*Eur J Med Chem* (1991) 26, 599–604



# Anti-mycobacterial 4-hydroxy-3-phenylpyridin-2 (1H)-ones*

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(Received 6 August 1990; accepted 14 January 1991)

**Summary** — 4-Hydroxy-3-phenylpyridin-2 (1H)-ones with different substituents either at N-1 or in the phenyl group were synthesized by reaction of ethyl β-aminocrotonates with dialkyl malonates or 'magic malonates' (2,4,6-trichlorophenyl malonates). The evaluation of these compounds on *Mycobacterium tuberculosis* H37Ra, *Escherichia coli* B and *Staphylococcus aureus* ATCC 25923 showed significant inhibitory effects on *M tuberculosis* (**5g** and **5s**, MIC = 8 μg/ml). A structure–activity relationship is discussed.

**Résumé** — **4-Hydroxy-3-phénylpyridine-2(1H)-ones anti-mycobactériens.** *Des 4-hydroxy-3-phénylpyridin-2(1H)-ones diversement substituées sur l'azote 1 ou sur le noyau phényl ont été synthétisées par réaction des 2-aminocrotonates d'éthyle avec des esters maloniques activés. L'étude de ces composés sur* Mycobacterium tuberculosis *H37Ra,* Escherichia coli *B et* Staphylococcus aureus *ATCC 25923 a révélé une activité forte sur* M tuberculosis *(**5g** et **5s**, MIC = 8 μg/ml). La relation entre structure et activité est discutée.*

**pyridin-2(1H)-ones / anti-mycobacterial activity**

Previous investigations have shown the significant inhibitory effects of 7-hydroxy-2,3-dihydro-6-phenyl-1H-indolizin-5-ones [1] and 2-hydroxy-4-oxo-3-phenyl-6,7,8,9-tetrahydro-4H-quinolizines [2] on *Mycobacterium tuberculosis*. Since it was found that variation of the aliphatic ring system did not lead to indicative changes of this effect, systems without such a ring became of interest.

The synthesis of 4-hydroxy-6-methyl-3-phenylpyridin-2(1H)-ones has already been described using β-aminocrotonates and active malonates as starting materials [3]. We adopted and improved this method for the synthesis of such pyridin-2(1H)-ones with a substituent either at N-1 or in the phenyl group.

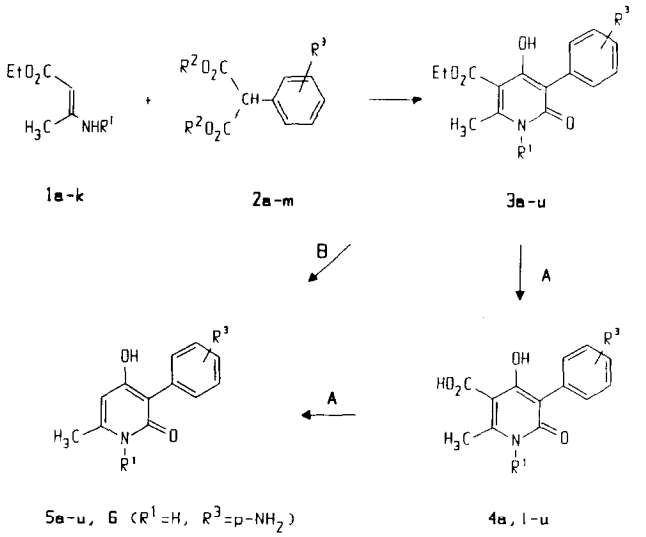
## Chemistry

Scheme 1 shows the synthetic pathway to obtain the 4-hydroxy-6-methyl-3-phenylpyridin-2(1H)-ones **5a–u**. First, an ethyl β-aminocrotonate was reacted with a phenylmalonate **2a–m** to yield the 5-ethoxycarbonyl compounds **3a–u**. Using the N-unsubstituted aminocrotonate **1a**, we were able to obtain the pyridin-2(1H)-ones **3a–k** with dimethyl and diethyl malonates.

The substituted dimethyl phenylmalonates **2b–i** were synthesized starting from the corresponding phenylacetic acids. After esterification they were treated with dimethyl oxalate and subsequent decarbonylation as it was previously described [4, 5]. The 4-nitrophenylmalonate **2k** could not be obtained by this procedure. Therefore, **2k** was synthesized according to Zvilichovsky *et al* [6] from 4-fluoro-nitro-benzene and diethyl malonate.

