactivity and Solidstate Structure of Two 4-Isoxazolyldihydropyridines Related to the 4-Aryldihydropyridine Calcium-Channel Blockers. *J. Med. Chem.*, **31**, 473 (1988).
12. Itahara, T., Fujii, Y. and Tada, M.: Oxidation of Thymines by Peroxosulfate Ions in Water. *J. Org. Chem.*, **53**, 3421 (1988).
13. Ressner, E.C., Kampt, A., Mertes, M.P. In Nucleic Acid Chem., Townsend, L.B. and Tipson, R.S., Eds., Wiley: New York, p.89 (1978).
14. Brossmer, R. und Ziegler, D.: Zur Darstellung Heterocyclischer Aldehyde. *Tetrahedron Letters*, **43**, 5253 (1966).
15. Abdulla, R.F. and Brinkmeyer, R.S.: The Chemistry of Formamide Acetals. *Tetrahedron*, **35**, 1675 (1979).