POLYFLUORINATED HETEROCYCLIC COMPOUNDS

II. Preparation of Heterocyclic Compounds Based on α-Benzamido-β-(Pentafluorophenyl) Acrylic Acid*

T. D. Petrova, V. P. Mamaev, G. G. Yakobson, and N. N. Vorozhsov, Jr.

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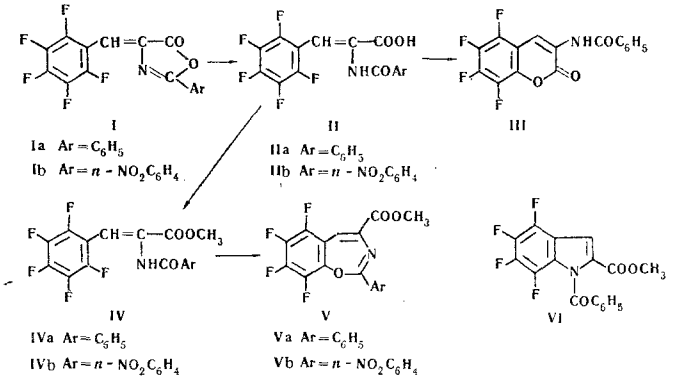
A study has been made of the possibility of intramolecular cyclization of α-benzamido-β-(pentafluorophenyl)acrylic acid (IIa) with the object of synthesizing heterocyclic compounds. When the acid IIa was heated with potassium fluoride in dimethylformamide, 3-benzamido-6,7,8,9-tetrafluorocoumarin (III) was formed. Under the same conditions the methyl ester of (IIa) gave 2-phenyl-4-carbomethoxy-6,7,8,9-tetrafluorobenz[f]oxazepine-1,3 (Va). Some reactions of the latter have been studied.

Recently the preparation and properties of polyfluorinated heterocyclic compounds have been much studied. One of the most useful routes to such compounds is the intramolecular cyclization of substituted polyfluorobenzenes [1, 2]. In a continuation of our work we have studied the possibility of intramolecular cyclization of α-benzamido-β-(pentafluorophenyl)acrylic acid, hopefully to give interesting polyfluorinated indole derivatives. Intramolecular cyclization should be facilitated because the ortho fluorine atom is additionally labilized by the carboxyl group conjugated to the pentafluorphenyl ring. Also the heterocyclic ring formed would probably be stabilized by the endocyclic double bond.

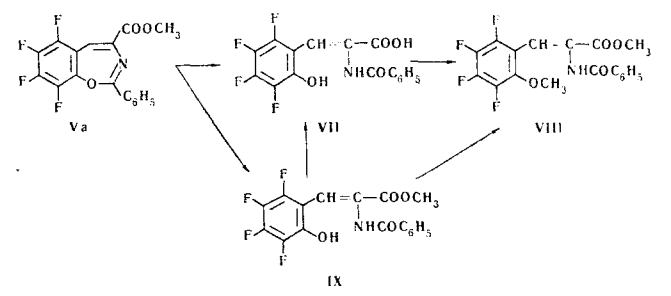
Potassium fluoride, which has a number of advantages over other alkaline compounds [4], was used to absorb the hydrogen fluoride evolved. A product, $C_{16}H_7F_4NO_3$, corresponding to the elimination of one molecule of hydrogen fluoride from IIa, was obtained by heating IIa with potassium fluoride in dimethylformamide. The IR spectrum of the product retained bands attributable to a secondary amide group (3380 cm^{-1}, N–H; 1683 cm^{-1}, C=O), but the carboxyl group bands were replaced by an intense band at 1740 cm^{-1} (C=O of an ester). These results indicate that the product is 3-benzamido-5,6,7,8-tetrafluorocoumarin (III). The UV spectrum of (III) is similar to that of its nonfluorinated analog (prepared according to [5]), but with a slight hypsochromic shift of the absorption maximum. Like coumarin [6], III dissolves in alkali to give a salt of α-benzamidotetrafluorocoumaric acid which was reconverted to III on acidification. The cyclization of IIa thus occurred at the carboxyl group under the conditions studied.

To carry out cyclization at the amido group, methyl α-benzamido-β-pentafluorophenylacrylate (IVa) was treated under the same conditions to give a product $C_{17}H_9F_4NO_3$, i.e., one molecule of HF was again evolved.

*For part I, see [1].

