Synthesis of 3-Methyl and 7-Methyl Regio Isomers of Medorinone

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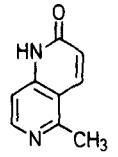
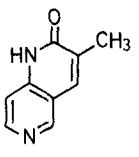
Reaction of 3-aminocrotononitrile (**2**) with methyl methacrylate (**3**) and methyl 2-propynolate (**9**) led to the formation of 1,4,5,6-tetrahydro-2,5-dimethyl-6-oxo-3-pyridinecarbonitrile (**4**) and 1,6-dihydro-2-methyl-6-oxo-3-pyridinecarbonitrile (**10**), respectively. Condensation of **4** with Bredereck's reagent [bis(dimethylamino)-*tert*-butoxymethane], and that of 6-methoxy-2-methyl-3-pyridinecarbonitrile (**12**) with *N,N*-dimethylacetamide dimethyl acetal gave the corresponding enamines **5** and **13** which in turn were cyclized with hydrogen bromide to bromonaphthyridinones **6** and **14**, respectively. Debromination of **6** followed by dehydrogenation gave 3-methyl-1,6-naphthyridin-2(1*H*)-one (**8**). Debromination of **14** with catalytic reduction gave 7-methyl-1,6-naphthyridin-2(1*H*)-one (**15**).

We have recently reported[2] the synthesis of 1,6-naphthyridin-2(1*H*)-ones. 5-Methyl-1,6-naphthyridin-2(1*H*)-one (medorinone)[3] was selected for advanced evaluation as a cardiotonic agent. The 3-methyl and 7-methyl regio isomers of medorinone, **8** and **15** were needed for structure activity relationship studies.

Ogata and Matsumoto[4] described the preparation of **8** by the dehydrogenation of the corresponding 3,4-dihydro compound **7** which in turn was synthesized by the photocyclization of *N*-(4-pyridinyl)methacrylamide. We found this procedure to be unsuitable for a large scale synthesis. We have prepared **8** and **15** via novel syntheses described in Schemes **1** and **2**, respectively.



1 (medorinone)



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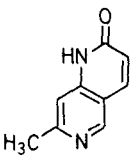
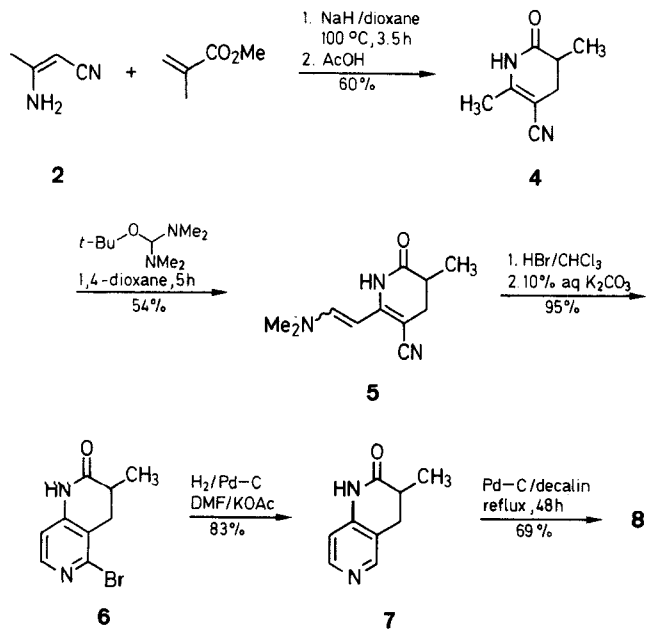


