

Highly Fluorinated Heterocycles. Part XIII.¹ Fluorination of 1-Methylpyrrole and Some Reactions of Derived Compounds

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1-Methylpyrrole has been fluorinated over potassium tetrafluorocobaltate(III) and cobalt(III) fluoride to yield octafluoro-1-methylpyrrolidine (I), octafluoro-1-fluoromethylpyrrolidine (II), 3*H*-heptafluoro-1-methylpyrrolidine (III), 3*H*,4*H*-hexafluoro-1-methylpyrrolidine (IV), 3*H*-heptafluoro-1-fluoromethylpyrrolidine (V), and 3*H*,4*H*-hexafluoro-1-fluoromethylpyrrolidine (VI). The proportions obtained depend on the temperature and the fluorinating agent. Re-fluorination of (I) over CoF₃ yielded perfluoro-1-methylpyrrolidine (VII), 1-difluoro-methyloctafluoropyrrolidine (VIII), and (II). Dehydrofluorination of (III) yielded hexafluoro-1-methyl-Δ³-pyrroline (IX), which reacted with cyclopentadiene to yield an *endo-exo* mixture of 2,6-difluoro-4-methyl-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (X) and in an attempted reaction with perfluorocyclohexa-1,3-diene gave 3,4-difluoro-1-methyl-Δ³-pyrroline-2,5-dione (XI). Reactions of (I) and (IV) with concentrated sulphuric acid gave the corresponding diones by hydrolysis of the α-CF₂ groups. Treatment of (VI) with aluminium chloride in methylene chloride gave 1-chloromethyl-3*H*,4*H*-hexafluoropyrrolidine and reaction of (II) with sodium ethoxide gave 1-ethoxymethyloctafluoropyrrolidine.

PREVIOUS papers in this series have reported the successful fluorinations of oxygen² and sulphur³ heterocycles over transition metal fluorides. These heterocycles were studied first because earlier results with nitrogen heterocycles were not very encouraging. Pyridine with cobalt(III) fluoride was reported to give a low yield of perfluoropyridine;⁴ recent repetition of this work using modern techniques indicates⁵ more products in better yields than found previously. 2-Fluoropyridine and elemental fluorine⁶ gave *inter alia* perfluoropyridine, and nitriles with silver(II) fluoride^{7,8} gave polyfluoropyridines and pyrrolidines. Recently Musgrave *et al.* described⁹ fluorinations of polyhalogenopyridines with CoF₃-CaF₂ in which the ring structure was retained. However, we have previously¹⁰ discussed the fluorination of pyridine with KCoF₄ which gives mainly acyclic products but also produces a small amount of a fluorinated 1-methylpyrrolidine. This led to a successful study of the fluorination of 1-methylpyrrole, which gives reasonable yields of a range novel polyfluoro-1-methylpyrrolidines.

Fluorination of 1-methylpyrrole over KCoF₄ at 220° yielded a mixture of six compounds of which three were major components. Attempts to separate the mixture by fractional distillation failed, since extensive decomposition occurred even on gentle heating; it was subsequently shown that this was due to the relatively easy hydrolysis of 3*H*,4*H*-hexafluoro-1-methylpyrrolidine (IV). Indeed this compound decomposed at -12° but it was possible to store it at -40°. Because of this instability the mixture was distilled *in vacuo* and then separated by preparative g.l.c. From the residue from the vacuum distillation a crystalline solid was obtained, subsequently identified as the cyclic imide 3,4-difluoro-1-methylpyrrolidine-2,5-dione. The first compound (I)

to be eluted in the g.l.c. was identified by ¹⁹F and ¹H n.m.r. spectroscopy, mass spectrometry, elemental analysis, and its subsequent reactions. The ¹H spectrum showed a singlet at τ 7.11 (NMe) and the ¹⁹F spectrum showed two groups of peaks in the ratio 1 : 1 at 96.6 and 132.5 p.p.m. (α- and β-CF₂); these values correspond well with the values¹¹ for perfluoro-1-methylpyrrolidine. The mass spectrum of this and our other compounds showed interesting features, particularly the cleavage of the 2,3- and 4,5-bonds to give the olefin derived from C-3 and -4 and the fragment corresponding to the remainder of the molecule, *i.e.* CF₂-NR-CF₂ (R = CH₃, CH₂F, CHF₂, or CF₃). These features appear general for all compounds in this series and are a useful diagnostic tool in structural assignment. Thus, (I) gave strong peaks at *m/e* 129 (CF₂-NR-CF₂) and 100 (C₂F₄) and is identified as octafluoro-1-methylpyrrolidine.

