SYNTHESIS OF 1-METHYL-2-HYDROXYIMINOMETHYL-ARYL-PYRIDINIUM SALTS WITH POTENTIAL AS ACETYL-CHOLINESTERASE REACTIVATORS

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Abstract : A series of 1-methyl-2-hydroxyiminomethyl-aryl-pyridinium salts has been prepared, as new potential antidotes of poisoning by organo-phosphorus compounds. Several synthetic sequences were tested and all but one, with an internal branch, rejected because they were judged inconvenient and/or because of low yields. 2-Picoline was oxidized to picolinic acid and this converted to 2-(4-X-benzoyl)pyridines either via decarboxylation followed by nucleophilic addition to selected aromatic aldehydes and oxidation of the secondary alcohols thus obtained or by conversion to picolinoyl chloride followed by Friedel-Crafts reactions with selected mono-substituted arenes. The 2-arylpyridines were then converted to the corresponding oximes (E and Z forms in some cases), followed by methylation of pyridine nitrogen.

Introduction

Organo-phosphorus insecticides are widely used. They, with nerve gases, are highly toxic anticholinesterase agents (inhibitors of acetyl-cholinesterase), acting primarily through the nervous system. It is clearly important that acetyl-cholinesterase reactivators should be available as antidotes of poisoning by such compounds. One of the most widely used is Pralidoxime (2-PAM) or 1-methyl-2-hydroxyiminomethyl-pyridinium chloride (1). The key action of these acetyl-cholinesterase reactivators is believed to stem from the nucleophilic attack by their hydroxy-imino oxygen on phosphorus in the inhibited enzyme eliminating the inhibitor in a complex with the reactivator, liberating the enzyme and exposing its esterase site. Despite its efficacy, 2-PAM being highly polar and water-soluble is rapidly eliminated from the organism. Thus its action is essentially restricted to the peripheral nervous system.

Other compounds are used and many of these are also 1-methyl-2-hydroxyiminomethyl-pyridinium salts. Some are more active but have undesirable characteristics such as pain on application, instability in aqueous media and higher incidence of adverse effects (2,3).

We were thus led to initiate a study of related compounds which might offer pharmacological and toxicological advantage over 2-PAM and other compounds used in treatment of organo-phosphorus poisoning.

Our aim has been to develop convenient syntheses of a group of 1-methyl-2-hydroxyiminomethyl-pyridinium salts of greater lipophilicity than 2-PAM, maintaining the essential molecular geometry, together with the nucleophilicity of the hydroxyimino oxygen. For this purpose we selected a group of 1-methyl-2-hydroxyiminomethyl-aryl-pyridinium iodides, some of which we obtained in both Z and E forms. Their skeletal structure is :

The efficacy of these compounds as acetyl-cholinesterase reactivators is the subject of a parallel study.

Results and Discussion

Various synthetic sequences were tested and all but one rejected because of low yields and/or because they were judged to be substantially less convenient.

The reaction sequence chosen, which has an internal branch, is outlined in Scheme 1.

Scheme 1 : Reaction sequence for synthesis of 1-methyl-2-hydroxyiminomethyl-aryl- pyridinium salts

The sequence, incorporating route A was used to obtain the product with $X = \text{Cl}$, F , NO_2 , OCH_3 ; while the sequence, incorporating route B was used to obtain the products with $X = \text{H}$, CH_3 .

The initial step, oxidation of 2-picoline to picolinic acid was carried out according to the literature (4), but with a modification to improve the isolation of the acid, which is highly soluble in water. We isolated it conveniently by continuous extraction with benzene in a Soxhlet apparatus.

Route A :

This route was preferred for $X = \text{Cl}$, F , NO_2 , OCH_3 , despite relatively low yields of only *ca* 40 % because it is so easily and rapidly carried out, without a catalyst, giving pure products.

It involves simply heating picolinic acid with the appropriate aromatic aldehyde in refluxing mesitylene (b.p. 165°C) (5). The reaction is considered to occur via decarboxylation, furnishing an anionic centre at the 2-position. This, acting as a nucleophile, adds to the carbonyl carbon atom (as shown) :

The oxidation of the carbinol to the desired ketone was carried out conveniently and in good yield using chromic acid in acetone (6,7). This step was unnecessary in the case of $X = \text{NO}_2$ because the carbinol function was oxidized *in situ* by the NO_2 group of the reagent. The yield was less (28 %) as expected, but as a one-pot sequence was quite acceptable.