In the synthesis of compounds **3** the unsubstituted and the 4-substituted malonates produced significantly better yields (about 50%) than other substituted phenylmalonates. Lowest yields were found using 2,4-dichlorophenylmalonate. The relatively poor yield of **3k** with diethyl 4-nitrophenylmalonate **2k** may be attributed to decomposition at the high reaction temperature. For the synthesis of the N-substituted pyridin-2(1H)-ones **3l–u** we had to use activated malonates **2l, m** [7, 8].

*Dedicated to Prof E Mutschler, Universität Frankfurt aM, on the occasion of his 60th birthday



Scheme 1.

| 1 | $R^1$ |
|---|---|
| a | H |
| b | Ph |
| c | $CH_3$ |
| d | $C_2H_5$ |
| e | $(CH_2)_2CH_3$ |
| f | $(CH_2)_3CH_3$ |
| g | $(CH_2)_4CH_3$ |
| h | $(CH_2)_5CH_3$ |
| i | $C_6H_{11}$ |
| k | $CH_2Ph$ |

| 2 | $R^2$ | $R^3$ |
|---|---|---|
| a | $C_2H_5$ | H |
| b | $CH_3$ | 4-$CH_3$ |
| c | $CH_3$ | 3-$CF_3$ |
| d | $CH_3$ | 4-F |
| e | $CH_3$ | 2-Cl |
| f | $CH_3$ | 3-Cl |
| g | $CH_3$ | 4-Cl |
| h | $CH_3$ | 2,4-di-Cl |
| i | $CH_3$ | 4-$OCH_3$ |
| k | $C_2H_5$ | 4-$NO_2$ |
| l | $C_6H_2Cl_3$ | H |
| m | $C_6H_2Cl_3$ | 4-$OCH_3$ |

| 3 | 4 | 5 | $R^1$ | $R^3$ | Route |
|---|---|---|---|---|---|
| a | a | a | H | H | A, B |
| b | – | b | H | 4-$CH_3$ | B |
| c | – | c | H | 3-$CF_3$ | B |
| d | – | d | H | 4-F | B |
| e | – | e | H | 2-Cl | B |
| f | – | f | H | 3-Cl | B |
| g | – | g | H | 4-Cl | B |
| h | – | h | H | 2,4-di-Cl | B |
| i | – | i | H | 4-$OCH_3$ | B |
| k | – | k | H | 4-$NO_2$ | B |
| l | l | l | $CH_3$ | H | A |
| m | m | m | $C_2H_5$ | H | A |
| n | n | n | $(CH_2)_2CH_3$ | H | A |
| o | o | o | $(CH_2)_3CH_3$ | H | A |
| p | p | p | $(CH_2)_4CH_3$ | H | A |
| q | q | q | $(CH_2)_5CH_3$ | H | A |
| r | r | r | $C_6H_{11}$ | H | A |
| s | s | s | $CH_2Ph$ | H | A |
| t | t | t | Ph | H | A |
| u | u | u | Ph | 4-$OCH_3$ | A |

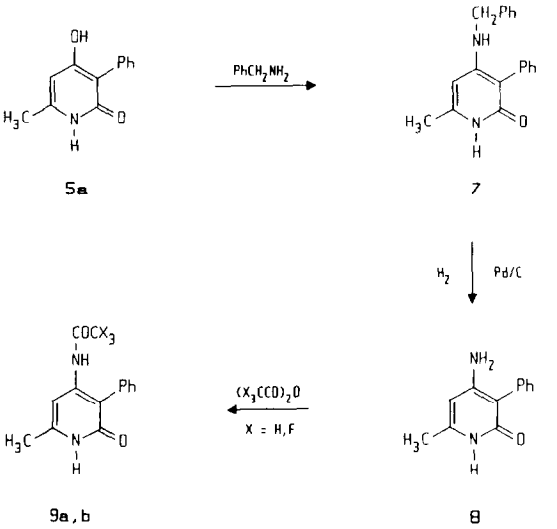
The further route for the synthesis of **5a–u** was also different for N-unsubstituted and N-substituted compounds. The treatment of **3a–k** with sodium hydroxide solution led directly to **5a–k**. Thus, we could not isolate the intermediate carboxylic acids. Only **3a** produced the carboxylic acid **4a** when treated with diluted sodium hydroxide solution. However, N-substituted pyridincarboxylates **3l–u** produced the carboxylic acids **4l–u** which had to be decarboxylated at high temperatures in 2,4,6-trichlorophenol to yield **5l–u**. Similar results were encountered with quinolizine carboxylates [2].

