HETEROCYCLIC ANALOGS OF PLEIADIENE. 42.* ACYLATION OF PERIMIDINES AND 2,3-DIHYDROPERIMIDINES WITH DERIVATIVES OF PERFLUOROCARBOXYLIC ACIDS

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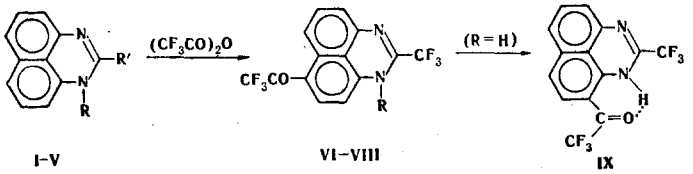
2-Perfluoroalkylperimidines, 2,3-dihydroperimidines, perimidones, and thioxoperimidines are acylated by anhydrides and chlorides of perfluorinated acids without catalysts. It was established that this reaction proceeds considerably more readily than in the case of perimidine and its alkyl-substituted derivatives, since 2-perfluoroalkylperimidines, 2,3-dihydroperimidines, perimidones, and thioxoperimidines, because of their low basicities, are acylated in the form of neutral molecules, whereas simple perimidines form cations with low reactivities under the same conditions.

We have established [1] that the reaction of N-methyl- and N-phenyl-1,8-naphthalenediamines with trifluoroacetic anhydride gives, in addition to 2-trifluoromethylperimidines I and II, which are the principal reaction products, the products of their trifluoroacetylation in the 7 position (VI, VII). This fact was somewhat unexpected, since it has been previously shown that the acylation of perimidines with carboxylic acids and their derivatives proceeds only in the presence of such catalysts as perchloric or polyphosphoric acid [2]. It is apparent that the possibility of trifluoroacetylation without catalysts in the case of I and II is determined by the increased electrophilicity of the trifluoroacetyl ion. In the present research we made a more detailed study of the trifluoroacetylation of perimidines, as well as 2,3-dihydroperimidine derivatives – perimidones, thioxoperimidines, and 2,3-dihydroperimidines themselves.



I–V VI–VIII IX

I R=CH_3, R′=CF_3; II R=C_6H_5, R′=CF_3; III R=H, R′=CF_3; IV R=R′=H; V R=CH_3, R′=H; VI R=CH_3; VII R=C_6H_5; VIII R=H

Compounds I and II are trifluoroacetylated extremely slowly when they are refluxed with excess trifluoroacetic anhydride in dichloroethane or without a solvent. The reaction takes place considerably more rapidly when the compounds are heated with pure trifluoroacetic anhydride in a sealed ampul at 100°C: after 2 h, trifluoroacetylation products VI and VII are obtained in 58 and 90% yields, respectively. One's attention is directed to the higher selectivity of the acylation of N-phenyl-substituted II. This is evidently explained by the somewhat lower reactivity of II as compared with I because of the electron-acceptor effect of the N-phenyl group. In fact, the trifluoroacetylation of perimidine I is accompanied by appreciable resinification and the formation of a number of side products, which we were unable to isolate in pure form.

2-Trifluoromethylperimidine (III) is trifluoroacetylated more easily than I and II. However, the product of this reaction is 9-trifluoroacetyl derivative IX. It is obtained in 86% yield when III is heated with trifluoroacetic anhydride in a sealed ampul at 80°C after 1.5 h. In analogy with the o-acylation of perimidines [2], we explain the formation of IX by means of higher thermodynamic stability as compared with isomer VIII due to the presence in it of a very strong intramolecular hydrogen bond. Thus only a very weak band of a chelated NH group at 3100–3200 cm^{-1} (ν_{NH} 3200–3250 cm^{-1} in the case of 9-acetylperimidine [2]) is observed in the IR

*See [1] for communication 41.

