# REACTIONS OF POLYFLUOROCARBONYL COMPOUNDS WITH 1,3,3-TRIMETHYL-3,4-DIHYDROISOQUINOLINE AND ITS DERIVATIVES

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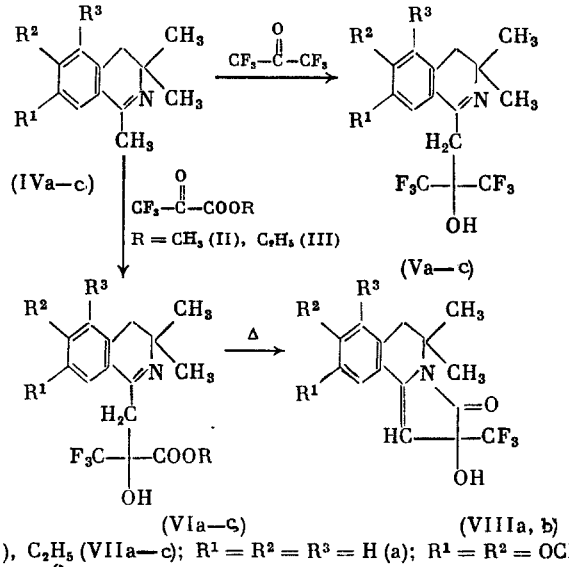
*1,3,3-Trimethyl-3,4-dihydroisoquinolines, which exist in the imine form, undergo C-hydroxyalkylation upon reaction with hexafluoroacetone and esters of trifluoropyruvic acid at the $C^1$–$CH_3$ group at 20°C. The products with the ketoesters are converted upon heating to γ-lactams. Derivatives of 1,3,3-trimethyl-3,4-dihydroisoquinoline substituted at $C^1$–$CH_3$ group and existing in the enamine form, react with esters of trifluoropyruvic acid at 20°C to give exclusively γ-lactams and do not give reaction products with hexafluoroacetone.*

The data on the reactions of piperidine derivatives with hexafluoroacetone (I) indirectly indicate the possibility of the efficient β-C-hydroxyalkylation of the imines formed in the first step in the oxidation of amines by ketone (I) [1-3]. In the present work, we studied the C-hydroxyalkylation of 1,3,3-trimethyl-3,4-dihydroisoquinoline and its derivatives by ketone (I) and the methyl (II) and ethyl esters of trifluoropyruvic acid (III).

1,3,3-Trimethyl-3,4-dihydroisoquinoline (IVa) and its 6,7-dimethoxy (IVb) and benzo[*f*] derivatives (IVc) alkylate ketone (I) at 20°C in Freon-113 (Table 1) to give the corresponding 1-(2-hydroxy-2-trifluoromethyl-3,3,3-trifluoropropyl)-3,3-dimethyl-3,4-dihydroisoquinolines (Va)-(Vc). Under the same conditions, isoquinolines (IVa)-(IVc) undergo C-hydroalkylation by ketoesters (II) and (III). The products, 1-(2-hydroxy-2-alkoxycarbonyl 3,3,3-trifluoropropyl)-3,3-dimethyl-3,4-dihydroiosoquinolines (VIa)-(VIc) and (VIIa)-(VIIc) were obtained in yields over 70% (Table 1). Cyclic γ-lactams (VIIIa) and (VIIIb) were formed upon heating alkoxycarbonyl derivatives (VIa), (VIb), (VIIa), and (VIIb) at reflux in heptane.



R = $CH_3$ (VIa—c), $C_2H_5$ (VIIa—c); $R^1 = R^2 = R^3 = H$ (a); $R^1 = R^2 = OCH_3$, $R_3 = H$ (b); $R^1 = H$, $R^2 = R^3 =$ ⟨benzo⟩ (c).

A. N. Nesmeyanov Institute of Heteroorganic Compounds, Academy of Sciences of the USSR, Moscow. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 6, pp. 1405-1410, June, 1990. Original article submitted June 1, 1989.