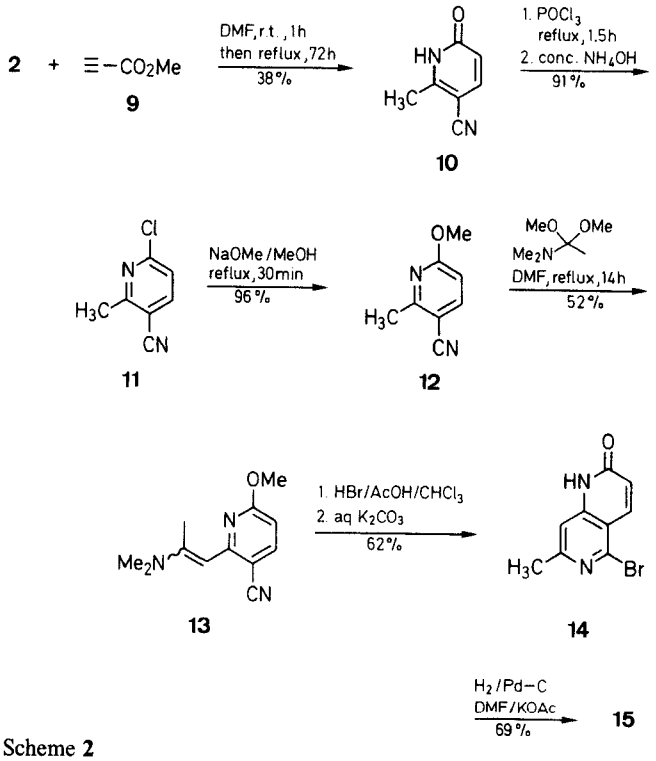
15

Michael addition of the anion of enamine **2** to methyl methacrylate followed by ring closure gave dihdropyridinone **4** which was condensed with Bredereck's reagent [bis(dimethylamino)-*tert*-butoxymethane], to form enamine **5**. Treatment of **5** with hydrogen bromide resulted in the intramolecular cyclization of the nitrile group with the enamine moiety forming bromonaphthyridinone **6**. Debromination of **6** by catalytic reduction in the presence of potassium acetate gave **7** which in turn was dehydrogenated by heating with palladium-carbon in decalin to give 3-methyl-1,6-naphthyridin-2(1*H*)-one (**8**).



Scheme 1

Michael addition of enamine (**2**) to the more reactive methyl 2-propynolate (**9**) followed by cyclization gave pyridinone **10**. Treatment of **10** with phosphoroyl chloride gave the corresponding chloro derivative **11** which in turn was converted to the corresponding methoxy compound **12** by the reaction of sodium methoxide. Condensation of **12** with *N,N*-dimethylacetamide dimethyl acetal resulted in the formation of enamine **13** which underwent cyclization upon treatment with hydrogen bromide to afford bromonaphthyridinone **14**. Debromination of **14** was accomplished by catalytic reduction over palladium on carbon in the presence of potassium acetate to provide 7-methyl-1,6-naphthyridin-2(1*H*)-one (**15**).



Scheme 2

1,4,5,6-Tetrahydro-2,5-dimethyl-6-oxo-3-pyridinecarbonitrile (4):
To a stirred mixture of 85% 3-aminocrotononitrile (**2**; 10 g, 0.1 mol), methyl methacrylate (**3**; 10 g, 0.1 mol), and 1,4-dioxane (150 mL) is added 50% NaH/oil dispersion (4.8 g, 0.1 mol). The resulting mixture is heated on a steam bath for 3.5 h. A brown oily product separates during the course of the reaction. The mixture is first cooled to r.t. and then concentrated under reduced pressure. The residual brown oil is treated with water (100 mL) and glacial AcOH (10 mL). The resulting tan solid product is collected, washed with water followed by hexane, and recrystallized from 2-propanol to afford a white granular solid; yield: 8.95 g (60%); mp 161–163 °C.

$C_8H_{10}N_2O$	calc.	C 63.98	H 6.71	N 18.65
(150.2)	found	63.93	6.79	18.63

IR (KBr): $\nu = 2205\ cm^{-1}$ (C≡N).

^{1}H-NMR (CF_3CO_2D/TMS): $\delta = 1.38$ (d, 3H, $J_{5-CH_3,5-H}$ = 6.0 Hz, 5-CH_3), 2.30 (s, 3H, 2-CH_3), 2.40–3.00 (m, 3H, H-4,5).