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TABLE 1. pK_a Values (in Acetonitrile at 25°C) of Perimidine Derivatives

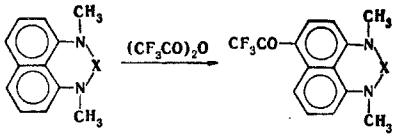
Perimidine	pK_a
Unsubstituted	13.58(see [6])
1-Methyl-	13.70
1-Methyl-2-trifluoromethyl-	6.64
1-Phenyl-2-trifluoromethyl-	5.95
1,3-Dimethyl-2,3-dihydro-	8.67

spectrum of a dilute solution of trifluoroacetyl derivative IX in chloroform. The signal at δ 12.72 ppm, i.e., at weaker field (by 0.27 ppm) than the N–H proton in 9-acetylperimidine [2], in the PMR spectrum of a solution of IX in deuterochloroform corresponds to the N–H proton. As in the case of the acylation of perimidine [2], the trifluoroacetylation of perimidine III under kinetic-control conditions evidently takes place in the 6 and 7 positions with subsequent rearrangement of the 6(7)-substituted compound to the more stable 9 isomer. However, in contrast to perimidines, we were unable to carry out the trifluoroacetylation of III in such a way as to isolate p-substituted VIII. This is undoubtedly explained by the higher stability of the intramolecular hydrogen bond in perimidine IX as compared with 9-acetylperimidines and the greater ease of the VIII → IX rearrangement.

Attempts to trifluoroacetylate perimidine IV and 1-methylperimidine V were unexpectedly unsuccessful. Only the starting compounds were isolated from the reaction mixture even after heating them in trifluoroacetic anhydride in a sealed ampul at 100-130°C for many hours. This result, the paradoxical character of which consists in the fact that the electron-acceptor 2-CF_3 group activates, as it were, electrophilic substitution, can be explained by the fact that I and II, because of their reduced basicity, undergo reaction in the form of neutral molecules, while perimidine and 1-methylperimidine form cations with low reactivities under the influence of $(CF_3CO)_2O$. Measurements of the basicities in acetonitrile (Table 1) showed that I and II are seven to eight orders of magnitude less basic than perimidines IV and V.

It is interesting that we were unable to accomplish the trifluoroacetylation of IV and V even in polyphosphoric acid (PPA), which is evidently an insufficiently strong catalyst for the formation of the CF_3CO^+ ion.

Considering the reduced basicities of perimidones (the basicity of X could not be measured even in acetonitrile, i.e., it is lower than 4-5 pK_a units) and their high activity in electrophilic substitution reactions [3], one might have expected that, like I and II, they would undergo trifluoroacetylation. In fact, 1,3-dimethylperimidone (X) undergoes quantitative conversion to 6-trifluoroacetyl derivative XIV when it is heated with trifluoroacetic anhydride for 12 h without a solvent in a sealed ampul for 2 h.



X–XIII XIV, XV

X, XIV X=CO; XI X=CS; XII X=CH_2; XIII, XV X=$C(CH_3)_2$

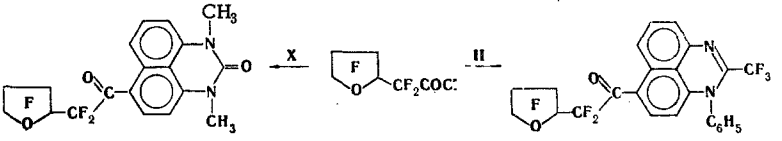
The trifluoroacetylation of 1,3-dimethylthioxoperimidine XI under the same conditions also led to the formation of 6-trifluoroacetylperimidone XIV. S-Acylation, which has been previously observed for XI [4], evidently takes place along with C-acylation in this case, as a result of which the thiouronium salt readily undergoes hydrolysis during decomposition of the reaction mixture to give the perimidone. It should be noted that we were also unable to measure the basicity of 1,3-dimethylthioxoperimidine in acetonitrile, i.e., it is lower than 4-5 pK_a units.