The second component (II) showed ¹⁹F n.m.r. peaks at 94.7 (α-CF₂), 133.4 (β-CF₂), and 174.5 p.p.m. (t, CH₂F). The ¹H n.m.r. spectrum showed a CH₂F signal at τ 4.56. The mass spectrum contained strong peaks at *m/e* 246 (M⁺), 147 [CF₂-N(CH₂F)-CF₂], and 100 (C₂F₄). These data, along with elemental analysis, indicated (II) to be octafluoro-1-fluoromethylpyrrolidine.

The third component (III) showed four groups of peaks in its ¹⁹F n.m.r. spectrum in the ratio 2 : 2 : 2 : 1, at 87.9 and 95.5 (α-CF₂), 126 (β-CF₂), and 212.6 p.p.m. (CFH). The ¹H spectrum indicated the presence of CH₃N (τ 7.2) and CHF (τ 4.9) group. The mass spectrum showed peaks at *m/e* 129 [CF₂-N(CH₃)-CF₂] and 82 (C₂HF₃). Thus, (III) is identified as 3*H*-heptafluoro-1-methylpyrrolidine.

The fourth component (IV) gave ¹⁹F and ¹H n.m.r. spectra which indicated a symmetrical molecule. The

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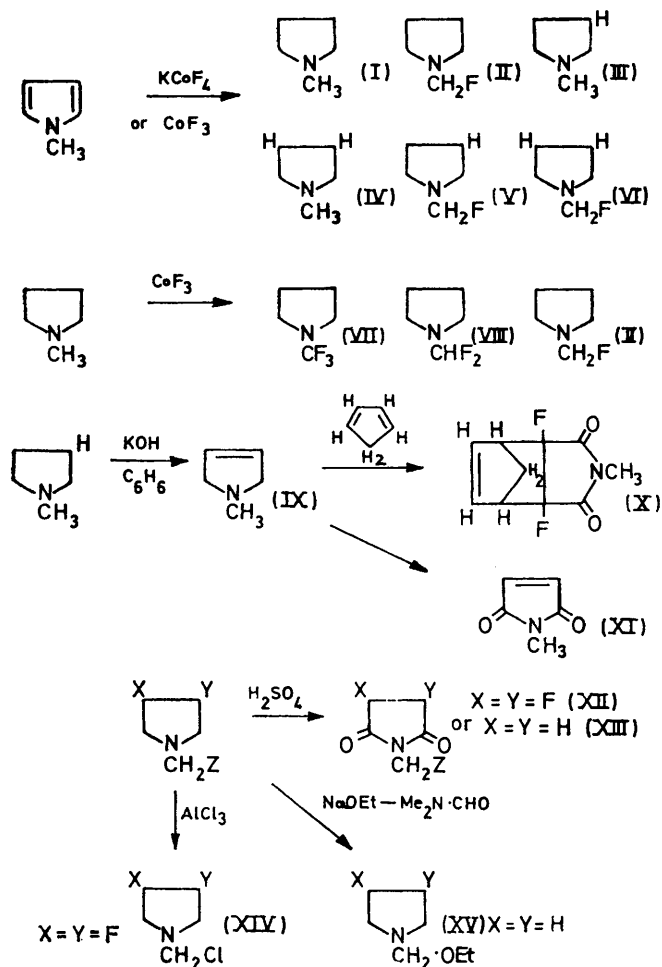
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^{19}F spectrum showed peaks at 89.2 ($\alpha\text{-CF}_2$) and 206.4 p.p.m. (CHF) in the ratio 2 : 1. The ^1H spectrum confirmed the presence of the CHF group (τ 5.09) and indicated an NCH_3 group (τ 7.12). These peaks were



in the integral ratio 2 : 3, suggesting two CHF groups. The mass spectrum gave strong peaks at m/e 129 [$\text{CF}_2\text{-N}(\text{CH}_3)\text{-CF}_2$] and 64 ($\text{C}_2\text{H}_2\text{F}_2$) as well as a molecular ion peak at m/e 193. These data suggest that (IV) is 3*H*,4*H*-hexafluoro-1-methylpyrrolidine.