Route B

This route was preferred for $X = \text{H}$, CH_3 . The indications of Villani *et al.* (8) were followed, though we studied various minor modifications for the preparation of picolinoyl chloride which then was reacted with benzene or toluene in a Friedel-Crafts reaction. The best yields (53 % for 2-benzoyl-pyridine and 68 % for p-toluoyl-pyridine) were obtained when most of the excess thionyl chloride, used in the first step, was removed by fractional distillation and the rest removed by azeotropic distillation with benzene and then with toluene.

There were also difficulties in extracting the ketones at the end of the reactions. The best method was by extraction with warm chloroform.

The ketones, obtained by route A or B, were converted into oximes following the indication of Huntress and Walter (9) or of Case and McMenamin (10), depending on the yields obtained in each method.

The stereo-isomer Z of the oximes has the OH group directed towards the benzene ring so that the pyridine nitrogen is free to co-ordinate to metals. It is also able to interact with the hydrogen of chloroform.

The stereo-isomer E of the oximes has the OH group directed towards the pyridine ring with hydrogen-bonding to the annular nitrogen.

These points led us to select the following two methods for separation of the E and Z stereo-isomers. The first method takes advantage of the differential solubility in chloroform obtaining the less soluble E stereo-isomer. The filtrate is treated with Cu(II)SO₄ (aqueous acid): the Z stereo-isomer precipitates as a complex. After passage of H₂S (g) and filtration the Z stereo-isomer is recovered by basification and filtration.

The second method involves initial treatment with Cu(II)SO₄ (aqueous acid) precipitating the Z stereo-isomer as a complex. Following passage of H₂S (g) and filtration the A stereo-isomer is recovered from the complex. The E isomer was obtained by neutralization of the initial filtrate. The final stage of quaternization of the pyridine nitrogen was carried out conventionally using methyl iodide at ambient temperature (11,12).

Experimental Section

2-Benzoyl-pyridine 1 : 0.5 Mole of previously dried picolinic acid was placed in a three-necked flask, fitted with a reflux condenser, a mechanical stirrer and a dropping funnel. Excess (0.5 mole) of thionyl chloride, recently distilled from quinoline and linseed oil, was added slowly with stirring and the mixture then refluxed for 90 minutes. The bath temperature was raised and most of the excess thionyl chloride distilled off. The last traces were removed by azeotropic distillation with benzene. Anhydrous benzene (0.247 mole) was added to the reaction mixture. It was cooled in an ice-bath and 0.185 mole of anhydrous aluminium chloride was added in small portions over 30 minutes. It was refluxed for 6 hours with vigorous stirring. After cooling it was added to a mixture of ice and conc. hydrochloric acid, With stirring. The warm chloroform extract was washed with water and dried over anhydrous sodium sulfate. After removal of solvent the product was vacuum-distilled at 130-135 °C and 3 torr. 2- Benzoyl-pyridine was obtained in 53 % yield; lit. (8) 87 % yield; b.p. 130-133 °C, 1-2 torr; NMR (CDCl₃) : δ = 8.5-8.8 (d, 1 H), 7.7-8.3 (m, 3H), 7.3-7.7 (m, 5H). lit. (13) : 8.5-8.7 (d, 1H), 7.6 - 8.2 (m, 3H), 7.2-7.6 (m, 5H), IR (NaCl film) : $\nu_{\max}$ (cm⁻¹) = 3150-3050 (Ar-H and Py-H); 1660 (C=O); lit. (14): 3200-3000 (Ar-H and Py-H), 1660 (C=O).