1,3-Dimethyl-2,3-dihydroperimidine (XII) reacts with trifluoroacetic anhydride in the cold. However, the initial yellow coloration of the reaction mixture deepens rapidly to dark-brown, and the reaction product is a resinous mass consisting of a complex mixture of difficult-to-separate substances. However, according to the data from thin-layer chromatography (TLC), the mixture does not contain a C-trifluoroacetylation product (the latter is always easily identified from its yellow-green luminescence in UV beams). It may be assumed that trifluoroacetic anhydride accepts a hydride ion from the CH_2 group of XII, and the resulting trifluoroacetaldehyde subsequently reacts both with dihydroperimidine XII and with the 1,3-dimethylperimidinium ion to give a complex mixture of substances. In particular, the fact that we were able to accomplish the tri-

fluoroacetylation of 1,2,2,3-tetramethyl-2,3-dihydroperimidine (XIII) under extremely mild conditions (at 30-40°C for 6 h in dichloroethane) constitutes evidence in favor of this assumption. Compound XV was obtained in 21% yield. The principal reaction product is a mixture of substances with low R_f values; we were unable to separate this mixture. Compound XIII undergoes resinification under more severe trifluoroacetylation conditions (above 50-70°C).

The basicities of XII and XIII are four to five orders of magnitude lower than the basicity of perimidine, and it is extremely likely that they undergo partial conversion to the cationic form under the influence of $(CF_3CO)_2O$. However, it has been noted [5] that the cations of dihydroperimidines are more reactive in electrophilic substitution reactions than perimidinium cations.

We have found that perimidines and perimidones are also acylated by anhydrides of perfluoro carboxylic acids; however, the latter are considerably more inert than trifluoroacetic anhydride. Thus, for example, II is acylated by perfluoro(2-tetrahydrofuryl)acetyl chloride to give perimidine XVI in 72% yield as a result of heating at 120°C for 7 h. Under similar conditions (100°C for 10 h) 1,3-dimethylperimidone is converted to acylation product XVII in 46% yield, whereas only traces of an acylation product are formed in the case of heating at 140°C with pentafluorobenzoyl chloride in a sealed ampul.



XVII XVI

EXPERIMENTAL

The IR spectra of solutions of the compounds in $CHCl_3$ were recorded with a UR-20 spectrometer. The PMR spectra of CF_3COOH solutions were recorded with a Tesla BS-467 spectrometer (60 MHz) at room temperature with hexamethyldisiloxane as the internal standard. Chromatography was carried out on activity IV (Brockmann classification) aluminum oxide with elution by benzene. The pK_a values were measured by the method in [7].

1-Methyl-2-trifluoromethyl-7-trifluoroacetylperimidine (VI). A 0.1-g (0.4 mmole) sample of perimidine I was heated with 1 ml of trifluoroacetic anhydride in a sealed ampul at 100°C for 2 h, after which the mixture was cooled and poured over 5 g of finely crushed ice. The mixture was stirred, and VI was removed by filtration and purified successively by chromatography and recrystallization from ethanol. The yield of light-yellow crystals, with mp 204°C, was 0.075 g (58%). IR spectrum: 1690 cm^{-1} (C=O). PMR spectrum, δ: 3.4 (3H, s, CH_3), 6.7 (d, J = 8.25 Hz, 9-H), 7.0 (d, J = 8.25 Hz, 4-H), 7.35 (t, 5-H), 7.9 (d, J = 8.25 Hz, 8-H), and 8.3 ppm (d, J = 8.25 Hz, 6-H). Found: C 52.0; H 2.4; N 8.0%. $C_{15}H_8F_6N_2O$. Calculated: C 52.0; H 2.3; N 8.2%.

1-Phenyl-2-trifluoromethyl-7-trifluoroacetylperimidine (VII). This compound, was similarly obtained in 90% yield in the form of yellow crystals with mp 198°C (from ethanol). IR spectrum: 1690 cm^{-1} (C=O). PMR spectrum, δ: 5.55 (d, J = 8.25 Hz, 9-H), 7.2 (m, 8H), and 8.25 ppm (d, J = 8.25 Hz, 6-H). Found: C 58.7; H 2.8; N 6.9%. $C_{20}H_{10}F_6N_2O$. Calculated: C 58.7; H 2.7; N 6.8%.

