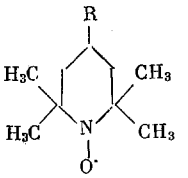
SYNTHESIS OF NEW STABLE FREE RADICALS IN THE 2,2,6,6,-TETRAMETHYLPIPERIDIN-1-OXYL SERIES

É.G.Rozantsev and V.I. Suskina

UDC 541.515+547.822.3

Recently many stable iminoxyl radicals have found broad and varied application [1-4] as a result of successful development of a method for their synthesis with reactions which do not affect the free valence [5-11]. Works associated with the use of free radical "labels" and "probes" for the investigation of polymers and proteins [12-16] have received particularly wide attention.

This communication is a continuation of work begun by us on synthesis [17] of new individual stable iminoxyls of the hydrogenated pyridine series.



R = $(CH_3)_3CCONH$ (I); $(C_2H_5)_2NCONH$ (II); $C_6H_5CHBrCONH$ (III); $C_6H_5CHClCONH$ (IV); $CH_3(CH_2)_6COO$ (V); $C_{15}H_{31}CONH$ (VI); $C_{17}H_{35}CONH$ (VII); $C_{17}H_{35}COO$ (VIII); $C_{16}H_{33}OC_6H_4COO$ (IX)

The radicals synthesized by us, apart from (V), are crystalline red compounds, very stable in relation to oxygen and heating.

EXPERIMENTAL

2,2,6,6-Tetramethyl-4-trimethylacetamidopiperidin-1-oxyl (I). To a solution of 1.79 g of 2,2,6,6-tetramethyl-4-aminopiperidin-1-oxyl in 35 ml of abs. benzene and 4 ml of triethylamine was added dropwise with stirring a solution of 1.5 g of trimethylacetyl chloride in 25 ml of abs. benzene. After stirring for 5 h the precipitated triethylamine hydrochloride was filtered and the solution was evaporated at reduced pressure. The residue remaining after evaporation was chromatographed on a column of Al_2O_3, eluting the lower red zone ($CHCl_3$ as eluent). The chloroform was evaporated and the solid residue was recrystallized from CCl_4. We obtained 2.15 g (84.4%) of amide (I) as rose-colored needles having mp 179°C. Found: C 66.07; H 10.58; N 10.86%. $C_{14}H_{27}N_2O_2$. Calculated: C 65.86; H 10.66; N 10.97%.

2,2,6,6-Tetramethyl-4-diethylcarbamidopiperidin-1-oxyl (II). The compound was obtained analogously to the preceding from 2 g of 2,2,6,6-tetramethyl-4-aminopiperidin-1-oxyl and 1.36 g of diethylcarbamyl chloride in a yield of 83.5% (2.25 g). Amide (II) forms orange needles having mp 153-154°C (from heptane). Found: C 61.98; H 10.37; N 15.43%. $C_{14}H_{28}N_3O_2$. Calculated: C 62.20; H 10.43; N15.53%.

2,2,6,6-Tetramethyl-4-α-bromophenylacetamidopiperidin-1-oxyl (III). To a solution of 3 g of freshly distilled α-bromomandelyl bromide in 35 ml of abs. benzene and 5 ml of triethylamine over 30 min was added dropwise a solution of 1.72 g of 2,2,6,6-tetramethyl-4-aminopiperidin-1-oxyl in 35 ml of benzene. After stirring for 4 h the precipitated triethylamine hydrochloride salt was filtered with suction and the solution was evaporated in vacuum. An oil was obtained from which by thin layer chromatography on Al_2O_3 ($CHCl_3$ as eluent) were isolated yellow crystals having mp 151°C (from heptane); R_f 0.36; yield 0.920 g (25%). Found: C 55.62; H 6.55; N 7.49; Br 21.63%. $C_{17}H_{24}N_2O_2Br$. Calculated: C 55.44; H 6.56; N 7.61; Br 21.70%.

2,2,6,6-Tetramethyl-4-α-chlorophenylacetamidopiperidin-1-oxyl (IV). The compound was obtained analogously to the preceding from 2 g of α-chloromandelyl chloride and 1.71 g of 2,2,6,6-tetramethyl-4-aminopiperidin-1-oxyl in a yield of 1.00 g (31%). Amide (IV) is an orange-colored crystalline material

Institute of Chemical Physics, Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 5, pp. 1191-1193, May, 1969. Original article submitted November 29, 1968.

having mp 143.5-144.3°C (from heptane). Found: C 63.24; H 7.43; N 8.63%. $C_{17}H_{24}N_2O_2Cl$. Calculated: C 63.05; H 7.47; N 8.65%.