2-p-Toluoyl-pyridine 2 : This was obtained analogously to preparation 1. Azeotropic distillation with toluene was used to remove the last traces of thionyl chloride before 0.247 mole of toluene was added to the reaction mixture. It was then heated at 75 °C for 4.30 hrs. Following solvent removal in the final stages, the product was distilled between 120-140 °C at 4 torr. 2-p-Toluoyl-pyridine was obtained in 68 % yield; NMR (CDCl₃) : δ = 8.5-8.8 (d, 1H), 7.6-8.2 (m, 3H), 7.0-7.6 (m, 4H), 2.3 (s, 3H); IR (NaCl film) : $\nu_{\max}$ (cm⁻¹) = 3100-3000 (Ar-H and Py-H), 2950 (CH₃), 1660 (C=O).

p-Methoxyphenyl-2-pyridinyl-methanol 3 : 0.0285 Mole of dried picolinic acid, 0.176 mole of p-anisaldehyde and 24.9 ml of mesitylene were placed in a two-necked flask fitted with a reflux condenser and a gas exit tube. The mixture was refluxed until the evolution of CO₂ ceased. After cooling, the reaction mixture was extracted with 3N HCl and this was neutralized with aq. NaOH. The precipitate thus obtained was filtered off, washed with water and dried at ambient temperature. p-Methoxyphenyl-2-pyridinyl-methanol was obtained in 38 % yield; m.p. 133-133 °C; NMR (CDCl₃) : δ = 8.5 -8.9 (d, 1H), 6.7-8.0

(m, 7H), 5.7 (s, 1H-carbinol), 3.8 (s, 3H); IR (KBr pellet) : $\nu_{\max}$ (cm^{-1}) = 3400-3000 (combined O-H; Ar-H; Py-H), 2850 (C-H, O-CH₃ and carbinol), 1250 (Ar-OR), 1025 (C-O).

2-p-Nitrobenzoyl-pyridine 4 : The procedure used in preparation 3 was followed. However, in this case, the carbinol formed was oxidized *in situ* by the nitro-group.

The quantities used were 0.0285 mole of picolinic acid, 0.114 mole of p-nitro-benzaldehyde and 24.0 ml of mesitylene. 2-p-Nitrobenzoyl-pyridine was obtained in 28 % yield. It had m.p. 95- 98 °C; NMR (DMSO-d₆) : δ = 8.6 - 8.9 (d, 1H), 8.3 (s, 4H), 7.4-8.3 (m, 3H); IR (KBr pellet) : $\nu_{\max}$ (cm^{-1}) = 3080-3020 (Ar-H and Py-H), 1670 (C=O), 1510 and 1350 (C-NO₂).

P-Fluorophenyl-2-pyridinyl-methanol 5 : The procedure used in preparation 3 was generally followed, using 0.0285 mole of picolinic acid, 0.114 mole of p-fluorobenzaldehyde and 15.0 ml of mesitylene. The viscous oil obtained was extracted with chloroform and dried over anhydrous sodium sulfate. A precipitate formed spontaneously and after filtration was recrystallized from ethanol. p-Fluorophenyl-2-pyridinyl-methanol was thus obtained in 40 % yield; m.p. 99-102 °C; NMR (CDCl₃) : δ = 8.3-8.6 (d, 1H); 6.7-8.2 (m, 7H); 5.6-6.0 (dd, 2H-carbinol); IR (KBr pellet): $\nu_{\max}$ (cm^{-1}) = 3300-3000 (O-H), 2920-2850 (C-H, carbinol), 1210 (C-F).

P-Chlorophenyl-2-pyridinyl-methanol 6 : This was obtained analogously to preparation 3, using 0.285 mole of picolinic acid, 0.142 mole of p-chlorobenzaldehyde and 15.0 ml of mesitylene. p-Chlorophenyl-2-pyridinyl-methanol was thus obtained in 35 % yield; m.p. 81-83 °C; NMR (CDCl₃) : δ = 8.3-8.5 (d, 1H), 6.9-7.9 (m, 7H), 5.7 (s, 1H carbinol); IR (KBr pellet): $\nu_{\max}$ (cm^{-1}) = 3300-3000 (combined O-H; Ar-H; Py-H), 2900-2800 (C-H-carbinol), 1050 (C-Cl).

2-p-Methoxybenzoyl-pyridine 7 : p-Methoxyphenyl-2-pyridinyl-methanol (0.0218 mole) was placed in a two-necked flask fitted with a mechanical stirrer and dropping-funnel, immersed in an ice-salt freezing-mixture. A mixture of 2.0 g of chromium trioxide, 2.0 ml of conc. H₂SO₄ and 9.0 ml of water was added slowly through the funnel, while stirring vigorously. The cooling-bath was removed and stirring continued for 3 hours at ambient temperature. The reaction mixture was then poured into a mixture of ice and water forming a yellow precipitate. This was filtered off and washed with cold water. 2-p-Methoxy-benzoyl-pyridine was thus obtained in 70 % yield; m.p. 95-96 °C; NMR (CDCl₃) : δ = 8.6-8.8 (d, 1H), 6.8-8.3 (m, 7H), 3.9 (s, 3H); IR (KBr pellet) : $\nu_{\max}$ (cm^{-1}) = 3080-3000 (Ar-H and Py-H), 2950-2850 (C-H, OCH₃), 1645 (CO), 1250 (Ar-OR).