Synthesis of the 4-aminophenyl compound **6** was easily performed by reduction of the corresponding nitro compound **5k** with hydrogen and palladium on charcoal as catalyst.

Furthermore, we wanted to modify the electronic situation at the 4-position of the pyridinone. Therefore the 4-amino-pyridin-2(1H)-one **8** was afforded through reaction of **5a** with benzyl amine to **7** [9] and subsequent hydrogenolysis of the benzyl group. Further modification was performed by reaction with acetic anhydride and trifluoroacetic anhydride to yield **9a** and **9b**, respectively.

*Biological data and structure–activity relationship*

In preceding investigations with 7-hydroxy-2,3-dihydro-indolizin-5-ones [1] and 2-hydroxy-6,7,8,9-tetrahydro-quinolizin-4-ones [2] it was shown that variation of the aliphatic ring did not change significantly the anti-mycobacterial activity. In fact, in both series the most active compounds had MIC values of 16 µg/ml against *Mycobacterium tuberculosis*. The monocyclic 4-hydroxypyridin-2(1H)-ones



Scheme 2.

now synthesized have been tested for antibacterial activity. The test strains used were *Escherichia coli* B, as an example of Gram-negative bacteria, and *Staphylococcus aureus*, as an example of Gram-positive bacteria. With exception of **5f** and **5l**, which showed MIC values of 64 and 128 μg/ml, respectively, against *E coli*, all the other compounds resulted inactive against these strains while five of the tested compounds (**5f**, **5l**, **5p**, **5q**, **5s**) inhibited the growth of *Mycobacterium tuberculosis* at concentrations ≤ 16 μg/ml (table I).

As pointed out earlier [1, 2], a phenyl group β to the nitrogen atom and an unoccupied β'-position in the heterocycle are essential (compare **4t/5t**, table I and see [1, 2]) for the anti-mycobacterial activity. Therefore 4-hydroxy-3-phenyl-2(1H)-pyridinone (**5a**) has been used as key molecule (MIC = 16–32 μg/ml). To enhance the activity variations at the nitrogen atom, the phenyl ring and the OH-group, respectively, were performed.

Compared to the key compound **5a**, most of the substituents at the phenyl ring (**5b–5k**) decreased the anti-mycobacterial activity, only the *m*-chloro derivative **5f** was comparable to **5a**. This result is in agreement with Topliss' operational scheme [12] for drug design which shows the *m*-chloro derivative as the most active compound if the *p*-chloro (**5g**) and the *p*-$OCH_3$ (**5i**) derivatives are less active than the key molecule (**5a**). On account of sterical effects, low activity is observed with bulky substituents at the *para* and *ortho* position, respectively, of the phenyl ring, therefore the fluoro compound **5d** is less active than **5a** ($R^3$ = H) but more active than the corresponding chloro derivative **5g** and all the other derivatives **5b**, **5c**, **5h**, **5i**, **5k**. *Meta* substitution does not decrease the activity so much as shown by comparison of **5f** (*meta* chloro) with **5e** (*ortho* chloro) and **5g** (*para* chloro).

The variation at the nitrogen atom leads to the most active pyridinones **5q** and **5s** (MIC = 8 μg/ml). Methyl, ethyl, *n*-propyl and *n*-butyl substituents decrease the effectiveness against *Mycobacterium tuberculosis* (**5l–o** compared to **5s**), the butyl derivative is in between **5l** and **5m**. Due to the higher lipophilicity increased activity is observed again with the *N*-pentyl (**5p**) and *N*-hexyl (**5q**) compound (MIC = 16 and 8 μg/ml, resp). The flexibility of the aliphatic N-substituents accounts for the difference of **5q** (*n*-hexyl) and **5r** (cyclohexyl) which is 8 times less active. The N-benzyl derivative **5s** is 16 times more active than the phenyl compound **5t**, **5r** (cyclohexyl) is equi-effective to **5m** (ethyl). The benzyl compound is at least twice more potent than the basic molecule **5a** whith the NH-function but identical in all other positions.

Inactive or weak active pyridones **9a**, **b** and **8**, respectively, were found if a NHR-function occupies position 4 instead of the OH-group (compare **5a** with **8**, **9a**, **b**).

Summarizing, the following structural requirements are available: all tested compounds are six-membered β-lactams which need a phenyl group and an H-atom β and β' to the nitrogen atom together with a hydroxyl function at the γ-position for anti-mycobacterial activity. Substituents at the N-atom and the phenyl ring, respectively, modulate the activity. Under the structural conditions discussed, this new series of compounds inhibits the growth of *Mycobacterium tuberculosis* with low MIC values, *eg* **5g** and **5s** are the most potent derivatives found to date.

