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UNEXPECTED REACTION ON BROMINATION OF 3,4-DIHYDROPYRIDIN-2(1H)-ONES WITH N-BROMOSUCCINIMIDE

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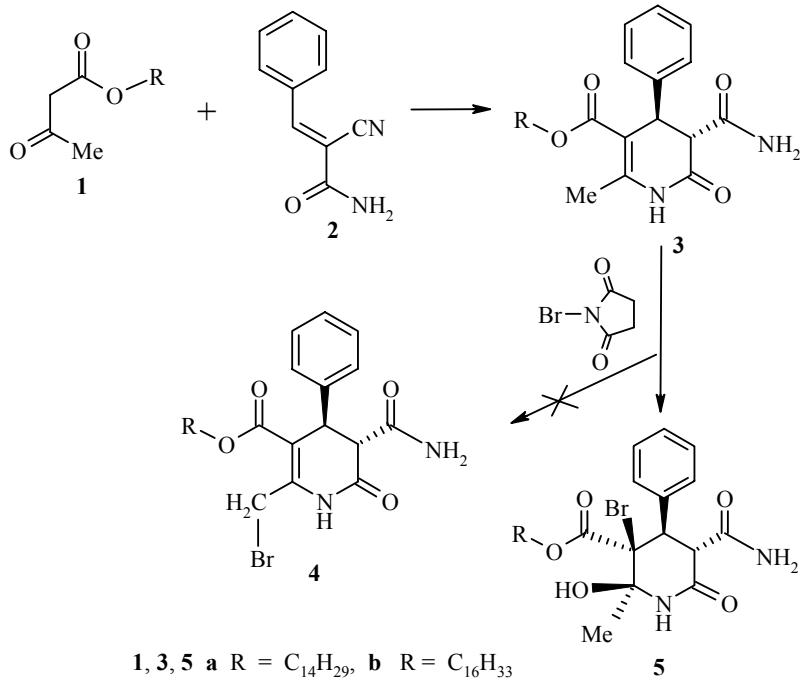
Potential agents for the transfection of genes appear in a series of 1,4-dihydropyridine derivatives of pyridine with long alkyl chains [1]. To elucidate these properties in a series of derivatives of dihydropyridin2)1H)-ones, 3,4-dihydropyrdin-2(1H)-ones with lipophilic substituents in the pyridine ring were synthesized for the first time by condensation of esters **1** with benzylidenecyanacetamide (**2**).



1, **3**, **5** **a** R = $C_{14}H_{29}$, **b** R = $C_{16}H_{33}$

On bromination of 5-tetradecyloxycarbonyl- and 5-hexadecyloxycarbonyl-3,4-dihydropyridones **3** with N-bromosuccinimide, in contrast to 5-methoxycarbonyl-3,4-dihydropyridones [2] and their 5-unsubstituted analogs [3], the lipophilic tetrahydropyridones **5**, containing a bromine atoms and a hydroxy group, not described in the literature, were formed instead of the expected bromo-substituted **4**.

* Dedicated to Professor I. Kalvinsh on his 60th Birthday

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Apparently the presence of water in the reaction mixture led to the formation of hypobromous acid (HOBr) from N-bromosuccinimide, which subsequently added to the double bond. The additive hydroxybromination in the 3,4-dihydropyridin-2(1H)-one series **3** was previously unknown. Although it has been studied in derivatives of pyrimidin-2(1H)-on and uracil [4]. In a series of dehydrogenated analogs – pyridine-2(1H)-ones – methoxybromination at the $C_{(5)}=C_{(6)}$ bond has been observed.

It is interesting that formerly N-bromosuccinimide has been used successfully for "allyl" bromination of 2- and 6-methyl groups in related 1,4-dihydropyridines and in protonated solvents (alcohols) [1,6]. The difference may be explained by the greater stabilization of the conjugated systems in 3,5-dicarbonyl-1,4-dihydropyridines than in 3,4-dihydropyridin-2(1H)-ones of type **3**.

^{1}H NMR spectroscopy was used to establish the special configuration of the compounds obtained. According to [7], compounds **3** with $J_{34} < 0.5$ Hz exist in the *trans*-form with Ph and $CONH_2$ in pseudoaxial positions. In the spectra of compounds **5** J_{34} = 11.4-11.6 Hz shows that the groups Ph and $CONH_2$ are in *trans*-diequatorial positions.

^{1}H NMR Spectra of DMSO-d_6 solutions with HMDS (δ = 0.055 ppm) as internal standard were recorded on Unity Inova 600 (600 MHz) and Varian Mercury-200 (200 MHz) spectrometers.

Tetradecyl (4*R*,5*R*)-5-carbamoyl-2-methyl-6-oxo-4-phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (3a). Piperidine (1 ml) was added to a solution of the tetradecyl ester **1a** (0.5 g, 1.68 mmol) and the amide **2** (0.29 g, 1.68 mmol) in ethanol (7ml) and the mixture was boiled for 2 h. After cooling the solution was kept at -30°C for 72 h. The precipitate formed was filtered off and washed with cold ethanol. Yield 0.4 g (51%) of compound **3a**; mp 176-178°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.83 (3H, t, ^3J = 6.6, CH_3, ether); 1.09-1.22 (22H, m, $(CH_2)_{11}$); 1.39 (2H, m, $\underline{CH_2}CH_2O$); 2.28 (3H, s, 2-CH_3); 3.23 (1H, s, H-5); 3.88 (1H, m, OCH); 3.92 (1H, m OCH); 4.33 (1H, s, H-4); 7.14-7.30 (6H, m, C_6H_5 + 5-CONH); 7.63 (1H, s, 5-CONH); 10.03 (1H, s, NH). Found, %: C 71.32; H 9.19; N 6.00. $C_{28}H_{42}N_2O_4$. Calculated, %: C 71.45; H 8.99; N 5.95.