The fifth product (V) had a complex ^{19}F n.m.r. spectrum with peaks at 90.3 and 93.6 ($\alpha\text{-CF}_2$), 129.2 ($\beta\text{-CF}_2$), 173.9 (CH_2F), and 215 p.p.m. (CHF) in the integral ratio 2 : 2 : 2 : 1 : 1. The peak at 173.9 p.p.m. showed triplet splitting (J_{HF} 58 Hz) and the 215 p.p.m. peak was a complex doublet (J_{HF} 52 Hz). The ^1H spectrum confirmed the ^{19}F data with peaks at τ 4.59 and 4.95 (2 : 1) showing the appropriate coupling patterns. The mass spectrum showed peaks at m/e 147 [$\text{CF}_2\text{-N}(\text{CFH}_2)\text{-CF}_2$] and 82 (C_2HF_3). The data together indicate (V) to be 3*H*-heptafluoro-1-fluoromethylpyrrolidine.

The final compound (VI), a minor product, was shown to be 3*H*,4*H*-hexafluoro-1-fluoromethylpyrrolidine. The

^{19}F n.m.r. spectrum showed three groups of peaks at 85.8, 172.6, and 207.6 p.p.m. (4 : 1 : 2). The band at 85.8 p.p.m. was characteristic of an AB system and was assigned to the $\alpha\text{-CF}_2$ groups. The band at 172.6 p.p.m. was a triplet (J_{HF} 54 Hz) assigned to the CF_2 group and that at 207.6 p.p.m., a complex doublet (J_{HF} 50.5 Hz) was assigned to the CHF groups. The ^1H spectrum confirmed these data. The mass spectrum showed the expected characteristic pattern.

A similar fluorination to that described above but using cobalt(III) fluoride at 140° gave the same products except that (III) was not isolated. The proportions of each component differed and are indicated in the Experimental section. In view of previous fluorinations of nitrogenous compounds this result was pleasing since, in view of the greater oxidising power of CoF_3 than of KCoF_4 , it was expected that extensive decomposition would occur.

The reaction also afforded a valuable method of extending the range of pyrrolidines available for study, since fluorination of (I) over CoF_3 at 140° gave three products in the ratio of 1 : 2 : 4. The mixture was readily separated by g.l.c. to yield first the known¹¹ perfluoro-1-methylpyrrolidine (VII) and secondly, a compound (VIII) which had the expected ^{19}F n.m.r. bands for the octafluoropyrrolidine ring and an additional band at 98.9 p.p.m. which was split into a doublet (J_{HF} 61 Hz) with further small splitting due to interaction with the ring fluorine atoms. The ^1H n.m.r. spectrum showed a single band at τ 3.51 with a triplet splitting confirming the presence of a CHF_2 group attached to nitrogen. The mass spectrum showed peaks at m/e 265 ($\text{C}_5\text{HF}_{10}\text{N}$), 165 [$\text{CF}_2\text{-N}(\text{CF}_2\text{H})\text{-CF}_2$], and 100 (C_2F_4) consistent with (VIII) being 1-difluoro-methyloctafluoropyrrolidine. The third major component was (II), identified by comparison with an authentic sample.

The above fluorinations have made available for study a new range of polyfluoroheterocycles and we have carried out some preliminary experiments to test their reactivity.

Octafluoro-1-methylpyrrolidine (I) was heated at 100° for 48 h with water, 18*N*-potassium hydroxide, or 4*N*-sulphuric acid without reaction, but with concentrated sulphuric acid the CF_2 groups were hydrolysed completely to give tetrafluoro-*N*-methylsuccinimide (XII) in good yield. Similarly 3*H*,4*H*-hexafluoro-1-methylpyrrolidine (IV) gave the corresponding difluorosuccinimide (XIII), identical with the crystals obtained from the original fluorination mixture. Subsequently it was found that leaving compound (IV) at room temperature for a week gave the same result. This suggests that a decrease in the fluorine content at the β -carbon atom increases the ease of hydrolysis of the $\alpha\text{-CF}_2$ group.