## Experimental protocols

*Chemistry*

The melting points were determined in open capillary tubes on a Gallenkamp melting point apparatus, Mod MFB-595, and are uncorrected. The infrared spectra were recorded on a Perkin-Elmer 298, using samples in potassium bromide disks. The $^1H$ NMR spectra were measured in DMSO-$d_6$ (unless otherwise stated) with tetramethylsilane (TMS) as the internal standard; the instruments used were the Varian EM 360 at 60 MHz and the Varian XL 200 at 200 MHz. Analyses indicated by the elemental symbols were within ± 0.4% of the theoretical values and were obtained with a Carlo Erba C, H, N-Automat 1106.

*General procedure for the synthesis of substituted dimethyl phenylmalonates* ***2b–i*** *[4, 5]*

A solution of sodium (0.2 mol) in methanol (80 ml) was heated to 60°C and dimethyl oxalate (0.2 mol) rapidly added. After stirring for another 10 min, the corresponding methyl phenylacetate was added *via* a dropping funnel and the mixture was stirred for one additional hour. Then the mixture was cooled to room temperature. After standing overnight the solvent was removed and the residue dissolved in 30% acetic acid (300 ml). This solution was extracted with diethyl ether (3 x 200 ml) and the organic layer washed with water (150 ml) and dried. After removing the solvent, decarbonylation took place at 180°C at reduced pressure. Purification of the product was achieved by distillation.

Dimethyl phenylmalonates prepared:

| *No* | *$R^3$* | *Yield (%)* | *bp [°C]/mm* | *mp[°C]* | *Lit* |
|---|---|---|---|---|---|
| **2b** | 4-methyl | 46 | 164/14 | 68–70 | [10] |
| **2c** | 3-trifluoromethyl | 46 | 154–6/17 | – | |
| **2d** | 4-fluoro | 49 | 152/14 | 50–51 | |
| **2e** | 2-chloro | 40 | 160–2/12 | – | |
| **2f** | 3-chloro | 41 | 168–9/15 | – | |
| **2g** | 4-chloro | 50 | 170/16 | 70–74 | [11] |
| **2h** | 2,4-dichloro | 33 | 172–4/14 | – | |
| **2i** | 4-methoxy | 45 | 180–4/14 | 44–47 | |

The ester **3k** was prepared according to [6]; **3l** and **3m** according to [7] and [8], respectively.

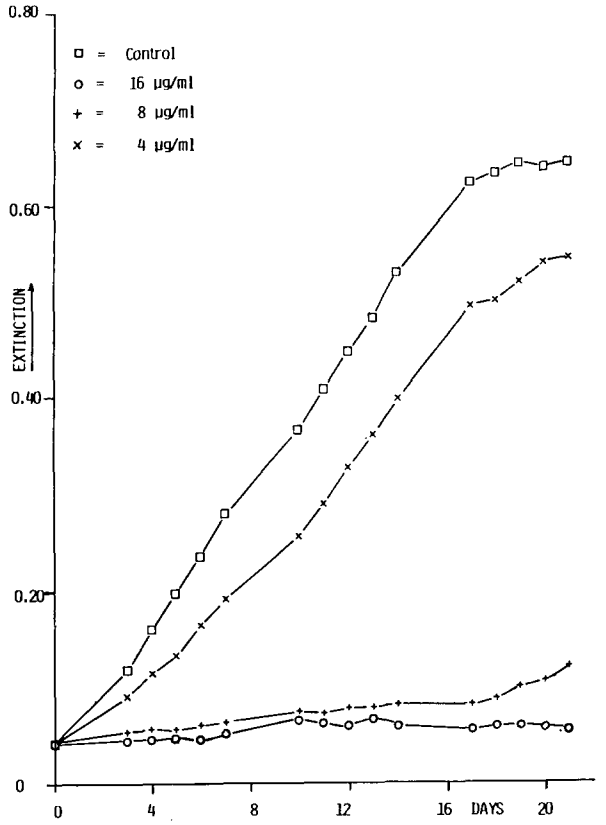



**Fig 1.** Growth of *Mycobacterium tuberculosis* H 37 Ra under the influence of **5s** (µg/ml).

*General procedure for the synthesis of 5-ethoxycarbonyl-4-hydroxy-6-methyl-3-(substituted)phenylpyridin-2(1H)-ones* ***3a–k***

A mixture of **1a** (20 mmol) and **2a–k** (20 mmol) was heated in an oil bath adjusted to 220°C for 30 min. The reaction mixture was cooled and quenched with toluene. The colorless solid obtained in this way was filtered and recrystallized from the appropriate solvent (indicated in parentheses after the mp).

