STABLE ESTERS AND AMIDES OF 2,2,6,6-TETRAMETHYL-1-OXYL-4-PIPERIDINE WITH CARBOXYLIC ACIDS

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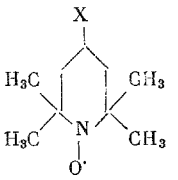
UDC 54-171+547.822.3

A method of synthesis of an independent free radical, extremely stable in air, has been proposed previously by one of us [1-6], which has proved to be of use in the solution of certain specific problems of chemistry [7-9], physics [10], and biology [11-13].

The present communication is devoted to a new series of independent radicals being amides and esters represented by the general formula



X = $NHCOOCH_3$ (I); $OCOCH{=}CH_2$ (II); $OCOC(CH_3){=}CH_2$ (III); $OCOCH{=}CH{-}C_6H_5$ (IV); $NHCOCH{=}CH_2$ (V); $NHCOC(CH_3){=}CH_2$ (VI); $NHCOCH{=}CH{-}C_6H_5$ (VII); $NHCOCH{=}CHCH_3$ (VIII); $OCOC_6H_4C_6H_4COOH$ (IX); $NHCOCH_2CH_2CH_3$ (X); $NHCOCH_2CH_3$ (XI); $NHCON(CH_3)_2$ (XII); $OCOCH_2CH_2CH_3$ (XIII)

The new radicals were smoothly obtained by the selective reaction of 2,2,6,6-tetramethyl-4-hydroxy- and of 2,2,6,6-tetramethyl-4-aminopiperidin-1-oxyls [14, 15] with the corresponding acid chloride in pyridine or triethylamine as medium. The compounds, self-contained radicals, were bright red crystalline substances, stable in air, readily distillable in vacuum without decomposition.

EXPERIMENTAL

2,2,6,6-Tetramethyl-4-carbomethoxyaminopiperidin-1-oxyl (I). To a solution of 3.3 g 2,2,6,6-tetramethyl-4-aminopiperidine-1-oxyl in 40 ml benzene and 15 ml pyridine was added, with stirring, a solution of 1.65 g freshly distilled methyl chloroformate in 20 ml benzene. After stirring for 7 h at room temperature the solution was filtered from the precipitate of pyridine hydrochloride and condensed in vacuum. The substance obtained was chromatographed on a column of Al_2O_3 using a mixture of $CHCl_3$ and ethyl acetate (2 : 1) as eluant. After concentrating the eluate 1.8014 g (45%) (I) was obtained as pink needles (from pentane) of mp 128.5°C. Found %: C 57.63; H 9.27; N 12.58. $C_{11}H_{21}N_2O_3$. Calculated %: C 57.61; H 9.23; N 12.22.

2,2,6,6-Tetramethyl-4-acryloyloxypiperidin-1-oxyl (II). Into a dry two-necked flask fitted with mercury sealed stirrer and dropping funnel with calcium chloride tube, was put a solution of 3.3 g 2,2,6,6-tetramethyl-4-hydroxypiperidin-1-oxyl in 90 ml abs. benzene and 18 ml triethylamine. Acrylic acid chloride (1.58 g) in 30 ml abs. benzene was added with stirring to the solution obtained. After the addition of all the acid chloride the reaction mixture was stirred at room temperature for 4 h, the precipitate of triethylamine hydrochloride which had separated was removed by filtration, the benzene and triethylamine evaporated and the solid residue chromatographed on a column of Al_2O_3 (eluant $CHCl_3$). The lower rose colored zone moved into the eluate from which 2.03 g (51.5%) (II) was isolated after evaporation of the chloroform. The substance was purified by sublimation and subsequent recrystallization from hexane; bright orange neeldes of mp 102.5-103°. Found %: N 6.06. $C_{12}H_{20}NO_3$. Calculated %: N 6.19.

2,2,6,6-Tetramethyl-4-methacryloyloxypiperidin-1-oxyl (III). From 3.3 g 2,2,6,6-tetramethyl-4-hydroxypiperidin-1-oxyl was obtained in a similar manner; 2.44 g (51.5%) paramagnetic methacrylate: pink lustrous plates of mp 88.7° (from hexane), readily soluble in CCl_4, benzene, $CHCl_3$, acetone, methanol,

Institute of Chemical Physics, Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 9, pp. 2106-2109, September, 1968. Original article submitted January 5, 1968.

nitromethane; insoluble in water, readily sublimable in vacuum: R_f 0.52. Found %: C 64.83; H 9.39; N 5.72. $C_{13}H_{22}NO_3$. Calculated %: C 64.97; H 9.23; N 5.83.