2,2,6,6-Tetramethyl-4-capryloxypiperidin-1-oxyl (V). To a solution containing 3.44 g of 2,2,6,6-tetramethyl-4-oxypiperidin-1-oxyl in 40 ml of abs. benzene and 10 ml of triethylamine was added dropwise over 40 min a solution of 4.00 g of capryl chloride in 40 ml of abs. benzene. After stirring for 5 h the triethylamine hydrochloride precipitate was filtered and the solution was evaporated at reduced pressure. The obtained liquid material was chromatographed on a column of Al_2O_3 ($CHCl_3$ as eluent), eluting the lower red-colored zone. The solvent was evaporated at reduced pressure and the remaining red liquid was distilled, collecting the fraction boiling at 138-139°C (0.1 mm). Yield of radical (V) was 4.02 g (67%). Found: C 68.47; H 10.75; N 4.57%. $C_{17}H_{32}NO_3$. Calculated: C 68.41; H 10.81; N 4.69%.

2,2,6,6-Tetramethyl-4-palmitylamidopiperidin-1-oxyl (VI). To a solution of 1.71 g of 2,2,6,6-tetramethyl-4-aminopiperidin-1-oxyl in 40 ml of abs. benzene and 8 ml of triethylamine was added dropwise over 30 min a solution of 4 g freshly distilled palmityl chloride. After stirring for 2 h and maintaining for one day at room temperature the solution was filtered from the precipitated triethylamine hydrochloride and evaporated under reduced pressure. The obtained solid material was chromatographed on a column of Al_2O_3 ($CHCl_3$ as eluent). The lower red-colored zone was eluted and the solvent was evaporated to give 3.45 g (84.3%) of the amide having mp 59.5° (from acetonitrile). Radical (VI) is very soluble in ether, benzene, chloroform, cyclohexane, acetone, methanol, and hexane. Found: N 6.68%. $C_{25}H_{49}N_2O_2$. Calculated: N 6.84%.

2,2,6,6-Tetramethyl-4-stearoylamidopiperidin-1-oxyl (VII). To a solution of 1.72 g of 2,2,6,6-tetramethyl-4-aminopiperidin-1-oxyl in 40 ml of abs. benzene and 8 ml of triethylamine over 1 h with continuous stirring was added dropwise a solution of 4.5 g of freshly distilled stearoyl chloride in 40 ml of abs. benzene. The mixture was stirred an additional 2 h and left overnight, after which the precipitated triethylamine hydrochloride was filtered and the solution was evaporated under reduced pressure. The residue was chromatographed on a column of Al_2O_3 ($CHCl_3$ as eluent), eluting the lower red-colored zone. Evaporation of the solvent under reduced pressure and subsequent recrystallization from hexane and acetonitrile yielded a rose-colored material having mp 62.0-63.0°C, R_f 0.44. The yield of radical (VII) was 3.23 g (74%). The material is very soluble in CCl_4, benzene, and chloroform; it is insoluble in water. Found: 6.47%. $C_{27}H_{53}N_2O_2$. Calculated: N 6.40%.

2,2,6,6-Tetramethyl-4-stearoyloxypiperidin-1-oxyl (VIII). The compound was obtained in a yield of 4.04 g (92.3%) analogously to (VII) from a solution of 1.72 g of 2,2,6,6-tetramethyl-4-aminopiperidin-1-oxyl in 40 ml of benzene, 8 ml of triethylamine, and 4.5 g of steroyl chloride in 40 ml of benzene. Radical (VIII) is a rose-colored material having mp 42° (from acetonitrile), and is very soluble in hexane, heptane, CCl_4, benzene, chloroform, ether, and cyclohexane; it is insoluble in water. Found: 6.47%. $C_{27}H_{53}N_2O_2$. Calculated: N 6.40%.

2,2,6,6-Tetramethyl-4-p-cetyloxybenzoyloxypiperidin-1-oxyl (IX). To a solution of 3.00 g of 2,2,-6,6-tetramethyl-4-oxypiperidin-1-oxyl in 50 ml of abs. benzene and 10 ml of triethylamine was added with stirring a solution of 5.93 g of p-cetyloxybenzoyl chloride in 50 ml of abs. benzene. After stirring for 6 h the mixture was left overnight and then evaporated at reduced pressure. The solid residue was chromatographed on a column of Al_2O_3 using chloroform as the eluent. Concentration of the eluent yielded 1.73 g (21.4%) of the radical; pale-rose crystals having mp 68-69°C (from heptane). Compound (IX) is very soluble in benzene and CCl_4. Found: C 73.96; H 10.86; N 2.99%. $C_{32}H_{55}NO_4$. Calculated: C 74.23; H 10.70; N 2.71%.

CONCLUSIONS

A series of new individual 2,2,6,6-tetramethyl-1-oxyl-4-piperidyl amides and esters of carboxylic acids was synthesized.

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