Attempts to introduce functional groups were made *via* reactions of these fluoropyrrolidines. Aluminium chloride in dichloromethane, in contrast to previous results with polyfluoro-oxolans,² caused ready replacement of the fluorine atom on the CH_2F group of com-

pound (VI) with no reaction of the CF_2 groups, to give (XIV).

Treatment of (II) with sodium ethoxide in dimethylformamide gave a moderate yield of 1-ethoxymethyl-octafluoropyrrolidine (XV). Attempts to cleave this ether have so far failed, as have reactions of (II) with sodium iodide in acetone or dimethylformamide.

Dehydrofluorination of 3*H*-heptafluoro-1-methylpyrrolidine (III) was investigated, first with aqueous 18N -potassium hydroxide at 100° , when the molecule was completely degraded, and then with a suspension of powdered potassium hydroxide in benzene at 80° , which gave the expected hexafluoro-1-methyl- Δ^3 -pyrroline (IX) in good yield. The ^{19}F n.m.r. spectrum of (IX) showed two groups of peaks only, at 94 and 158.6 p.p.m. in the integral ratio 2:1, attributable to two $\alpha\text{-CF}_2$ groups and two olefinic fluorine atoms. These data indicate the olefin to be the Δ^3 - rather than the Δ^2 -compound.

Reaction of (IX) with cyclopentadiene gave an inseparable 1:1 (by n.m.r.) *endo-exo* mixture of 2,6-difluoro-4-methyl-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (X). The ^{19}F n.m.r. spectrum of (X) showed two peaks in the ratio 1:1 at 181.2 and 182 p.p.m., attributable to bridgehead fluorine atoms. No evidence for a CF_2 group α to the nitrogen atom was found. The ^1H n.m.r. spectrum showed eight signals in the ratio 3:3:2:2:2:2:2:2, assigned to CH_3N , CH_2 , bridgehead CH , and vinylic CH . These data suggested that (X) was a 1:1 *endo-exo* mixture. The i.r. spectrum confirmed the presence of a carbonyl group [ν_{max} , 1715br cm^{-1} ; cf. (XII), 1715br cm^{-1}]. This conversion again reflects the ready hydrolysis of $\alpha\text{-CF}_2$ groups with decreasing β -fluorine content. Although it is not possible to say for certain when the hydrolysis occurs in this reaction, *i.e.* before or after the reaction with the diene, an indication that hydrolysis occurs first is given by the result of an attempt to form an adduct with perfluorocyclohexa-1,3-diene: the only isolable product was difluoro-*N*-methylmaleimide.

EXPERIMENTAL

^{19}F and ^1H N.m.r. spectra were measured either on a Perkin-Elmer R10 or a Varian HA 100 instrument. Separations were carried out either with home-made large-scale g.l.c. equipment or with a Pye 104 or 105 instrument with 9 m columns containing dinonyl phthalate on Chromosorb P (30—60 mesh) (1:4) or SE30 on Chromosorb P (30—60 mesh) (1:10).

Fluorinations.—Fluorinations were carried out as described in previous papers with CoF_3 or KCoF_4 as the fluorinating agent. In a typical run, 1-methylpyrrole (100 g) was fed into the reactor packed with KCoF_4 (6 kg), in a stream of nitrogen (10 l h^{-1}) at a reactor temperature of $220\text{--}240^\circ$ to give a product (130 g) which was washed with iced water and cold dilute aqueous sodium hydrogen carbonate and dried (MgSO_4).