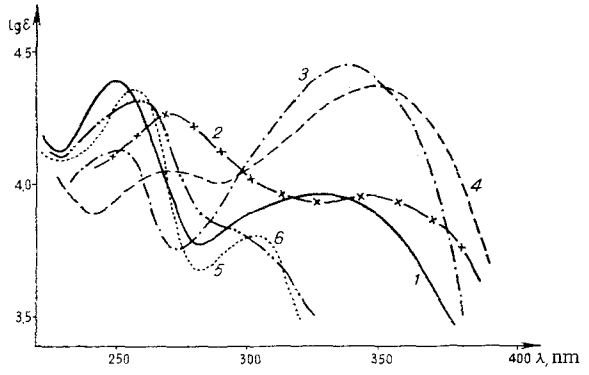


The absence of bands in the N–H region in the IR spectrum showed that cyclization had occurred at the benzamido group, while four equally intense lines in the ^{19}F NMR spectrum (δ_1 2.12, δ_2 7.87, δ_3 11.25, and δ_4 22.00 ppm, relative to hexafluorobenzene as internal standard) indicated the elimination of an ortho fluorine atom. Additional IR bands occurred at 1745 (C=O, ester) and 1650 cm^{-1} (amide C=O or C=N). However the combination of elemental composition and spectroscopic data does not permit an unambiguous assignment of a structure to the product. There are at least two compounds—which are reasonable and agree with the spectroscopic data. Some of the reactions of the product were therefore studied to establish its structure.



Compound VI is an N-acylated indole compound which readily undergoes alkaline scission of the N-acyl group. The product was therefore treated with both an equimolar amount and an excess of 5% aqueous potassium hydroxide. In both cases a compound $C_{16}H_9F_4NO_4$ was formed, in the former case in addition to unreacted product. The formula shows that neither tetrafluoroindole-2-carboxylic acid nor its ester was produced as would have been expected from VI. The new compound was acidic and contained a phenolic hydroxyl group as shown by the qualitative test with iron (III) chloride. Together with the amide

and carboxyl bands in the IR spectrum, these results indicate that the new compound is α-benzamido-β-(2-hydroxy-3,4,5,6-tetrafluorophenyl)acrylic acid (VII). It is probable that the carboxyl group and the phenyl ring are in the trans configuration in VII, in contrast to the cis-isomer which is formed from the coumarin (III). Compound VII was converted to methyl α-benzamido-β-(2-methoxy-3,4,5,6-tetrafluorophenyl)-acrylate (VIII) with diazomethane. The absence of a hydroxyl band and the presence of intense bands at 1695 cm^{-1} (amide C=O), 1730 cm^{-1} (ester C=O), and 3400 cm^{-1} (amide N–H) in the IR spectrum of (VIII) confirmed its identity.



UV absorption spectra: 1) 2-phenyl-4-carbomethoxy-6,7,8,9-tetrafluorobenz[f]oxazepine-1,3 (Va); 2) 2-(p-nitrophenyl)-4-carbomethoxy-6,7,8,9-tetrafluorobenz[f]oxazepine-1,3 (Vb); 3) 2-phenyl-4-(pentafluorobenzal)oxazolone-5 (Ia); 4) 2-(p-nitrophenyl)-4-(pentafluorobenzal)oxazolone-5 (Ib); 5) N-benzoylindole; 6) N-(p-nitrobenzoyl)indole.

The formation of the acid VII from the compound Va is understandable since oxygen-containing heterocycles fused to a benzene ring are known to ring open to give o-hydroxybenzenes [6, 7]. To form VII from VI requires scission of a bond between nitrogen and the benzene ring which appears unlikely since no such cases are known for indole derivatives. Consequently the benzoxazepine Va is the more likely.

Since benzoxazepines-1,3 have not been described previously we have carried out some simple reaction with Va, particularly the hydrolysis of the ester group. Hydrolysis in aqueous acetone containing a small amount of concentrated hydrochloric acid caused opening of the heterocyclic ring to give a product which gave a color with iron (III) chloride and which had an IR spectrum containing bands at 3550 cm^{-1} (O–H), 3390 cm^{-1} (N–H), 1720 cm^{-1} (ester C=O), and 1680 cm^{-1} (amide C=O). In composition and spectra this compound corresponds to methyl α-benzamido-β-(2-hydroxy-3,4,5,6-tetrafluorophenyl)-acrylate (IX) and it was converted to ether VIII* by treatment with diazomethane.

Thus compound Va undergoes ring opening more readily than hydrolysis of the ester group in acid media. In contrast, we have shown previously that polyfluorinated five- and six-membered heterocycles are more stable than their nonfluorinated analogs [2, 8]. Hence the ease of scission of the heterocyclic ring also indicates the oxazepine structure Va rather than the indolic structure VI.