2-p-Fluorobenzoyl-pyridine 8 : The procedure of preparation 7 was followed, using the corresponding aryl-pyridyl-methanol and in the same molar proportions. 2-p-Fluorobenzoyl-pyridine was thus obtained in 41 % yield; m.p. 83-84 °C; NMR (CDCl₃): δ = 8.5-8.8 (d, 1H) 7.6-8.5 (m, 4H) 6.8-7.5 (m, 3H); IR (KBr pellet) : $\nu_{\max}$ (cm^{-1}) = 3060 (Ar-H and Py-H), 1655 (C=O), 1220 (C-F).

2-p-Chlorobenzoyl-pyridine 9 : The procedure of preparation 7 was followed, using the corresponding aryl-pyridinyl-methanol and in the same molar proportions.

2-p-Chlorobenzoyl-pyridine was thus obtained in 86 % yield; m.p. 64-65 °C; NMR (CDCl₃): δ =8.4-8.8 (d, 1H), 7.6-8.3 (m, 4H), 7.2-7.5 (m, 3H); IR (KBr pellet) : $\nu_{\max}$ (cm⁻¹)=3080 (Ar-H and Py-H), 1655 (C=O), 1080 (C-Cl).

2-Hydroxyiminomethyl-phenyl-pyridine 10 : The method of Huntress and Walter (9) was followed. 2-Benzoyl-pyridine (0.01 mole) in 3.0 ml of ethanol was placed in a round-bottomed flask, fitted with a condenser. Hydroxylamine hydrochloride (0.026 mole) dissolved in 4.0 ml of water was added with magnetic stirring. Then 0.045 mole of sodium hydroxide in 4.0 ml of water was added and the mixture heated until it began to boil. After cooling, the mixture was acidified with glacial acetic acid then allowed to stand. The rose-coloured precipitate which formed was filtered off and washed with water.

The Z- and E-stereoisomeric mixture was refluxed with dry chloroform for 15 minutes. The less soluble E-stereoisomer precipitated and was filtered off and recrystallized from ethanol. The chloroformic and ethanolic filtrates were united and evaporated to dryness. The residue was dissolved in 15.0 ml of 3N aq. HCl and treated with 0.4 g of copper sulfate dissolved in water. After standing for several hours the green precipitate was filtered off and washed with water. Hydrogen sulfide was bubbled through the filtrate and copper sulfide filtered off. The filtrate was treated with aq. NH₃ until it reached pH 6. A white precipitate formed, was filtered off and recrystallized from ethanol. The E-stereoisomer, obtained in 43 % yield; m.p. 152-155.5 °C. lit. (9) : yield = 51 % m.p. 150-152.5 °C; NMR (DMSO-d₆): δ =11.5 (1H, OH); 8.4-8.6 (d, 1H), 7.4 (s, 5H), 7.0-8.0 (m, 3H); IR (KBr pellet) : $\nu_{\max}$ (cm⁻¹) = 3400-2600 (combined O-H, Ar-H, Py-H), 1550 (C=N). Z-isomer : yield=12.6 %; m.p. 166-166.5 °C. lit. (9) : yield 11 %; m.p. 165-167 °C. The NMR and IR spectra were similar to those of the E-isomer.

2-Hydroxyiminomethyl-(p-methylphenyl)-pyridine 11 : This was prepared analogously to preparation 10, substituting 2-p-toluoyle-pyridine. The E-isomer was obtained in 23 % yield; m.p. 168-170 °C; NMR (DMSO-d₆) : δ =8.5-8.8 (d, 1H), 7.0-8.2 (m, 7H), 2.3 (s, 3H); IR (KBr pellet) : $\nu_{\max}$ (cm⁻¹)=3400-2700 (combined O-H, Ar-H, Py-H), 1585 (C=N). The Z-isomer was obtained in 13 % yield; m.p. 182-185 °C. The NMR and IR spectra were similar to those of E-isomer.

