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Synthesis of 1,6-Disubstituted 2,4-Pyridinediones from 5-Acetoacetyl-2,2-dimethyl-1,3-dioxane-4,6-dione

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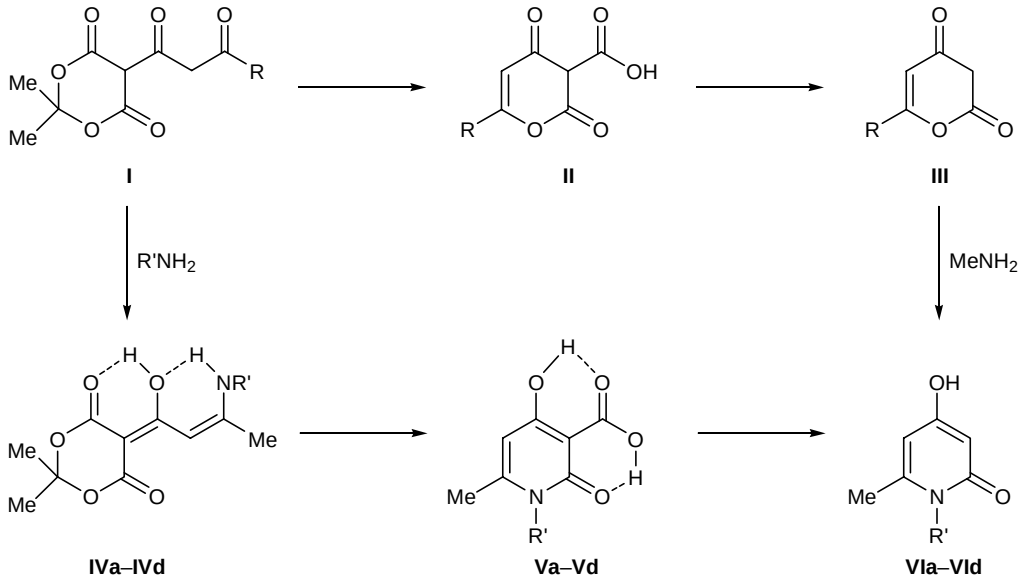
Abstract—5-Acetoacetyl-2,2-dimethyl-1,3-dioxane-4,6-dione reacts with aliphatic amines and *p*-methoxyaniline to afford the corresponding 5-[3-alkyl(or aryl)amino-2-butenoyl] derivatives. Heating of the latter in boiling toluene gives 86–90% of N-substituted 6-methylpyridine-3-carboxylic acids which undergo decarboxylation in diethylene glycol dimethyl ether at 160°C, leading to N-substituted 6-methyl-1,2,3,4-tetrahydropyridine-2,4-diones in high yields.

Polyketones **I**, which are readily available from Meldrum's acid, are convenient synthons for the preparation of 6-substituted 2,4-pyrandiones **III** via decarboxylation of acid **II** [1, 2]. While developing synthetic approaches to heterocyclic β-triketones [3, 4], we used 5-acetoacetyl-2,2-dimethyl-1,3-dioxane-4,6-dione (**I**, R = Me) as model compound and found that it reacts under mild conditions with aliphatic amines and *p*-methoxyaniline to give enamino derivatives **IVa**–**IVd** in 82–96% yield (Scheme 1). The presence in the ^{1}H NMR spectra of compounds **IVa**–**IVd** of two sharp one-proton singlets at δ 9–10 and 15–16 ppm indicates that they exist as the enamino tautomer in which both enol proton and proton on the nitrogen atom are involved in intramolecular hydrogen bonds (H-chelate rings).

By heating of enamines **IVa**–**IVd** in boiling toluene for 30 min we obtained the corresponding pyridinecarboxylic acids **Va**–**Vd** which, according to the ^{1}H NMR data, are completely enolized. The enol form

Scheme 1.



IV–**VI**, R = Me: R' = Me (**a**), Pr (**b**), Bzl (**c**), C_6H_4OMe-4 (**d**).

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is stabilized by intramolecular hydrogen bonds. Unlike derivatives of pyran **II**, compounds **Va**–**Vd** do not undergo decarboxylation on prolonged heating in boiling toluene. However, pyridinecarboxylic acids **Va**–**Vd** were converted into the corresponding N-substituted 6-methyl-1,2,3,4-tetrahydropyridine-2,4-diones **VIa**–**VId** in 85–90% yield by heating for 3–4 h in diethylene glycol dimethyl ether at 160°C. 1,6-Dimethyl-1,2,3,4-tetrahydropyridine-2,4-dione (**VIa**) was also synthesized in 20% yield from 6-methylpyrandione **III**, following the procedure described in [5]. The products obtained by the two methods had identical physical constants. We failed to reproduce the yield given in [5], and our attempts to obtain by the same procedure compounds **VIb**–**VId** (using aqueous medium, methanol, and acetic acid) were unsuccessful.