Separation of the Products.—The products (260 g) from two runs were left overnight in a refrigerator and crystals were deposited. These were filtered off and purified by sublimation to yield 3,4-difluoro-1-methylpyrrolidine-2,5-

dione (3.6 g), m.p. $155\text{--}156^\circ$ (Found: C, 40.0; H, 3.2; F, 25.7%; M^+ , 149. $\text{C}_5\text{H}_5\text{F}_2\text{NO}_2$ requires C, 40.3; H, 3.4; F, 25.5%; M , 149) (see below). The residual liquid was distilled at 0.2 mmHg to give a clear distillate (220 g) and a viscous brown residue (36 g) which was discarded. The distillate was separated by a series of runs on preparative g.l.c. (4.8 m \times 75 mm dinonyl phthalate on Chromosorb P (30—60 mesh) (1:5) at 80° ; $75 \text{ l N}_2 \text{ h}^{-1}$) to yield octafluoro-1-methylpyrrolidine (I) (68 g), b.p. 55° (Found: C, 26.5; H, 1.4; F, 66.6%; M^+ , 229. $\text{C}_5\text{H}_5\text{F}_8\text{N}$ requires C, 26.2; H, 1.3; F, 66.4%; M , 229); octafluoro-1-fluoromethylpyrrolidine (II) (16 g), b.p. 75.5° (Found: C, 24.5; H, 1.0; F, 69.4%; M^+ , 247. $\text{C}_5\text{H}_5\text{F}_9\text{N}$ requires C, 24.3; H, 0.8; F, 69.2%; M , 247); 3*H*-heptafluoro-1-methylpyrrolidine (III) (68 g), b.p. 83.5° (Found: C, 28.1; H, 2.1; F, 63.4%; M^+ , 211. $\text{C}_5\text{H}_4\text{F}_7\text{N}$ requires C, 28.4; H, 1.9; F, 63.0%; M , 211); 3*H*,4*H*-hexafluoro-1-methylpyrrolidine (IV) (13 g), b.p. 94° (Found: C, 31.1; H, 2.6; F, 59.4%; M^+ , 193. $\text{C}_5\text{H}_5\text{F}_6\text{N}$ requires C, 31.1; H, 2.6; F, 59.1%; M , 193); 3*H*-heptafluoro-1-fluoromethylpyrrolidine (V) (26 g), b.p. 103° (Found: C, 26.5; H, 1.3; F, 66.8%; M^+ , 229. $\text{C}_5\text{H}_5\text{F}_8\text{N}$ requires C, 26.2; H, 1.3; F, 66.4%; M , 229); and 3*H*,4*H*-hexafluoro-1-fluoromethylpyrrolidine (VI) (8 g), b.p. 118.5° (Found: C, 28.5; H, 2.1; F, 62.6%; M^+ , 211. $\text{C}_5\text{H}_4\text{F}_7\text{N}$ requires C, 28.4; H, 1.9; F, 63.0%; M , 211).

In a similar fluorination but over cobalt(III) fluoride at 140° , 1-methylpyrrole (6 g) gave a product (5.2 g) which was separated to give compounds (I) (1.7 g), (II) (0.3 g), (IV) (1.3 g), (V) (0.7 g), and (VI) (0.2 g). No product corresponding to (III) was obtained.

Fluorination of Octafluoro-1-methylpyrrolidine.—The pyrrolidine (I) (5 g) was fluorinated over cobalt(III) fluoride (200 g) at 140° in a stream of nitrogen (2 l h^{-1}). The product (5 g) was collected in a liquid-air-cooled trap. Analytical g.l.c. showed the presence of three components. The combined products of three runs (14.8 g) were separated by preparative g.l.c. to yield perfluoro-1-methylpyrrolidine (VII) ¹¹ (2 g), b.p. 26° , M^+ 283; 1-difluoromethyloctafluoropyrrolidine (VIII) (4 g), b.p. 61° (Found: C, 22.9; H, 0.5; N, 5.0. $\text{C}_5\text{HF}_{10}\text{N}$ requires C, 22.6; H, 0.4; N, 5.3%); and octafluoro-1-fluoromethylpyrrolidine (II) (8 g), b.p. 75.7° .

Hydrolysis of Octafluoro-1-methylpyrrolidine.—The pyrrolidine (I) (1.5 g) was shaken for 12 h at 100° with concentrated sulphuric acid (5 cm^3). Water (25 cm^3) was carefully added and the mixture was extracted with ether (3 \times 50 cm^3). The combined dried (MgSO_4) extracts were distilled to leave a brown solid. Sublimation *in vacuo* and recrystallisation from *n*-hexane afforded 3,3,4,4-tetrafluoro-1-methylpyrrolidine-2,5-dione (0.85 g), m.p. $50\text{--}51^\circ$ (Found: C, 32.3; H, 1.6; F, 41.6; N, 7.4. $\text{C}_5\text{H}_3\text{F}_4\text{NO}_2$ requires C, 32.4; H, 1.6; F, 41.1; N, 7.6%). In a similar experiment 3*H*,4*H*-hexafluoro-1-methylpyrrolidine (IV) (3 g) yielded 3,4-difluoro-1-methylpyrrolidine-2,5-dione (2.1 g), identical with that described above. When compound (IV) (2 g) was kept for 1 week at room temperature the same dione (1.2 g) was obtained.