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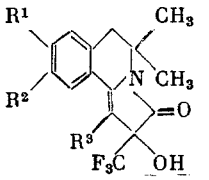
TABLE 1. Conditions for the Formation and Yields of Products (Va)-(Vc), (VIa)-(VIc), (VIIa)-(VIIc), (VIIIa), (VIIIb), (Xa), and (Xb)

| Reaction products | Time, h | Solvent | T, °C | Reagent ratio | Yield, % |
|---|---|---|---|---|---|
| 1-(2-Hydroxy-2-trifluoromethyl-3,3,3-(trifluoropropyl)-3,3-dimethyl-3,4-dihydroisoquinoline (Va) | 1 | Freon-113 | 20 | 1,3,3-Trimethyl-3,4-dihydroisoquinoline (IVa)-(I), 1:1 | 95 |
| 1-(2-Hydroxy-2-trifluoromethyl-3,3,3-(trifluoropropyl)-3,3-dimethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (Vb) | 8 | » | 20 | 1,3,3-Trimethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (IVb)-(I), 1:1 | 80 |
| 1-(2-Hydroxy-2-trifluoromethyl-3,3,3-trifluoropropyl)-3,3-dimethyl-3,4-dihydrobenzo[h]isoquinoline (Vc) | 8 | » | 20 | 1,3,3-Trimethyl-3,4-dihydrobenzo[f]isoquinoline (IVc)-(I), 1:1 | 93 |
| 1-(2-Hydroxy-2-methoxycarbonyl-3,3,3-trifluoropropyl)-3,3-dimethyl-3,4-dihydroisoquinoline (VIa) | 1 | » | 20 | 1,3,3-Trimethyl-3,4-dihydroisoquinoline (IVa)-(II), 1:1 | 78 |
| 1-(2-Hydroxy-2-methoxycarbonyl-3,3,3-trifluoropropyl)-3,3-dimethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (VIb) | 8 | » | 20 | 1,3,3-Trimethyl-6,7-dimethoxy- 3,4-dihydroisoquinoline (IVa)-(III), 1:1 | 94 |
| 1-(2-Hydroxy-2-methoxycarbonyl-3,3,3-trifluoropropyl)-3,3-dimethyl-3,4-dihydrobenzo[h]isoquinoline (VIc) | 8 | » | 20 | 1,3,3-Trimethyl-3,4-dihydrobenzoisoquinoline (IVc)-(II), 1:1 | 86 |
| 1-(2-Hydroxy-2-ethoxycarbonyl-3,3,3-trifluoropropyl)-3,3-dimethyl-3,4-dihydroisoquinoline (VIIa) | 1 | » | 20 | 1,3,3-Trimethyl-3,4-dihydroisoquinoline (IVa)-(I), 1:1 | 71 |
| 1-(2-Hydroxy-2-ethoxycarbonyl-3,3,3-trifluoropropyl)-3,3-dimethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (VIIb) | 8 | » | 20 | 1,3,3-Trimethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (IVb)-(II), 1:1 | 91 |
| 1-(2-Hydroxy-2-ethoxycarbonyl-3,3,3- trifluoropropyl)-3,3-dimethyl-3,4-dihydrobenzo[h]isoquinoline (VIIc) | 8 | » | 20 | 1,3,3-Trimethyl-3,4-dihydrobenzoisoquinoline (IVc)-(III), 1:1 | 86 |
| 2-Hydroxy-5,5 -dimethyl-3-oxo-2-trifluromethyl-2,3,5,6-tetrahydropyrrolo[2,1-a]-isoquinoline (VIIIa) | 25 | Heptane | 100 | (VIa) | 78 |
| 2-Hydroxy-5,5-dimethyl-8,9-dimethoxy-3-oxo-2-trifluoromethyl-2,3,5,6-tetrahydropyrrolo[2,1-a]isoquinoline (VIIIb) | 40 | Heptane | 100 | (VIb) | 70 |
| 2-Hydroxy-5,5-dimethyl-8,9-dimethoxy- 3-oxo-2-trifluoromethyl-1-cyano-2,3,5,6-tetrahydropyrrolo-[2,1-a]isoquinoline (Xa) | 70 | $CH_3NO_2$ | 20 | 3,3-Dimethyl-6,7-dimethoxy-1-cyanomethylidene-3,4-tetrahydroisoquinoline (IXa)-(II), 1:2 | 64 |
| 2-Hydroxy-5,5-dimethyl-8,9-dimethoxy-1-(3,3-dimethyl-3,4-dihydroisoquinol-1-yl)-3-oxo-2-trifluoromethyl-2,3,5,6-tetrahydropyrrolo[2,1-a]-isoquinoline (Xb) | 48 | Freon-113 | 20 | Bis(3,3-dimethyl-3,4-dihydroisoquinol-1-yl)methane (IXb)-(II), 1:2 | 87 |