EXPERIMENTAL

The IR spectra were recorded in KBr on a UR-20 spectrometer. The ^{1}H NMR spectra were obtained on a Bruker AT-200 instrument using DMSO-d_6–chloroform-*d* (1:2) (compounds **VIb**–**VId**) and chloroform-*d* as solvents (the other products); the chemical shifts were measured relative to tetramethylsilane as internal reference. The mass spectra were recorded on an MKh-1320 mass spectrometer. The melting points were determined on a Boetius device. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 or Alufol UV-254 plates; spots were visualized under UV irradiation, followed by spraying with a solution of iron(III) chloride.

2,2-Dimethyl-5-[(*Z*)-3-methylamino-2-butenoyl]-1,3-dioxane-4,6-dione (IVa). To a solution of 2.28 g (10 mmol) of 5-acetoacetyl-2,2-dimethyl-1,3-dioxane-4,6-dione (**I**) in 20 ml of methanol we added 2 ml of 25% aqueous methylamine, and the mixture was stirred for 10 h at room temperature. Methanol and excess methylamine were removed under reduced pressure, the product was extracted into chloroform, and the extract was washed with 1% hydrochloric acid and water, dried over anhydrous magnesium sulfate, and evaporated on a rotary evaporator. Yield 1.98 g (82%), mp 145–147°C (decomp.). IR spectrum, ν, cm^{-1}: 3260, 3150, 1695, 1680, 1630, 1550, 1500. ^{1}H NMR spectrum, δ, ppm: 1.71 s (6H, CH_3CCH_3), 2.17 s (3H, CH_3), 3.10 d (3H, NCH_3, J = 5.5 Hz), 6.42 s (1H, CH=C), 8.85 br.s (1H, NH), 15.91 s (1H, OH, enol). Found, %: C 54.60; H 6.31; N 6.01. $[M]^+$ 241. $C_{11}H_{15}NO_5$. Calculated, %: C 54.77; H 6.27; N 5.81.

General procedure for the synthesis of enamines IVb–IVd. A mixture of 2.28 g (10 mmol) of 5-acetoacetyl-2,2-dimethyl-1,3-dioxane-4,6-dione (**I**) and 10 mmol of the corresponding amine in 20 ml of chloroform was stirred for 8–10 h at room temperature. When the reaction was complete (TLC), the mixture was washed with 10 ml of 1% hydrochloric acid and water and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure.

2,2-Dimethyl-5-[(*Z*)-3-propylamino-2-butenoyl]-1,3-dioxane-4,6-dione (IVb). Yield 2.60 g (97%), mp 130–131°C (decomp.). IR spectrum, ν, cm^{-1}: 3285, 3100, 1690, 1630, 1580, 1535. ^{1}H NMR spectrum, δ, ppm: 1.04 t (3H, C**H**$_3$CH$_2$, J = 7.5 Hz), 1.68 m (2H, CH$_3$C**H**$_2$), 1.74 s (6H, CH_3CCH_3), 2.18 s (3H, CH_3), 3.38 m (2H, NCH_2), 6.40 s (1H, CH=C), 8.92 br.s (1H, NH), 15.90 s (1H, OH, enol). Found, %: C 58.10; H 7.22; N 5.43. $[M]^+$ 269. $C_{13}H_{19}NO_5$. Calculated, %: C 57.98; H 7.11; N 5.20.

5-[(*Z*)-3-(Benzylamino)-2-butenoyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (IVc). Yield 2.90 g (96%), mp 136–137°C (decomp.). IR spectrum, ν, cm^{-1}: 3285, 3100, 1690, 1630, 1580, 1535. ^{1}H NMR spectrum, δ, ppm: 1.68 s (6H, CH_3CCH_3), 2.18 s (3H, CH_3), 4.56 d (2H, C**H**$_2$Ph, J = 6.0 Hz), 6.48 s (1H, CH=C), 7.20–7.40 m (5H, C_6H_5), 9.16 br.s (1H, NH), 16.00 s (1H, OH, enol). Found, %: C 58.10; H 7.22; N 5.43. $[M]^+$ 303. $C_{16}H_{17}NO_5$. Calculated, %: C 63.36; H 5.65; N 4.62.