*General procedure for the synthesis of N-substituted 5-ethoxycarbonyl-4-hydroxy-6-methyl-3-(substituted)phenylpyridin-2(1H)-ones* ***3l–u***

A solution of the corresponding N-substituted ethyl β-amino-crotonate (10 mmol) and the active malonate **2l, m** [7, 8] (10 mmol) in bromobenzene (20 ml) was refluxed for 1 h. After cooling the solvent was evaporated under reduced pressure and the oily mass obtained in this way was digested with low boiling petroleum ether (40–60°C), filtered and recrystallized from the appropriate solvent (given in parentheses after the mp) to yield colorless crystals.

*5-Ethoxycarbonyl-4-hydroxy-6-methyl-3-phenylpyridin-2(1H)-ones*

| *No* | $R^1$ | $R^3$ | *Yield (%)* | *mp[°C]* | *(recryst solvent)* | *Formula* |
|---|---|---|---|---|---|---|
| **3a** | H | H | 59 | 286 | (DMF) | $C_{15}H_{16}NO_4$ |
| **3b** | H | 4-$CH_3$ | 58 | 270–2 | (DMF) [3] | $C_{16}H_{18}NO_4$ |
| **3c** | H | 3-$CF_3$ | (not isolated)+ | | | |
| **3d** | H | 4-F | 45 | 280 | (DMF) | $C_{15}H_{14}FNO_4$ |
| **3e** | H | 2-Cl | 36 | 231 | (DMF/$H_2O$ 1:1) | $C_{15}H_{14}ClNO_4$ |
| **3f** | H | 3-Cl | 35 | 227–8 | (DMF/$H_2O$ 1:1) | $C_{15}H_{14}ClNO_4$ |
| **3g** | H | 4-Cl | 59 | 272 | (1-butanol) | $C_{15}H_{14}ClNO_4$ |
| **3h** | H | 2,4-di-Cl | 29 | 229–32 | (DMF/$H_2O$ 1:1) | $C_{15}H_{13}Cl_2NO_4$ |
| **3i** | H | 4-$OCH_3$ | 57 | 260–3 | (ethanol) | $C_{16}H_{17}NO_5$ |
| **3k** | H | 4-$NO_2$ | 31 | 274 dec | (DMF) | $C_{15}H_{14}N_2O_4$ |
| **3l** | $CH_3$ | H | 64 | 146–7 | (ligroin) | $C_{16}H_{17}NO_4$ |
| **3m** | $C_2H_5$ | H | 52 | 106–7 | (ligroin) | $C_{17}H_{19}NO_4$ |
| **3n** | $(CH_2)_2CH_3$ | H | 50 | 144 | (ethyl acetate) | $C_{18}H_{21}NO_4$ |
| **3o** | $(CH_2)_3CH_3$ | H | 46 | 134 | (ligroin) | $C_{19}H_{23}NO_4$ |
| **3p** | $(CH_2)_4CH_3$ | H | 82 | 63 | (cyclohexane) | $C_{20}H_{25}NO_4$ |
| **3q** | $(CH_2)_5CH_3$ | H | 81 | 65 | (cyclohexane) | $C_{21}H_{27}NO_4$ |
| **3r** | $C_6H_{11}$ | H | 64 | 164–5 | (ligroin) | $C_{21}H_{25}NO_4$ |
| **3s** | $CH_2Ph$ | H | 77 | 121–2 | (ligroin) [3] | $C_{22}H_{21}NO_4$ |
| **3t** | Ph | H | 66 | 182–4 | (ethanol) | $C_{21}H_{19}NO_4$ |
| **3u** | Ph | 4-$OCH_3$ | 40 | 152–3 | (1-butanol) | $C_{22}H_{21}NO_5$ |

**3c** did not crystallize; therefore it was directly treated with sodium hydroxide solution to give **5c**.

With the exception of **3c** all compounds gave satisfactory C, H, N-analyses. The IR and $^1H$ NMR spectra [14] are in good agreement with the proposed structures, however, it should be noted that the ester carbonyl absorption for compounds **3** (found in the 1740–1690 $cm^{-1}$ region) are very weak or even completely absent. This is due to hydrogen bonding and in accordance with the literature [1, 3].