TABLE 2. Indices of (Va)-(Vc), (VIa)-(VIc), (VIIa)-(VIIc), (VIIIa), (VIIIb), (Xa), and (Xb)

| Compound | Mp, °C | $R_f$ (system) | Found / Calculated, % C | H | N | Chemical formula |
|---|---|---|---|---|---|---|
| (Va) | 48–49 (pentane) | 0.9 (C) | 53.10 / 53.09 | 4.54 / 4.42 | 4.19 / 4.13 | $C_{15}H_{15}F_6NO$ |
| (Vb) | 109–110 (hexane) | 0.66 (C) | 51.28 / 51.12 | 4.56 / 4,76 | 3.66 / 3.50 | $C_{17}H_{19}F_3NO_3$ |
| (Vc) | 68–69 (pentane) | 0.8 (A) | 58.69 / 58.61 | 4.92 / 4.37 | 4.13 / 3,66 | $C_{19}H_{17}F_6NO$ |
| (VIa) | 48–50 (pentane) | 0.56 (C) | 58.03 / 58.36 | 5.55 / 5.47 | 4.24 / 4.25 | $C_{16}H_{18}F_3NO_3$ |
| (VIb) | 110–112 (hexane) | 0.66 (C) | 55.35 / 55.52 | 5.92 / 5.65 | 3.72 / 3.59 | $C_{18}H_{22}F_3NO_5$ |
| (VIc) | 95–96 (pentane) | 0.8 (A) | 63.10 / 63.32 | 5.33 / 5.27 | 3.27 / 3.69 | $C_{20}H_{20}F_3NO_3$ |
| (VIIa) | 30–31 (pentane) | 0.7 (C) | 59.70 / 59.47 | 5.99 / 5.83 | 4.15 / 4.08 | $C_{17}H_{20}F_3NO_3$ |
| (VIIb) | 78–79 (pentane) | 0.57 (A) | 56.22 / 56.57 | 6.04 / 5.95 | 3.49 / 3.47 | $C_{19}H_{24}F_3NO_5$ |
| (VIIc) | 93–95 (Freon-113) | 0.8 (A) | 64.10 / 64.12 | 6.07 / 5.59 | 3.82 / 3.56 | $C_{21}H_{22}F_3NO_3$ |
| (VIIIa) | 139–141 (pentane) | 0.4 (C) | 60.66 / 60,60 | 4.48 / 4.71 | 4.54 / 4.71 | $C_{15}H_{14}F_3NO_2$ |
| (VIIIb) | 160–162 (hexane) | 0,5 (A) | 56.80 / 57,14 | 5.09 / 5.04 | 3.67 / 3.92 | $C_{17}H_{21}F_3NO_4$ |
| (Xa) | 245–247 ($CH_3NO_2$) | 0,3 (A) | 61.67 / 61,74 | 4.85 / 4,85 | 7.69 / 8,00 | $C_{18}H_{17}F_3N_2O_2$ |
| (Xb) | 170–172 (acetone–water) 1 : 10) | 0,4 (B) | 68.90 / 68.72 | 5.60 / 5.50 | 5.85 / 6,14 | $C_{26}H_{25}F_3N_2O_2$ |

TABLE 3. $^1H$ and $^{19}F$ NMR Spectra of (VIIIa), (VIIIb), (Xa), and (Xb)