9-Trifluoroacetyl-2-trifluoromethylperimidine (IX). A mixture of 0.2 g (0.8 mmole) of perimidine III and 2 ml of trifluoroacetic anhydride was heated in a sealed ampul at 80°C for 1.5 h, after which it was cooled and poured over 10 g of finely crushed ice. The mixture was stirred thoroughly, and the precipitate was removed by filtration to give 0.24 g (86%) of orange-yellow crystals of IX with mp 161°C (from ethanol). IR spectrum: 3100-3200 (N-H) and 1645 cm^{-1} (C=O). PMR spectrum (in $CDCl_3$), δ: 7.25 (m, 5H) and 12.72 ppm (s, 1H, N-H) (this band vanishes when the compound is deuterated). Found: C 50.5; H 1.8; N 8.3%. $C_{14}H_6F_6N_2O$. Calculated: C 50.6; H 1.8; N 8.4%.

6-Trifluoroacetyl-1,3-dimethylperimidone (XIV). A) Trifluoroacetylation in an ampul at 100°C for 2 h was carried out as in the synthesis of VI and VII. The product was obtained in quantitative yield.

B) A 0.2-ml (1.5 mmole) sample of trifluoroacetic anhydride was added to a solution of 0.1 g (0.5 mmole) of perimidone X in 5 ml of dry dichloroethane, and the mixture was refluxed for 12 h. It was then cooled thoroughly, and the resulting precipitate was dried and recrystallized from benzene to give light-green crystals of XIV, with mp 258°C, in quantitative yield (140 mg). PMR spectrum, δ: 2.95 (s, 6H, CH_3), 6.05 (d, J = 9 Hz, 9-H), 6.25 (d, J = 9 Hz, 4-H), 7.03 (m, 8-H), 7.65 (d, J = 9 Hz, 5-H), and 8.15 ppm (d, J = 10.5 Hz, 7-H). Found: C 58.4; H 3.6; N 9.0%. $C_{15}H_{11}F_3N_2O_2$. Calculated: C 58.4; H 3.6; N 9.1%.

C) A mixture of 50 mg (0.2 mmole) of thioxoperimidine XI and 800 mg (4 mmole) of trifluoroacetic anhydride was heated in a sealed ampul at 100°C for 2 h, after which it was cooled and treated with 5 ml of cold water. The yellow-green precipitate of perimidone XIV was removed by filtration, washed with 50 ml of water, and dried at 90-100°C. The yield was quantitative. The yellow-green crystals had mp 257-258°C (from benzene).

6-Trifluoroacetyl-1,2,2,3-tetramethyl-2,3-dihydroperimidine (XV). A 150-mg (0.7 mmole) sample of trifluoroacetic anhydride was added to a solution of 100 mg (0.44 mmole) of dihydropermidine XIII in 5 ml of dry dichloroethane, and the mixture was heated at 30-40°C for 6 h. The dichloroethane was evaporated in vacuo (with a water aspirator), and the residue was dissolved in benzene and chromatographed on aluminum oxide. Workup of the first fraction gave 30 mg (21%) of yellow crystals with mp 219°C (from benzene–petroleum ether). IR spectrum: 1675 cm^{-1} (C=O). Found: C 63.4; H 5.3; N 8.8%. $C_{17}H_{17}F_3N_2O$. Calculated: C 63.4; H 5.3; N 8.7%.

General Method for the Acylation of Perfluorinated Acid Chlorides. A solution of 1 mmole of the perimidine and 2 mmole of the corresponding acid chloride in 2 ml of dry dichloroethane was heated in a sealed ampul, after which it was cooled and diluted with 5 ml of benzene. The benzene solution was washed three times with 10 ml of 10% ammonium hydroxide and twice with 20 ml of water. The solvent was evaporated, and the product was recrystallized (where necessary, it was first purified by chromatography on aluminum oxide with elution with benzene). The yield of XVI was 72%; the yellow crystals had mp 175-177°C (from ethanol). Found: C 49.0; H 2.0; N 4.8%. $C_{24}H_{10}F_{12}N_2O_2$. Calculated: C 49.1; H 1.7; N 4.8%. The yield of perimidone XVII was 46%; the light-green crystals had mp 110-112°C (from octane). Found: C 46.8; H 2.3; N 5.8%. $C_{19}H_{11}F_9N_2O_3$. Calculated: C 46.9; H 2.3; N 5.8%.

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