*4-Hydroxy-6-methyl-2-oxo-3-phenyl-1,2-dihydropyridin-5-carboxylic acid* ***4a***

The ester **3a** (10 mmol) was dissolved in 0.5 N NaOH solution (100 ml) and refluxed for 4 h. After cooling the solution was acidified with hydrochloric acid. The product precipitated, was filtered and recrystallized from dimethylformamide. Yield 91%, colorless prisms, mp = 269°C dec [3].

*General procedure for the synthesis of N-substituted 4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-5-carboxylic acids* ***4l–u***

The ester **3l–u** (5 mmol) was dissolved in 2 N NaOH solution (20 ml) and refluxed for 2 h. After cooling the solution was acidified with HCl and the product precipitated. After filtering and drying it was recrystallized from the appropriate solvent (indicated in parentheses after the mp).

*4-Hydroxy-1-$R^1$-6-methyl-2-oxo-3-phenyl-1,2-dihydropyridin-5-carboxylic acids* ***4l–u***

| *No* | $R^1$ | $R^2$ | *Yield (%)* | *mp[°C] dec* | *(recryst solvent)* | *Formula* |
|---|---|---|---|---|---|---|
| **4l** | $CH_3$ | H | 95 | 191 | (ethyl acetate) | $C_{15}H_{13}NO_4$ |
| **4m** | $C_2H_5$ | H | 92 | 163–5 | (ethyl acetate) | $C_{15}H_{15}NO_4$ |
| **4n** | $(CH_2)_2CH_3$ | H | 91 | 210 | (ethanol) | $C_{16}H_{17}NO_4$ |
| **4o** | $(CH_2)_3CH_3$ | H | 97 | 185–6 | (ethyl acetate) | $C_{17}H_{19}NO_4$ |
| **4p** | $(CH_2)_4CH_3$ | H | 99 | 198 | (ethanol) | $C_{18}H_{21}NO_4$ |
| **4q** | $(CH_2)_5CH_3$ | H | 99 | 184 | (ethanol) | $C_{19}H_{23}NO_4$ |
| **4r** | $C_6H_{11}$ | H | 96 | 212–3 | (ethyl acetate) | $C_{19}H_{21}NO_4$ |
| **4s** | $CH_2Ph$ | H | 95 | 210–2 | (1-butanol) [3] | $C_{20}H_{17}NO_4$ |
| **4t** | Ph | H | 94 | 283 | (ethanol) | $C_{19}H_{15}NO_4$ |
| **4u** | Ph | 4-$OCH_3$ | 94 | 256–60 | (ethyl acetate) | $C_{20}H_{17}NO_5$ |

*General procedure for the synthesis of 4-hydroxy-6-methyl-3-(substituted)phenylpyridin-2(1H)-ones* ***5a–k***

The corresponding ester **3a–k** (5 mmol) was refluxed in 2 N NaOH hydroxide solution (20 ml) for 2 h. After cooling the solution was acidified with hydrochloric acid. The precipitated product was filtered, dried and recrystallized from the appropriate solvent (given in parentheses after the mp).

*General procedure for the synthesis of N-substituted 4-hydroxy-6-methyl-3-(substituted)phenylpyridin-2(1H)-ones* ***5l–u***

The corresponding carboxylic acid **4l–u** (5 mmol) was added in small portions to 2,4,6-trichlorophenol (5 ml) at 220°C. At the end of $CO_2$ evolution this mixture was held at this temperature for another 5 min, then it was cooled and quenched with petroleum ether (40–60°C). The product precipitated, was filtered and washed with ether. Recrystallization was performed in the appropriate solvent (given in parentheses after the mp).