Reaction of 3*H*,4*H*-Hexafluoro-1-fluoromethylpyrrolidine with Aluminium Chloride.—The pyrrolidine (VI) (2.1 g) in dry dichloromethane (5 cm^3) was added over 30 min to a stirred suspension of aluminium chloride (2.1 g) in dichloromethane (20 cm^3). Evaporation left a liquid (2.0 g). Distillation afforded 1-chloromethyl-3*H*,4*H*-hexafluoropyrrolidine (1.8 g), b.p. $140\text{--}141^\circ$ (Found: C, 26.8; H, 1.9; F, 50.4. $\text{C}_5\text{H}_4\text{ClF}_6\text{N}$ requires C, 26.4; H, 1.8; F, 50.2%).

Reaction of Octafluoro-1-fluoromethylpyrrolidine with

Sodium Ethoxide.—A mixture of the pyrrolidine (II) (2.5 g), sodium ethoxide (2.54 g), and dimethylformamide (10 cm³) was heated in a sealed tube at 100° for 15 h. After work-up by pouring into water and extraction with ether, a mixture of two components resulted. Preparative g.l.c. afforded starting material (0.6 g) and 1-ethoxymethyl-octafluoropyrrolidine (0.4 g), b.p. 119–120° (Found: C, 31.1; H, 2.7; F, 56.1; N, 4.8. C₇H₇F₈NO requires C, 30.8; H, 2.6; F, 55.7; N, 5.1%).

Dehydrofluorination of 3H-Heptafluoro-1-methylpyrrolidine.—The pyrrolidine (III) (2.1 g) in dry benzene (3 cm³) was stirred at 80° with powdered potassium hydroxide (1 g) for 2 h. The liquid fraction was distilled *in vacuo* and combined with dried ethereal extracts (3 × 20 cm³) of the residue. G.l.c. afforded hexafluoro-1-methyl-Δ³-pyrroline (IX) (1.3 g), b.p. 56° (Found: C, 31.1; H, 1.9; F, 59.8; N, 7.1. C₆H₃F₆N requires C, 31.4; H, 1.6; F, 59.7; N, 7.3%).

Reaction of Hexafluoro-1-methyl-Δ³-pyrrolidine with Cyclopentadiene.—The olefin (2.0 g) and freshly distilled cyclo-

pentadiene (0.8 g) were sealed in a Carius tube and heated at 180° for 18 h. The black product mixture was extracted with ether (3 × 50 cm³) and the extracts were distilled to leave a pale brown solid. Sublimation *in vacuo* afforded 2,6-difluoro-4-methyl-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (X) (0.6 g), m.p. 82° (Found: C, 56.3; H, 4.5; F, 17.9; N, 6.7. C₁₀H₉F₂NO₂ requires C, 56.3; H, 4.2; F, 17.8; N, 6.6%). A sample of this solid in acetone showed two peaks on g.l.c. in the ratio 1 : 1, which were presumed to be the *endo*- and *exo*-isomers. ¹⁹F and ¹H N.m.r. studies confirmed this view.

Attempted Reaction of Hexafluoro-1-methyl-Δ³-pyrroline with Perfluorocyclohexa-1,3-diene.—The olefin (2.0 g) and the diene (2.4 g) were heated together at 230° for 13 h in a sealed Carius tube. Work-up as above gave a solid (0.7 g) which was sublimed *in vacuo* to give 3,4-difluoro-1-methyl-Δ³-pyrroline-2,5-dione, m.p. 110° (Found: C, 40.7; H, 2.4; F, 25.5; N, 9.3. C₈H₃F₂NO₂ requires C, 40.8; H, 2.1; F, 25.8; N, 9.5%).

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