2-Hydroxyiminomethyl-p-methoxyphenyl-pyridine 12 : This was prepared analogously to preparation 10, substituting 2-p-methoxybenzoyl-pyridine. However, no precipitate was obtained on cooling the chloroform solution. It was concentrated and the solid then obtained dissolved in 3N aq. HCl Using copper sulfate as previously described, a green precipitate was obtained, which was then converted to copper sulfide, the filtrate being treated with aq. NH₃ until pH 6 was reached. The Z-isomer was thus obtained in 85 % yield; m.p. 169-170 °C; NMR (CDCl₃) : δ =8.6-8.8 (d, 1 H), 6.7-8.4 (m, 7H), 3.8 (s, 3H); IR (KBr pellet) : $\nu_{\max}$ (cm⁻¹) =3300-2500 (combined O-H, Ar-H, Py-H); 2900- 2800 (C-H, OCH₃), 1600 (C=N), 1250 (Ar-OR).

2-Hydroxyiminomethyl-p-nitrophenyl-pyridine 13 : This was prepared analogously to preparation 10. As in preparation 12 only the Z-isomer was obtained, though in only 8 % yield; m.p. 252-255 °C; NMR (DMSO-d₆): δ =12.1 (s, 1H, OH), 8.5-8.8 (d, 1H), 8.4-7.2 (m, 7H); IR (KBr pellet) : $\nu_{\max}$ (cm⁻¹)=3300-2500 (combined O-H, Ar-H, Py-H), 1590 (C=N), 1500, 1340 (C-NO₂).

2-Hydroxyiminomethyl-p-fluorophenyl-pyridine 14 : This was prepared analogously to preparation **10**, both Z- and E-isomers being obtained. The E-isomer was obtained in 24 % yield; m.p. 167-169 °C; NMR (DMSO- d_6) : δ = 11.9 (s, 1 H, O-H), 8.4-8.7 (d, 1 H), 7.1-8.2 (m, 7H); IR (KBr pellet) : $\nu_{\max}$ (cm^{-1}) = 3450-2700 (combined O-H, Ar-H, Py-H), 1600 (C=N), 1220 (C-F). The Z-isomer was obtained in only 6 % yield; m.p. 194-197 °C. The NMR and IR spectra were similar to those of E-isomer.

2-Hydroxyiminomethyl-p-chlorophenyl-pyridine 15 : This was prepared analogously to preparation **10**, with some modification in the separation of E-and Z-isomers.

The crude product was dissolved in 3N aq. HCl and copper (II) sulfate solution added. The green precipitate was resuspended in 3N aq. HCl and saturated with H_2S (g). Copper sulfide was filtered off and aq. NH_3 added until pH 6 was obtained. The Z-isomer was thus attained in 25 % yield; m.p. 170-175 °C; NMR (DMSO- d_6) : δ = 11.6 (s, 1H, O-H), 8.4-8.6 (d, 1H), 7.3 (s, 4H), 7.0-8.3 (m, 3H); IR (KBr pellet) : $\nu_{\max}$ (cm^{-1}) = 3450-2500 (combined O-H, Ar-H, Py-H), 1600 (C=N), 1090 (C-Cl).

The filtrate of the precipitation of the Z-isomer was saturated with H_2S (g). Copper sulfide was filtered off and aq. NH_3 added until pH 6 was obtained. The E-isomer was thus attained in only 8 % yield; m.p. 201-202 °C. The NMR and IR spectra were similar to those of Z-isomer.

1-Methyl-2-hydroxyiminomethyl-phenyl-pyridinium iodide 16 (E-and Z-isomers) : 0.001 mole (0.198 g) of E- or Z-2-hydroxyiminomethyl-phenyl-pyridine was dissolved in 2.5 ml of warm acetone. 0.5 ml of methyl iodide was added, while stirring manually. The mixture was then cooled and allowed to stand in the dark for 3 days. The pyridinium salt precipitated on addition of dry ether. The E-isomer was obtained in 87 % yield; m.p. 206-208 °C; NMR (DMSO- d_6) : δ = 13.1 (s, O-H), 9.2-9.4 (d, 1H), 8.6-9.1 (t, 1H), 8.0-8.5 (dd, 2H), 7.3-7.9 (m, 5H), 4.2 (s, 3H); IR (KBr pellet) : $\nu_{\max}$ (cm^{-1}) = 3400-2700 (combined O-H, Ar-H, Py-H), 2980 (C-H : $\text{Py}^+\text{-CH}_3$), 1600 (C=N). The Z-isomer was obtained in 74 % yield; m.p. 183-188 °C. The NMR and IR spectra were similar to those of E-isomer.