Hexadecyl (4*R*,5*R*)-5-carbamoyl-2-methyl-6-oxo-4-phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (3b) was prepared analogously to compound **3a** from the hexadecyl ester **1b**. Yield 54%; mp 175-176°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.82 (3H, t, ^3J = 6.6, CH_3, ether); 1.03-1.22 (26H, m, $(CH_2)_{13}$); 1.38 (2H, m, $\underline{CH_2}CH_2O$); 2.28 (3H, s, 2-CH_3); 3.22 (1H, s, H-5); 3.85 (1H, m, OCH); 3.92 (1H, m OCH); 4.33 (1H, s, H-4); 7.12 (1H, s, 5-CONH); 7.16-7.26 (5H, m, C_6H_5); 7.61 (1H, s, 5-CONH); 10.00 (1H, s, NH). Found, %: C 72.24; H 9.54; N 5.52. $C_{30}H_{46}N_2O_4$. Calculated, %: C 72.25; H 9.30; N 5.62.

Tetradecyl (2*S*,3*S*,4*R*,5*R*)-3-bromo-5-carbamoyl-2-hydroxy-2-methyl-6-oxo-4-phenylpiperidine-3-carboxylate (5a). N-Bromosuccinimide (0.21 g, 1.17 mmol) and benzoyl peroxide (0.02 g) were added to a suspension of amide **3a** (0.5 g, 1.06 mmol) in ethanol (25 ml) and the mixture was stirred at room temperature. The mixture became clear after 15 min and a precipitate appeared over 1 h. Stirring was continued for a further 6 h. On the next day the precipitate was filtered off and washed with ethanol to give compound **5a** (0.3 g, 50%); mp 133-134°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.83 (3H, t, ^3J = 5.8, CH_3, ether); 1.05-1.30 (22H, m, $(CH_2)_{11}$); 1.37 (2H, m, $\underline{CH_2}CH_2O$); 1.58 (3H, s, 2-CH_3); 3.71 (1H, d, ^3J = 11.6, H-5); 3.87 (2H, m, OCH_2); 4.66 (1H, d, ^3J = 11.6, H-4); 6.53 (1H, s, OH); 6.80 (1H, s, 5-$CONH_2$); 7.17-7.29 (3H, m, C_6H_5); 7.39 (1H, s, 5-CONH); 7.43-7.53 (2H, m, C_6H_5); 8.57 (1H, s, NH). Found, %: C 59.05; H 7.64; N 4.88. $C_{28}H_{43}BrN_2O_5$. Calculated, %: C 59.25; H 7.64; N 4.93.

Hexadecyl (2*S*,3*S*,4*R*,5*R*)-3-bromo-5-carbamoyl-2-hydroxy-2-methyl-6-oxo-4-phenylpiperidine-3-carboxylate (5a) was prepared analogously to compound **5a** from tetrahydropyridine **3b** in a yield of 52%; mp 115-118°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.82 (3H, t, ^3J = 6.2, CH_3, ether); 1.05-1.24 (26H, m, $(CH_2)_{13}$); 1.37 (2H, m, $\underline{CH_2}CH_2O$); 1.58 (3H, s, 2-CH_3); 3.68 (1H, d, ^3J = 11.4, H-5); 3.86 (2H, m, OCH_2); 4.62 (1H, d, ^3J = 11.4, H-4); 6.52 (1H, s, OH); 6.78 (1H, s, 5-$CONH_2$); 7.15-7.23 (3H, m, C_6H_5); 7.37 (1H, s, 5-CONH); 7.41-7.48 (2H, m, C_6H_5); 8.55 (1H, s, NH). Found, %: C 61.26; H 8.30; N 4.50. $C_{30}H_{47}BrN_2O_5$. Calculated, %: C 60.50; H 7.95; N 4.70.

REFERENCES

1. Z. Hyvönen, A. Plotniece, I. Reine, B. Chekavichus, G. Duburs, A. Urtti. *Biochem. Biophys. Acta,* **1509**, 451 (2000).
2. Z. A. Kalme, R.A. Zhalubovskis, A. Shmidlers, J. Celmins, and G. Duburs, *Khim. Geterotsikl. Soed.,* 1006 (2004). [*Chem. Heterocycl. Comp.,* **40**, 862 (2004)]
3. N. Martin, M. Quinteiro, C. Seone, and J. L. Soto, *J. Heterocycl. Chem.,* **33**, 103 (1996).
4. T. K. Bradshaw and D. W. Hutchison, *Chem. Soc. Revs.,* **6**, 43 (1977).
5. R. L. Shone. *Tetrahedron Lett.,* **20**, 2185 (1979).
6. I. Skrastiņš, V. Kastron, B. Cekavičus, A. Sausiņš, R. Zolotoyabko, and G. Dubur, *Khim. Geterotsikl. Soedin*., 1230 (1991). [*Chem. Heterocycl. Comp.,* **27,** 989 (1991)].
7. A. A. Krauze, E. E. Liepin'sh, Z. A. Kalme, Yu. Pelcher, and G. Ya Dubur, *Khim. Geterotsikl. Soedin*., 1504 (1984). [*Chem., Heterocycl. Comp.,* **20,** 1241 (1984)].