2-[2-(Dimethylamino)ethenyl]1,4,5,6-tetrahydro-5-methyl-6-oxo-3-pyridinecarbonitrile (5):
A mixture consisting of **4** (15 g, 0.1 mol), Bredereck's reagent (20.75 mL, 0.1 mol), and 1,4-dioxane (75 mL) is refluxed for 5 h during which a shiny yellow product crystallizes. The reaction mixture is cooled to r.t., the product is filtered and washed with Et_2O; yield: 11.1 g (54%); mp > 235 °C dec.

$C_{11}H_{15}N_3O$	calc.	C 64.37	H 7.37	N 20.47
(205.3)	found	64.30	7.46	20.44

IR (KBr): $\nu = 2178\ cm^{-1}$ (C≡N).

^{1}H-NMR (DMSO-d_6/TMS): $\delta = 1.09$ (d, 3H, $J_{CH_3,5-H}$ = 6.0 Hz, CH_3), 2.10–2.60 (m, 3H, H-4,5), 2.82 [s, 6H, $N(CH_3)_2$], 4.79 (d, 1H, J = 14.0 Hz, NCH=C<u>H</u>), 7.35 (d, J = 14.0 Hz, 1H, NC<u>H</u>=CH), 9.58 (s, 1H, NH).

5-Bromo-3,4-dihydro-3-methyl-1,6-naphthyridin-2(1*H*)-one (6):
A stirred slurry of **5** (40 g, 0.2 mol) and $CHCl_3$ (750 mL) in a 2 L 3-necked round bottom flask fitted with a drying tube is cooled in an ice bath. Gaseous HBr is bubbled gently until the mixture becomes saturated (1.25 h, clouds of HBr fill the flask). A few minutes after the addition of HBr, all the solid dissolves forming a clear light brown solution. About half an hour later, a white product starts crystallizing. The resulting mixture is left at r.t. overnight. The product is collected and the filtrate is concentrated to dryness under reduced pressure. The pale yellow solid residue is combined with the product already collected and treated with 10% aq K_2CO_3 (300 mL). The product is collected, washed with water, dried, and recrystallized from EtOH/$CHCl_3$ as a white granular solid; yield: 46.1 g (95%); mp 212–215 °C.

$C_9H_9BrN_2O$	calc.	C 44.84	H 3.76	N 11.62
(241.1)	found	45.02	3.83	11.60

IR (KBr): $\nu = 1704\ cm^{-1}$ (C=O).

^{1}H-NMR (DMSO-d_6/TMS): $\delta = 1.24$ (d, $J_{CH_3,3-H}$ = 6.0 Hz, 3H, CH_3), 2.50–3.40 (m, 3H, H-3,4), 6.84 (d, 1H, $J_{7-H,8-H}$ = 5.0 Hz, 8-H), 7.48 (d, 1H, $J_{7-H,8-H}$ = 5.0 Hz, 7-H), 10.60 (s, 1H, NH).

3,4-Dihydro-3-methyl-1,6-naphthyridin-2(1*H*)-one (7):
A mixture of **6** (24 g, 0.1 mol), 10% Pd/C (1 g), KOAc (12 g, 0.12 mol), and DMF (200 mL) is hydrogenated on a Paar hydrogenator until the required amount of H_2 is absorbed (1.5 h). The resulting mixture is heated on a steam bath and then filtered through a Celite pad. The filtrate is concentrated under reduced pressure and the white solid residue is recrystallized from EtOH; yield: 13.5 g (83%); mp 265–266 °C (Lit.[4] mp 254–255 °C).

IR (KBr): $\nu = 1688\ cm^{-1}$ (C=O).

^{1}H-NMR (CF_3CO_2D/TMS): $\delta = 1.47$ (d, 3H, $J_{CH_3,3-H}$ = 6.0 Hz, CH_3), 2.90–3.60 (m, 3H, H-3,4), 7.52 (d, 1H, $J_{7-H,8-H}$ = 6.5 Hz, 8-H), 8.51 (d, 1H, $J_{7-H,8-H}$ = 6.5 Hz, 7-H), 8.54 (s, 1H, 5-H).