5-[(*Z*)-3-(4-Methoxyphenylamino)-2-butenoyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (IVd). Yield 3.20 g (96%), mp 135-138°C (decomp.). IR spectrum, ν, cm^{-1}: 3295, 1705, 1650, 1620, 1585, 1520. ^{1}H NMR spectrum, δ, ppm: 1.74 s (6H, CH_3CCH_3), 2.12 s (3H, CH_3), 3.84 s (3H, OCH_3), 6.60 d (1H, CH=C, J = 1.5 Hz), 6.94 d (2H, C_6H_4, J = 9.0 Hz), 7.10 d (2H, C_6H_4, J = 9.0 Hz), 10.20 br.s (1H, NH), 16.10 d (1H, OH, enol, J = 1.5 Hz). Found, %: C 61.17; H 5.68; N 4.37. $[M]^+$ 333. $C_{17}H_{19}NO_6$. Calculated, %: C 61.25; H 5.75; N 4.20.

General procedure for the synthesis of pyridinecarboxylic acids Va–Vd. A solution of 5 mmol of enamine **IVa**–**IVd** in 20 ml of toluene was heated for 0.5 h under reflux. The mixture was cooled to room temperature and was placed for several hours in a freezing chamber. The crystals were filtered off, washed with cold toluene on a filter, and dried under reduced pressure.

1,6-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyridine-3-carboxylic acid (Va). Yield 0.78 g (85%), mp 185–187°C (decomp.). IR spectrum, ν, cm^{-1}: 1705, 1620, 1605, 1560, 1500, 1480. ^1H NMR spectrum, δ, ppm: 2.41 s (3H, CH_3), 3.90 s (3H, NCH_3), 6.11 s (1H, CH=C), 13.31 s (1H, OH), 15.45 br.s (1H, OH, enol). Found, %: C 52.60; H 5.05; N 7.61. $[M]^+$ 183. $C_8H_9NO_4$. Calculated, %: C 52.46; H 4.95; N 7.65.

6-Methyl-2,4-dioxo-1-propyl-1,2,3,4-tetrahydropyridine-3-carboxylic acid (Vb). Yield 0.93 g (88%), mp 96–97°C (decomp.). IR spectrum, ν, cm^{-1}: 1705, 1620, 1605, 1560, 1500, 1480. ^1H NMR spectrum, δ, ppm: 1.02 t (3H, C**H**$_3$CH$_2$, J = 7.5 Hz), 1.68 m (2H, CH$_3$C**H**$_2$), 2.44 s (3H, CH_3), 3.96 m (3H, NCH_2), 6.08 s (1H, CH=C), 13.26 s (1H, OH), 15.40 br.s (1H, OH, enol). Found, %: C 55.57; H 7.15; N 6.60. $[M]^+$ 211. $C_{10}H_{13}NO_4$. Calculated, %: C 56.87; H 6.20; N 6.63.

1-Benzyl-6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyridine-3-carboxylic acid (Vc). Yield 1.17 g (90%), mp 142–143°C (decomp.). IR spectrum, ν, cm^{-1}: 1705, 1620, 1605, 1560, 1500, 1480. ^1H NMR spectrum, δ, ppm: 2.38 s (3H, CH_3), 5.30 s (2H, C**H**$_2$Ph), 6.12 s (1H, CH=C), 7.06–7.40 m (5H, C_6H_5), 13.42 s (1H, OH), 15.18 br.s (1H, OH, enol). Found, %: C 65.07; H 5.13; N 5.36. $[M]^+$ 259. $C_{14}H_{13}NO_4$. Calculated, %: C 64.86; H 5.05; N 5.40.

1-(4-Methoxyphenyl)-6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyridine-3-carboxylic acid (Vd). Yield 1.22 g (89%), mp 170–173°C (decomp.). IR spectrum, ν, cm^{-1}: 1715, 1640, 1620, 1600, 1525, 1500. ^1H NMR spectrum, δ, ppm: 2.04 s (3H, CH_3), 3.86 s (3H, OCH_3), 6.12 s (1H, CH=C), 7.08 m (4H, C_6H_4), 13.50 s (1H, OH), 14.84 s (1H, OH, enol). Found, %: C 61.18; H 4.63; N 5.22. $[M]^+$ 275. $C_{14}H_{13}NO_5$. Calculated, %: C 61.09; H 4.76; N 5.09.