| *No* | *$R^1$* | *$R^3$* | *Yield (%)* | *mp[°C] dec* | *(recryst solvent)* | *Formula* |
|---|---|---|---|---|---|---|
| **5a** | H | H | 93 | 290 | (1-butanol) [3] | $C_{12}H_{11}NO_2$ |
| **5b** | H | 4-$CH_3$ | 94 | 295 | (DMF) | $C_{13}H_{13}NO_2$ |
| **5c** | H | 3-$CF_3$ | 18 | 276 | (1-butanol) | $C_{13}H_{10}F_3NO_2$ |
| **5d** | H | 4-F | 63 | 279 | (ethanol) | $C_{12}H_{10}FNO_2$ |
| **5e** | H | 2-Cl | 78 | 295 | (ethanol) | $C_{12}H_{10}ClNO_2$ |
| **5f** | H | 3-Cl | 85 | 292 | (ethanol) | $C_{12}H_{10}ClNO_2$ |
| **5g** | H | 4-Cl | 99 | 309 | (1-butanol) | $C_{12}H_{10}ClNO_2$ |
| **5h** | H | 2,4-di-Cl | 94 | 312 | (ethanol) | $C_{12}H_9Cl_2NO_2$ |
| **5i** | H | 4-$OCH_3$ | 95 | 299 | (1-butanol) | $C_{13}H_{13}NO_3$ |
| **5k** | H | 4-$NO_2$ | 77 | 299 | (DMF) | $C_{12}H_{10}N_2O_2$ |
| **5l** | $CH_3$ | H | 95 | 266–8 | (toluene) | $C_{13}H_{13}NO_2$ |
| **5m** | $C_2H_5$ | H | 68 | 252–4 | (toluene) | $C_{14}H_{15}NO_2$ |
| **5n** | $(CH_2)_2CH_3$ | H | 92 | 226 | (ethanol) | $C_{15}H_{17}NO_2$ |
| **5o** | $(CH_2)_3CH_3$ | H | 94 | 206–7 | (toluene) | $C_{16}H_{19}NO_2$ |
| **5p** | $(CH_2)_4CH_3$ | H | 25 | 187 | (toluene) | $C_{17}H_{22}NO_2$ |
| **5q** | $(CH_2)_5CH_3$ | H | 48 | 184 | (toluene) | $C_{18}H_{23}NO_2$ |
| **5r** | $C_6H_{11}$ | H | 83 | 244–5 | (toluene) | $C_{18}H_{21}NO_2$ |
| **5s** | $CH_2Ph$ | H | 84 | 235 | (toluene) [3] | $C_{19}H_{17}NO_2$ |
| **5t** | Ph | H | 85 | 278 | (1-butanol) | $C_{18}H_{15}NO_2$ |
| **5u** | Ph | 4-$OCH_3$ | 83 | 257–9 | (toluene) | $C_{19}H_{17}NO_3$ |

The lactam carbonyl absorption in the IR appears at ν = 1660–1650 $cm^{-1}$. The $^1H$ NMR signal of the proton in position 5 is found at δ = 5.8–6.0 in DMSO-$d_6$, and at 6.8–6.9 ppm in $CF_3COOH$.

*3-(4-Aminophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one* ***6***

The 4-nitrophenyl compound **5k** (5 mmol) was dissolved in glacial acetic acid (100 ml) at 40°C and 5% Pd on charcoal was added. This solution was treated with hydrogen at 80°C. After cooling the solution was filtered and the solvent evaporated under reduced pressure. The residue was recrystallized from ethanol. Yield 87%, colorless prisms, mp = 298°C. Anal $C_{12}H_{12}N_2O_2$ (C, H, N).

*4-Benzylamino-6-methyl-3-phenylpyridin-2(1H)-one 7*

A solution of **5a** (50 mmol) in benzylamine (40 ml) was refluxed for 16 h. The product precipitated at cooling and was recrystallized from ethanol. Yield 77%, colorless prisms, mp = 261–262°C. IR ν $cm^{-1}$: 3420 m, 3260 w, 3120 w, 3100–3080 w, 3020 w, 2980–2800 m, 1650 sh, 1640 sh, 1630 s. $^1H$ NMR (200 MHz) δ: 2.04 (s, $CH_3$), 4.28 (d, $J$ = 7 Hz, $CH_2$), 5.62 (s, CH), 7.15–7.52 (m, 10 ArH), 10.75–10.95 (b, NH). Anal $C_{19}H_{18}N_2O$ (C, H, N).

*4-Amino-6-methyl-3-phenylpyridin-2(1H)-one* ***8***

Compound **7** (30 mmol) was dissolved in glacial acetic acid (250 ml), charcoal with 5% Pd was added and this solution treated with hydrogen at 70°C. The hot solution was filtered, the solvent removed under reduced pressure and the oily residue digested with water. Recrystallization was performed from ethanol. Yield 87%, colorless needles, mp = 262–265°C. IR ν $cm^{-1}$: 3480 w, 3440 w, 3300 w, 3200–3120 w, 2960–2880 w, 1670 sh, 1655 sh, 1650 m, 1640 sh, 1620 sh, 1600 s. $^1H$ NMR δ: 2.0 (s, $CH_3$), 5.2–5.4 (s, b, $NH_2$), 5.6 (s, CH), 7.3 (s, 5 ArH), 10.4–10.7 (b, NH). Anal $C_{12}H_{12}N_2O$ (C, H, N).