The authentic ester was obtained under analogous conditions from 3.3 g 2,2,6,6-tetramethyl-4-hydroxypiperidin-1-oxyl and 2.46 g β-chloroisobutyric acid chloride in a yield of 2.4117 g (49.9%); R_f 0.52.

2,2,6,6-Tetramethyl-4-cinnamoyloxypiperidin-1-oxyl (IV). Obtained similarly from 3.3 g 2,2,6,6-tetramethyl-4-hydroxypiperidin-1-oxyl and 2.9 g cinnamic acid chloride in a yield of 1.1246 g (29.6%); bright orange lustrous needles of mp 101° (from hexane). Found %: C 71.95; H 8.08; N 4.46. $C_{18}H_{24}NO_3$. Calculated %: C 71.50; H 8.00; N 4.63.

2,2,6,6-Tetramethyl-4-acrylamidopiperidin-1-oxyl (V). To a solution of 2.2 g 2,2,6,6-tetramethyl-4-aminopiperidin-1-oxyl in 70 ml abs. benzene and 12 ml triethylamine was added over ½ h with stirring a solution of 1.06 g acrylic acid chloride in 20 ml abs. benzene. After 4 h stirring at room temperature, the benzene solution was filtered from the precipitate of triethylamine hydrochloride which had separated, the benzene and excess triethylamine were evaporated off and the residual red crystalline substance chromatographed on Al_2O_3 using a mixture of $CHCl_3$ and ethyl acetate (2 : 1) as eluant. After evaporating the eluate 1.498 g (56.8%) amide was obtained; dark red needles of mp 148-149° (from benzene). Found %: C 63.85; H 9.41; N 12.48. $C_{12}H_{21}N_2O_2$. Calculated %: C 63.96; H 9.40; N 12.48.

2,2,6,6-Tetramethyl-4-methacrylamidopiperidin-1-oxyl (VI). Obtained similarly from 0.55 g 2,2,6,6-tetramethyl-4-aminopiperidin-1-oxyl in 10 ml abs. benzene and 3 ml triethylamine, and 0.306 g methacrylic acid chloride in 5 ml benzene. After chromatography on Al_2O_3 (eluant—$CHCl_3$) and recrystallization from heptane 0.4323 g (61.2%) amide was obtained; yellow glistening plates of mp 149-150°. Found %: N 11.91. $C_{13}H_{23}N_2O_2$. Calculated %: N 11.70.

2,2,6,6-Tetramethyl-4-cinnamoylamidopiperidin-1-oxyl (VII). Obtained similarly from 2.2 g 2,2,6,6-tetramethyl-4-aminopiperidin-1-oxyl in 60 ml abs. benzene, 12 ml triethylamine and 1.94 g cinnamoyl chloride in 20 ml benzene. After chromatography on Al_2O_3 (eluant – a mixture of $CHCl_3$ and ethyl acetate, 2 : 1) 2.2085 g (62.8%) amide was obtained; fine pink needles of mp 178-178.5° (from benzene), insoluble in hexane and heptane. Found %: C 72.03; H 8.30; N 9.56%. $C_{18}H_{25}N_2O_2$. Calculated %: C 71.73; H 8.36; N 9.30.

2,2,6,6-Tetramethyl-4-crotonylamidopiperidin-1-oxyl (VIII). Obtained similarly from 2.2 g 2,2,6,6-tetramethyl-4-aminopiperidin-1-oxyl in 60 ml abs. benzene, 12 ml triethylamine and 1.22 g crotonic acid chloride in 20 ml benzene. After chromatography on Al_2O_3 (eluant – a mixture of $CHCl_3$ with ethyl acetate, 2 : 1) 1.48 g (53.3%) amide was obtained; pink needles of mp 155-156° (from benzene); R_f 0.69. Found %: C 65.44; H 9.90; N 11.74. $C_{13}H_{23}N_2O_2$. Calculated %: C 65.25; H 9.69; N 11.71.