Decarboxylation of pyridinecarboxylic acids Va–Vd. A solution of 5 mmol of pyridinecarboxylic acid **IVa–IVd** in 20 ml of diethylene glycol dimethyl ether was heated for 3–4 h at 160°C. When the reaction was complete (TLC), the mixture was cooled to room temperature and was placed for several hours in a freezing chamber. The crystals were filtered off, washed on a filter with cold diethyl ether, and dried under reduced pressure.

1,6-Dimethyl-1,2,3,4-tetrahydropyridine-2,4-dione (VIa). Yield 0.60 g (86%), mp 235–236°C; published data [5]: mp 230°C. IR spectrum, ν, cm^{-1}: 1665, 1630, 1680, 1550, 1500. ^1H NMR spectrum, δ, ppm: 2.30 s (3H, CH_3), 3.85 s (3H, CH_3), 6.05 br.s (2H, CH=C), 10.08 br.s (1H, OH, enol). Found, %: C 60.60; H 6.61; N 9.97. $[M]^+$ 139. $C_7H_9NO_2$. Calculated, %: C 60.42; H 6.52; N 10.07.

6-Methyl-1-propyl-1,2,3,4-tetrahydropyridine-2,4-dione (VIb). Yield 0.70 g (84%), mp 199–200°C. IR spectrum, ν, cm^{-1}: 1665, 1630 s, 1580, 1550, 1500. ^1H NMR spectrum, δ, ppm: 0.98 t (3H, C**H**$_3$CH$_2$, J = 7.5 Hz), 1.66 m (2H, CH$_3$C**H**$_2$), 2.32 s (3H, CH_3), 3.92 (2H, NCH_2), 5.90 d (1H, CH=C, J = 2.5 Hz), 5.98 d (1H, CH=C, J = 2.5 Hz), 10.50 br.s (1H, OH, enol). Found, %: C 64.72; H 7.81; N 8.14. $[M]^+$ 167. $C_9H_{13}NO_2$. Calculated, %: C 64.65; H 7.84; N 8.38.

1-Benzyl-6-methyl-1,2,3,4-tetrahydropyridine-2,4-dione (VIc). Yield 1.00 g (93%), mp 208–210°C. IR spectrum, ν, cm^{-1}: 1665, 1630 s, 1580, 1550, 1500. ^1H NMR spectrum ($CDCl_3$–DMSO-d_6), δ, ppm: 2.20 s (3H, CH_3), 5.24 s (2H, C**H**$_2$Ph), 5.80 br.s (2H, CH=C), 7.10–7.34 m (5H, C_6H_5), 10.10 br.s (1H, OH, enol). Found, %: C 72.66; H 6.18; N 6.67. $[M]^+$ 215. $C_{13}H_{13}NO_2$. Calculated, %: C 72.54; H 6.09; N 6.51.

1-(4-Methoxyphenyl)-6-methyl-1,2,3,4-tetrahydropyridine-2,4-dione (VId). Yield 1.00 g (87%), mp 278–280°C. IR spectrum, ν, cm^{-1}: 1665, 1630, 1540, 1520. ^1H NMR spectrum ($CDCl_3$–DMSO-d_6), δ, ppm: 1.88 s (3H, CH_3), 3.84 s (3H, OCH_3), 5.60 d (1H, CH=C, J = 3.0 Hz), 5.86 d (1H, CH=C, J = 3.0 Hz), 7.04 m (4H, C_6H_4), 10.30 br.s (1H, OH, enol). Found, %: C 67.45; H 5.81; N 6.17. $[M]^+$ 231. $C_{13}H_{13}NO_3$. Calculated, %: C 67.52; H 5.67; N 6.06.

REFERENCES

1. Hausler, J., *Monatsh. Chem*., 1982, vol. 113, p. 1213.
2. Lokot, I.P., Pashkovski, F.S., and Lakhvich, F.A., *Tetrahedron*, 1999, vol. 55, p. 4783.
3. Budnikova, M.V., Gulyakevich, O.V., Zheldakova, T.A., Mikhal'chuk, A.L., and Rubinov, D.B., *Russ. J. Org. Chem*., 2002, vol. 38, 1696.
4. Zheldakova, T.A., Budnikova, M.V., Rubinova, I.L., and Rubinov, D.B., *Russ. J. Org. Chem*., 2003, vol. 39, 1772.
5. Butt, A. and Elvidge, J.A., *J. Chem. Soc*., 1963, p. 4483.