3-Methyl-1,6-naphthyridin-2(1*H*)-one (8):
A stirred mixture of **7** (1.6 g, 10 mmol), 10% Pd/C (400 mg) and decalin (100 mL) is refluxed for 48 h and then most of the decalin is removed under reduced pressure. The residue is dissolved in hot DMF and filtered through a Celite pad. The filtrate is concentrated

to dryness and the residue is crystallized from EtOH to afford a white solid; yield: 1.1 g (69%); mp > 300°C (Lit.[4] mp 302–303°C).

IR (KBr): ν = 1664 cm^{-1} (C=O).

^{1}H-NMR (CF_3CO_2D/TMS): δ = 2.47 (s, 3H, $-CH_3$), 7.94 (d, 1H, $J_{7-H,8-H}$ = 6.5 Hz, 8-H), 8.12 (s, 1H, 4-H), 8.65 (d, 1H, $J_{7-H,8-H}$ = 6.5 Hz, 7-H), 9.12 (s, 1H, 5-H).

1,6-Dihydro-2-methyl-6-oxo-3-pyridinecarbonitrile (10):

A mixture of 85% 3-aminocrotononitrile (**2**, 9.5 g, 0.1 mol), methyl 2-propynolate (**9**; 8.4 mL, 0.1 mol) and DMF (50 mL) is stirred at r.t. for 1 h, refluxed for 72 h, and then cooled to r.t. The tan crystalls are collected, washed with MeOH and dried; yield: 5.1 g (38%); mp > 300°C.

$C_7H_6N_2O$	calc.	C 62.68	H 4.51	N 20.88
(134.1)	found	62.85	4.49	20.88

IR (KBr): ν = 2230 cm^{-1} (C≡N).

^{1}H-NMR (CF_3CO_2D/TMS): δ = 2.79 (s, 3H, CH_3), 6.97 (d, 1H, $J_{4-H,5-H}$ = 9.0 Hz, 5-H), 8.0 (d, 1H, $J_{4-H,5-H}$ = 9.0 Hz, 4-H).

6-Chloro-2-methyl-3-pyridinecarbonitrile (11):

A stirred mixture of **10** (76.8 g, 0.57 mol) and $POCl_3$ (450 mL) is refluxed for 1.5 h. All the solid dissolves to give a dark brown solution. After cooling to r.t., most of the unreacted $POCl_3$ is removed under reduced pressure. The residual oil is poured onto ice and the mixture is neutralized by treating with conc. aq ammonia. The dirty yellow product is collected, washed with water, dried, and recrystallized from Et_2O after treating with charcoal to afford a pale yellow crystalline solid; yield: 79.0 g (91%); mp 106–108°C.

$C_7H_5ClN_2$	calc.	C 55.10	H 3.30	N 18.40
(152.58)	found	54.94	3.32	18.32

IR (KBr): ν = 2222 cm^{-1} (C≡N).

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.78 (s, 3H, CH_3), 7.30 (d, 1H, $J_{4-H,5-H}$ = 8.0 Hz, 5-H), 7.86 (d, 1H, $J_{4-H,5-H}$ = 8.0 Hz, 4-H).

6-Methoxy-2-methyl-3-pyridinecarbonitrile (12):

To a stirred mixture of **11** (69 g, 0.45 mol) and MeOH (700 mL) is added NaOMe (32 g, 0.59 mol) whereupon an exothermic reaction ensues. After the reaction subsides, the mixture is heated under reflux for 30 min and then cooled to r.t.. The insoluble NaCl is filtered and the filtrate is concentrated to dryness. The residue is crystallized from Et_2O to give a tan solid; yield: 64 g (96%); mp 80–80.5°C.

$C_8H_8N_2O$	calc.	C 64.85	H 5.44	N 18.91
(148.2)	found	65.07	5.62	18.91

IR (KBr): ν = 2225 cm^{-1} (C≡N).