1-Methyl-2-hydroxyiminomethyl-p-tolyl-pyridinium iodide 17 (E-and Z-isomers): These were prepared analogously to preparation **16**. The E-isomer was obtained in 64 % yield; m.p. 181-185 °C; NMR (DMSO- d_6) : δ = 13.0 (s, OH), 9.1-9.4 (d, 1H), 8.5-8.9 (t, 1H), 7.9-8.4 (t, 2H), 7.1-7.7 (dd, 4H), 4.1 (s, 3H), 2.3 (s, 3H); IR (KBr pellet) : $\nu_{\max}$ (cm^{-1}) = 3500-2500 (combined O-H, Ar-H, Py-H), 2980 (C-H: $\text{Py}^+\text{-CH}_3$), 2850 C-H (Ar- CH_3), 1600 (C=N). The Z isomer was obtained in 27 % yield; m.p. 110-120 °C. The NMR and IR spectra were similar to those of E-isomer.

1-Methyl-2-hydroxyiminomethyl-p-anisyl-pyridinium iodide 18 (Z-isomer): This was prepared analogously to preparation **16**. The Z-isomer was obtained in 60 % yield; m.p. 176-180 °C; NMR (DMSO- d_6) : δ = 12.9 (s, O-H); 9.0-9.3 (d, 1H); 8.5-8.9 (t, 1 H); 8.0-8.5 (t, 2 H); 7.5-7.8 (d, 2H); 6.8-7.2 (d, 2H); 4.2 (s, 3H); 3.8 (s, 3H); IR (KBr pellet): $\nu_{\max}$ (cm^{-1}) = 3500-2600 (combined O-H, Ar-H, Py-H); 2980 (C-H: $\text{Py}^+\text{-CH}_3$); 2840 C-H (Ar- OCH_3); 1600 (C=N); 1260 (Ar-OR).

1-Methyl-2-hydroxyiminomethyl-p-fluorophenyl-pyridinium iodide 19 (E- and Z-isomers): These were prepared analogously to preparation 16. The E-isomer was obtained in 24 % yield; m.p. 180-182 °C; NMR (DMSO-d₆) : δ = 9.0-9.3 (d, 1 H), 7.0-8.9 (m, 7H), 4.2 (s, 3H); IR (KBr pellet) : $\nu_{\max}$ (cm⁻¹) = 3500-2600 (combined O-H, Ar-H, Py-H), 3000 (C-H : Py⁺-CH₃), 1600 (C=N), 1230 (C-F). The Z-isomer was obtained in quantitative yield; m.p. 114-120 °C. The NMR and IR spectra were similar to those of E-isomer.

1-Methyl-2-hydroxyiminomethyl-p-chlorophenyl-pyridinium iodide 20 (E- and Z-isomers) : These were prepared analogously to preparation 16. The E-isomer was obtained in 62 % yield; m.p. 212-218 °C; NMR (DMSO-d₆) : δ = 13.2 (s, O-H), 9.1-9.3 (d, 1H), 8.5-8.9 (t, 1H), 8.0-8.4 (dd, 2H), 7.4-7.8 (dd, 4H), 4.2 (s, 3H); IR (KBr pellet): $\nu_{\max}$ (cm⁻¹) = 3300-2800 (combined O-H, Ar-H, Py-H), 3000 (C-H : Py⁺-CH₃), 1620 (C=N); 1170 (C-Cl). The Z-isomer was obtained in 48 % yield; m.p. 196-198 °C. The NMR and IR spectra were similar to those of E-isomer.

1-Methyl-2-hydroxyiminomethyl-p-nitrophenyl-pyridinium iodide 21 (Z-isomer) : This prepared analogously to preparation 16. The Z-isomer was obtained in 42 % yield; m.p. 219-220 °C.

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