2,2,6,6-Tetramethyl-1-oxyl-4-piperidyl Diphenoic Acid Ester (IX). To a solution of 1.08 g 2,2,6,6-tetramethyl-4-hydroxypiperidin-1-oxyl in 6.5 ml abs. pyridine was added 1.56 g diphenoic acid chloride and the mixture heated for 3 h 15 min with a reflux condenser fitted with a calcium chloride tube. After cooling, the mixture was poured onto 100 g crushed ice and the solution acidified with dilute HCl to pH 4. The precipitated yellow resiny substance was extracted with $CHCl_3$. The chloroform extract was shaken with a dilute solution of sodium carbonate which was subsequently acidified with conc. HCl. The solid which separated was once again extracted into $CHCl_3$, the chloroform solution was washed with water and dried with Na_2SO_4. The major portion of $CHCl_3$ was evaporated under reduced pressure and the residue poured onto a large watch glass. After evaporation of $CHCl_3$, a substance was obtained which was recrystallized successively from mixtures of cyclohexane, benzene, and acetone with hexane. Yield 0.81 g (29.3%) of orange prisms of mp 159-160°. Found %: C 70.01; H 6.58; N 3.55. $C_{23}H_{26}NO_5$. Calculated %: C 69.69; H 6.61; N 3.53.

2,2,6,6-Tetramethyl-4-butyramidopiperidin-1-oxyl (X). To a two-necked round-bottomed flask, containing 2 g amino radical in 30 ml abs. benzene and 5 ml triethylamine was added dropwise with stirring a solution of 1 g n-butyric acid chloride in 20 ml abs. benzene. After stirring for 5 h at room temperature the precipitate of triethylamine hydrochloride which had separated was filtered off, washed several times with small quantities of benzene and the solution obtained evaporated under vacuum. A bright red resin remained in the flask which, after standing for 2 days was converted into bright red crystals. On chromatography on a column packed with Al_2O_3 (eluant – $CHCl_3$), the lower red zone was removed and the solvent evaporated under reduced pressure. An oil remained which solidified on cooling. A pink colored substance (1.9487 g: 80.8%) was obtained having mp 84° (from hexane). The substance was very soluble at room temperature in CCl_4, acetonitrile, nitromethane, acetone, $CHCl_3$, benzene, ethyl alcohol, and methanol. Found %: C 64.30; H 10.17; N 11.85. $C_{13}H_{25}N_2O_2$. Calculated %: C 64.67; H 10.44; N 11.61.

2,2,6,6-Tetramethyl-4-propionamidopiperidin-1-oxyl (XI). Obtained similarly by the method described for the butyramide with a yield of 0.7965 g (70.61%) from 1 g amino radical in 25 ml benzene and 5 ml triethylamine, and 0.46 g propionyl chloride in 25 ml abs. benzene. Light pink needles of mp 101.5° (from heptane). Found %: C 63.11; H 10.06; N 12.43. $C_{12}H_{23}N_2O_2$. Calculated %: C 63.40; H 10.20; N 12.33.

N,N-Dimethyl-N'-(2,2,6,6-tetramethyl-1-oxyl-4-piperidyl)urea (XII). Obtained according to the method described above from 2 g amino radical in 30 ml abs. benzene with 5 ml triethylamine, and 1.07 g dimethylcarbamoyl chloride in 30 ml benzene in a yield of 1.7564 g (72.6%). Amide (XII) formed red crystals of mp 173° (from benzene); it was insoluble in hexane and heptane but easily soluble in acetonitrile, methanol, acetone, nitromethane, and water. Found %: C 59.26; H 9.68; N 16.98. $C_{12}H_{24}N_3O_2$. Calculated %: C 59.48; H 9.98; N 17.34.

2,2,6,6-Tetramethyl-4-butyryloxypiperidin-1-oxyl (XIII). To a solution of 17.2 g 2,2,6,6-tetramethyl-4-hydroxypiperidin-1-oxyl in 150 ml abs. benzene and 25 ml triethylamine, was added a solution of 13 g n-butyryl chloride in 150 ml benzene. After stirring for 5 h the precipitate of triethylamine hydrochloride, which had separated, was filtered off, the solvent evaporated under reduced pressure and the liquid obtainedchromatographed on a column packed with Al_2O_3. The lower red zone was eluted, the solvent evaporated in vacuum and the liquid remaining twice distilled in vacuum at 95-97° (0.1 mm). The ester (16.0624 g: 66.5%) was obtained as a liquid which, after standing for a month, crystallized in fine bright red needles of mp 28°. Found %: C 65.06; H 9.89; N 5.72. $C_{13}H_{24}NO_3$. Calculated %: C 64.43; H 9.98; N 5.78.

CONCLUSIONS

A series of separate 2,2,6,6-tetramethyl-1-oxyl-4-piperidyl amides and esters of carboxylic acids has been synthesized.

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