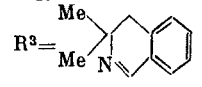
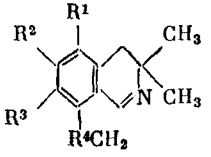
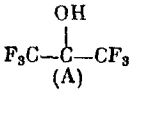
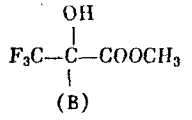

| Compound | Substitutent R | Chemical shifts, ppm (acetone-$d_6$) H¹ | H⁴ | $CH_3$ | $OCH_3$ | OH | $H_{arom}$ | $^{19}F$ |
|---|---|---|---|---|---|---|---|---|
| (VIIIa) | $R^1=R^2=H$, $R^3=H$ | 5,8 s | 2,9 q | 1,3 s<br>1,5 s | – | 6,05 br.s | 7,3–7,8 m | – |
| (VIIIb) | $R^1=R^2=OCH_3$, $R^3=H$ | 5,8 s | 2,85 q | 1,4 s<br>1,6 s | 3,9 br.s | 6,0 br.s | 6,85 s<br>7,4 s | – |
| (Xa) | $R^1=R^2=OCH_3$, $R^3=CN$ | – | 3,02 q | 1,5 s<br>1.7 s | 3,9s, 4,0 s | 6,9 br.s | 7,05 s<br>8,00 s | – |
| (Xb) | $R^1=R^2=H$, $R^3=$  | – | 2,87 q | 1,0 s<br>1,7 s | – | – | 6,9–7,4 | 0,2 s |

TABLE 4. $^{1}H$ and $^{19}F$ NMR Spectra of (Va)-(Vc), (VIa)-(VIc), and (VIIa)-(VIIc)

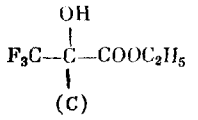




(A)



(B)

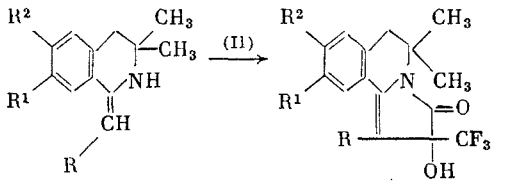


(C)

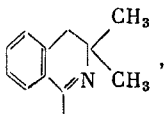
| Compound | Substitutent $R_F$ | Chemical shifts, ppm (acetone-$d_6$) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | $OCH_2$ | H' | $CH_2$—C' | $CH_3$ | $OCH_3$ | H-arom | $^{19}F$ |
| (Va) | $R^4$=A, $R^1$=$R^2$=$R^3$=H | – | 2,8 br.s | 3,15 br.s | 1,2 s | – | 7,17–7,45 m | 1,1 s |
| (Vb) | $R^4$=A, $R^2$=$R^3$=$OCH_3$, $R^1$=H | – | 2,7 s | 3,3 br.s | 1,2 s | 3,9 s<br>3,95 s | 6,9 s 7,3 s | –0,4 s |
| (Vc) | $R^4$=A, $R^1$, $R^2$=(–CH=CH–)$_2$, $R^3$=H | – | 3,2 s | 3,4 br.s | 1,3 s | – | 7,6–8,31 m | |
| (VIa) | $R^4$=B, $R^1$=$R^2$=$R^3$=H | – | 2,73 q | $CH_2$ -AB-system 3,02, 3,5 $J_{AB}$=15 Hz | 1,1 s<br>1,2 s | 3,75 s | 7,1–7,45 m | 2,2 s |
| (VIb) | $R^4$=B, $R^2$=$R^3$=$OCH_3$, $R^1$=H | – | 2,6 q | $CH_2$ AB-system 3,1, 3,5 $J_{AB}$=15 Hz | 1,2 s<br>1,22 s | 4,7 s<br>4,8 s | 6,8–7,25 m | 0,4 s |
| (VIc) | $R^4$=B, $R^1$, $R^2$=(–CH=CH–)$_2$, $R^3$=H | – | 3,2 q | $CH_2$ AB-system 3,2, 3,6 $J_{AB}$=15 Hz | 1,25 s | 3,65 s | 7,6–8,25 m | 0,4 s |
| (VIIa) | $R^4$=C, $R^1$=$R^2$=$R^3$=H | 4,25 q $J_{H-H}$=8 Hz | 2,72 s | $CH_2$ AB-system 3,1, 3,5 $J_{AB}$=15 | 1,1 s<br>1,2 s | 1,3 t | 7,1–7,5 m | 2,2 s |
| (VIIb) | $R^4$=C, $R^2$=$R^3$=$OCH_3$, $R^1$=H | 4,25 q $J_{H-H}$=8 Hz | 2,58 q | $CH_2$ AB-system 3,1, 3,5 $J_{AB}$=15 Hz | 1,1 s<br>1,12 s<br>1,2 t | 3,8 s | 6,65 s<br>7,25 s | |
| (VIIc) | $R^4$=C, $R^1$, $R^2$=(–CH=CH–)$_2$, $R^3$=H | 4,2 q | 3,2 q | $CH_2$ AB-system 3,3, 3,7 $J_{AB}$=15 Hz | 1,25 s | – | 7,58–8,25 m | |