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.67 (s, 3H, CH_3), 4.0 (s, 3H, OCH_3), 6.65 (d, 1H, $J_{4-H,5-H}$ = 8.0 Hz, 5-H), 7.70 (d, $J_{4-H,5-H}$ = 8.0 Hz, 4-H).

6-Methoxy-2-[2-(dimethylamino)1-propenyl]-3-pyridinecarbonitrile (13):

A mixture containing **12** (47.2 g, 0.32 mol), *N,N*-dimethylacetamide dimethyl acetal (100 mL, 0.68 mol), and DMF (100 mL) is heated with stirring in an oil bath at 145–150°C for 14 h allowing MeOH formed during the reaction to distill off using an air condenser. After the reaction cools to r.t., the solvent is removed under reduced pressure, and the residue is crystallized from EtOAc after treating with charcoal; yield: 33.5 g (48%); mp 103–104°C.

$C_{12}H_{15}N_3O$	calc.	C 66.34	H 6.96	N 19.34
(217.3)	found	66.53	6.99	19.33

IR (KBr): ν = 2195 cm^{-1} (C≡N).

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.68 (s, 3H, CH_3), 3.05 [s, 6H, $N(CH_3)_2$], 3.93 (s, 3H, OCH_3), 5.5 (s, 1H, =CH), 6.18 (d, 1H, $J_{4-H,5-H}$ = 8.0 Hz, 5-H), 7.5 (d, 1H, $J_{4-H,5-H}$ = 8.0 Hz, 4-H).

5-Bromo-7-methyl-1,6-naphthyridin-2(1*H*)-one (14):

Gaseous HBr is bubbled into a stirred solution of **13** (10.8 g, 0.05 mol) in AcOH (25 mL) and $CHCl_3$ (150 mL) cooled in an ice bath until it becomes saturated (30 min). A solid starts crystallizing during this time. The ice bath is removed and the resulting mixture is stirred at r.t. for 2 h. The product is collected and suspended in a stirred solution of water (200 mL) and 2N aq K_2CO_3 (20 mL). The product is collected, washed with water, dried, and recrystallized from DMF to give a tan solid; yield: 9.0 g (76%); mp 276–278°C.

$C_9H_7BrN_2O$	calc.	c 45.22	H 2.95	N 11.72
(239.1)	found	45.47	3.13	11.73

IR (KBr): ν = 1688 cm^{-1} (C=O).

^{1}H-NMR (CF_3CO_2D/TMS): δ = 2.92 (s, 3-H), CH_3), 7.23 (d, $J_{3-H,4-H}$) = 10.0 Hz, 1H, 3-H), 7.70 (s, 1H, 8-H), 8.35 (d, 1H, $J_{3-H,4-H}$ = 10.0 Hz, 4-H).

7-Methyl-1,6-naphthyridin-2(1*H*)-one (15):

A mixture of **14** (11.9 g, 0.05 mol), KOAc (5.9 g, 0.06 mol), 10% Pd/C (700 mg), and DMF (200 mL) is reduced on a Paar hydrogenator until 0.05 mol of H_2 is absorbed. The catalyst is filtered off on a Celite pad and the filtrate is concentrated to dryness under reduced pressure. The resulting solid residue is recrystallized from EtOH to give a tan product; yield: 5.53 g (69%); mp 244–245°C.

$C_9H_8N_2O$	calc.	C 67.49	H 5.03	N 17.49
(160.2)	found	67.50	5.12	17.49

IR (KBr): ν = 1698 cm^{-1} (C=O).

^{1}H-NMR (CF_3CO_2D/TMS): δ = 2.99 (s, 3-H, CH_3), 7.24 (d, 1H, $J_{3-H,4-H}$ = 9.5 Hz, 3-H), 8.35 (d, 1H, $J_{3-H,4-H}$ = 9.5 Hz, 4-H), 7.82 (s, 1H, 8-H), 9.15 (s, 1H, 5-H).

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(1) Deceased.
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