*4-Acetylamino-6-methyl-3-phenylpyridin-2(1H)-one* ***9a***

The amino-pyridone **8** (5 mmol) was refluxed in acetic anhydride (10 ml) for 30 min. After cooling the solution was poured into water (50 ml). The product crystallizes within some days and is recrystallized from ethanol. Yield 85%, colorless prisms, mp = 249–250°C. IR ν $cm^{-1}$: 3420 w, 3140 w, 3000 w, 2860 w, 1720 sh, 1710 m, 1700 sh, 1640 sh, 1630 s, 1600 m, 1580 m, 1560 sh, 1485 m. $^1H$ NMR δ: 1.8 (s, $CH_3$), 2.1 (s, $CH_3$), 6.5 (s, CH), 7.2 (s, 5 ArH), 8.6 (s, NH), 11.2–11.5 (b, NH). Anal $C_{14}H_{14}N_2O_2$ (C, H, N).

*6-Methyl-3-phenyl-4-trifluoroacetylamino-pyridin-2(1H)-one* ***9b***

The amino-pyridine **8** (5 mmol) was refluxed in trifluoroacetic anhydride (4.5 ml) for 20 min. After cooling the solution was diluted with water (100 ml) and the product precipitated. It was recrystallized from ethanol. Yield 72%, colorless needles, mp = 253–254°C. IR: ν $cm^{-1}$: 3390 w, 3160–2600 w, 1750 m, 1740 sh, 1640 sh, 1630 s, 1620 sh, 1600 m. Anal $C_{14}H_{11}F_3N_2O_2$ (C, H, N).

*Biological methods*

The compounds listed in table I were screened for activity against *M tuberculosis* H 37 Ra, *E coli* B and *S aureus* ATCC 25 923. Test compounds with minimal inhibition concentrations (MIC) of more than 256 μg/ml were considered to be inactive.

**Table I.** Minimal inhibition concentrations (MIC [μl/ml]) of compounds tested against *Mycobacterium tuberculosis* H 37 Ra.

| Compd | **4t** | **5a** | **5b** | **5c** | **5d** | **5e** | **5f** | |
|---|---|---|---|---|---|---|---|---|
| MIC | > 256 | 16–32 | > 256 | ≥ 256 | 64 | 128 | 16 | |
| Compd | **5g** | **5h** | **5i** | **5k** | **5l** | **5m** | **5n** | **5o** |
| MIC | > 256 | > 256 | >256 | > 256 | 16 | 64 | 64 | 32 |
| Compd | **5p** | **5q** | **5r** | **5s** | **5t** | **8** | **9a** | **9b** |
| MIC | 16 | 8 | 64 | 8 | 128 | 128 | > 256 | > 256 |

*Test for anti-mycobacterial activity*
The test compounds were dissolved in dimethyl sulfoxide and added to the Middlebrook-7H9 broth in a geometric dilution series beginning at 256 μg/ml; the final concentration of DMSO was 2.5%. The test tubes with the liquid medium were inoculated with a suspension of *M tuberculosis* H 37 Ra (obtained from the Max-von-Pettenkofer-Institut für Hygiene und Medizinische Mikrobiologie, University of Munich, Germany) in 0.85% saline to give an extinction difference of 0.04 in the 18 mm culture tube (546 nm filter, Eppendorf 1101 M spectrophotometer). During incubation in a shaker (100 rpm, TR-1 and ITH-1 B, Braun-Melsungen) for 21 days at 37°C, extinctions were measured once a day, five times a week. An extinction down to 0.15 was regarded as no growth of *M tuberculosis* H 37 Ra.

*Test for activity against E coli and S aureus*
The tests were done with the strains *E coli* B and *S aureus* ATCC 25 923 (obtained from the Institut für Botanik, University of Regensburg, Germany) in Müller-Hinton broth in a geometric dilution series beginning at 256 μg/ml, using the microtiter techniques of Brinkmann [13]. The inoculum was $5 \times 10^5$ germs/ml and incubation at 37°C lasted 18 h. Absence of growth was noted as MIC. The test compounds were dissolved in DMSO and added to the medium to give a final concentration of 5% DMSO. The corresponding control with the same amount of DMSO showed no visible inhibition of growth and was defined as no inhibition.

## Acknowledgments

Support of this work by the Fonds der Chemischen Industrie, Frankfurt/Main for one of us (GD) is gratefully acknowledged.

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