PMR spectroscopy indicates that (V)-(VII) exist in the imine form. An analogous situation is also observed for the starting isoquinoline derivatives (IVa)-(IVc). The PMR spectrum of (IVa) in $CDCl_3$ at −30 and −65°C shows steady broadening of the signals for the $CH_3$ and $CH_2$ groups. One of the possible reasons for this temperature behavior of the width of the spectral lines on the NMR time scale (200 MHz) may be a tautomeric equilibrium between the imine and enamine forms with an insignificantly small fraction of the enamine form.

We may assume that it is specifically the highly reactive enamine which undergoes alkylation. Hence, we undertook the study of the reactions of 3,3-dimethyl-6,7-dimethoxy-1-cyanomethylidene-1,2,3,4-tetrahydroisoquinoline (IXa) and bis(3,3-dimethyl-3,4-dihydroisoquinol-1-yl)methane (IXb), which exist as enamines; the PMR spectra of these compounds at 20°C in $CDCl_3$ contain methine proton signals. The state of the imine-enamine equilibrium has a significant effect on the reactivity of the isoquinoline derivatives. γ-Lactams (Xa) and (Xb) are formed in high yield even at 20°C from ketoester (II), (IXa), and (IXb). The excess ketoester is consumed in this case in the binding of the methanol released. Ketone (I) does not react with (IXa) and (IXb) at 20°C




(IXa, b) (Xa, b)

R = CN, $R^1 = R^2 = OCH_3$ (a); R =  , $R^1 = R^2 = H$ (b).

The differences in the reactivities of ketone (I) and ketoester (II) relative to the β-substituted enamines are apparently a result of the stabilization of the C-hydroxyalkylation product due to the formation of cyclic lactams in the case of ketoester (II). These results also indicate that the vigorous conditions for the lactamization of (VI) and (VII) are dictated by the tautomeric equilibrium.

The properties of these products and their elemental analyses are summarized in Tables 1 and 2. The $^1H$ and $^{19}F$ NMR spectra are given in Tables 3 and 4. The conditions for the formation and yields of products (Va)-(Vc), (VIa)-(VIc), (VIIa)-(VIIc), (VIIIa), (VIIIb), (Xa), and (Xb) are summarized in Table 1.

## EXPERIMENTAL

The $^1H$ and $^{19}F$ NMR spectra were obtained at 20°C on a Bruker WP-200 SY spectrometer at 200.13 and 188.31 MHz, respectively. The chemical shifts were determined relative to TMS as the internal standard for the $^1H$ NMR spectra and $CF_3CO_2H$ as the external standard for the $^{19}F$ NMR spectra. The $R_f$ values were given for Silufol UV-254 plates in the following systems: A) 3:1 $CCl_4$–acetone, B) 6:1 $CCl_4$–acetone, C) chloroform. Products (Va)-(Vc), (VIa)-(VIc), (VIIa)-(VIIc), (VIIIa), (VIIIb), (Xa), and (Xb) were obtained in a sealed vessel under the conditions given in Table 1.

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