The UV spectrum provided an additional basis for the distinction between Va and VI. Since the azomethine does not interrupt a chromophoric system, the system of conjugated bonds in Va includes the phenyl ring so that the UV spectrum of the latter should show a change, whereas the phenyl group in VI is not included in the chromophoric system and the UV spectrum of the phenyl group should not show much change.

We have obtained, by a method similar to that for Va, an analog of Va containing a p-nitro group on the phenyl ring (Vb). This group normally causes a bathochromic shift of the absorption maximum.

From a comparison of the UV spectra of Va and Vb (see figure) it is seen that both absorption maxima of the latter are shifted to longer wavelength by 18 nm. It is interesting that a comparison of the UV spectra of 2-phenyl-4-(pentafluorobenzal)oxazolone-5 (Ia) and 2-(p-nitrophenyl)-4-(pentafluorobenzal)oxazolone-5 (Ib)*, intermediates in the synthesis of Va and Vb and with chromophores similar to them, shows a noticeable long wavelength shift in the absorption maxima of Ib, the compound containing the p-nitro group. In contrast, introduction of a p-nitro group into the phenyl ring of N-benzoylindole causes almost no change (see figure).

All the above data indicate that Va and Vb are examples of the previously undescribed benzoxazepines-1,3. The formation of these compounds is explicable if it is remembered that an amide group can react either at oxygen [9] or at nitrogen [10].

EXPERIMENTAL

IR spectra were recorded on a UR-10 spectrometer. Strong bands around 1500 cm^{-1} (fluorinated benzene ring) were observed in the spectra of all fluorinated compounds. UV spectra were recorded on an SFD-2 spectrometer at a concentration of 10^{-4} in a 0.5 cm cell. The ^{19}F NMR spectra were recorded with a JNM-3H spectrometer at 50 MHz. The identities of products were established by comparison of IR spectra and by determination of mixed melting points.

2-Phenyl-4-(pentafluorobenzal)oxazolone-5 (Ia) was prepared according to [3], mp 171°–172° C, $\lambda_{max\ I}$ 250 nm (lg ε 4.13); $\lambda_{max\ II}$ 338 nm (lg ε 4.45), in dioxane.

2-(p-nitrophenyl)-4-(pentafluorobenzal)oxazolone-5 (Ib) was prepared from pentafluorobenzaldehyde, p-nitrohippuric acid, and sodium acetate in a manner analogous to Ia. Yield 33.5%, mp 153°–155° C (from a mixture of cyclohexane and acetone). Found, %: C 50.52, 50.51; H 1.45, 1.44; F 24.97, 24.61; N 7.44, 7.28. Calculated for $C_{16}H_5F_5N_2O_4$, %: C 50.00; H 1.30; F 24.70; N 7.30. The following bands were observed in the IR spectrum (CCl_4 solution): 1350 and 1540 cm^{-1} (nitrogroup), 1820 cm^{-1} (lactone group). The UV spectrum in dioxane showed bands at $\lambda_{max\ I}$ 268 nm (lg ε 4.04) and $\lambda_{max\ II}$ 348 nm (lg ε 4.36).

*A separate paper is concerned with other products obtained from Va by treatment with acid.

*The oxazolone, Ib, containing the nitro group, is more reactive than Ia. For example, even on attempted crystallization from methanol it was converted to methyl α-(p-nitrobenzamido)-β-pentafluorophenylacrylate (IVb)

α-Benzamido-β-(pentafluorophenyl)acrylic acid (IIa) was obtained from Ia according to [3], mp 231°–232° C.

α-(p-Nitrobenzamido)-β-(pentafluorophenyl)acrylic acid (IIb) was obtained from Ib analogously to **IIa**, yield 90%, mp 217°–219° C (from aqueous methanol). Found, %: C 47.51, 47.82; H 1.77, 1.92; F 23.06, 23.20. Calculated for $C_{16}H_7F_5N_2O_5$, %: C 47.70; H 1.74; F 23.60. The following bands were found in the IR spectrum (KBr disc): 1350 and 1540 cm^{-1} (nitro group), 1680 cm^{-1} (amide C=O), 1715 cm^{-1} (acid C=O), and 3000-3400 cm^{-1} (broad, OH and NH).

Methyl α-benzamido-β-(pentafluorophenyl)acrylate (IVa) was obtained by treating the acid **IIa** with diazomethane in the normal way. Yield 93%. After washing with potassium hydroxide solution and water, followed by drying, it has mp 137.5°–138.5° C (from aqueous methanol). Found, %: F 25.42, 25.64; N 4.05, 4.11. Calculated for $C_{17}H_{10}F_5NO_3$, %: F 25.60; N 3.77. IR spectrum (in CCl_4): 1710 cm^{-1} (amide C=O), 1740 cm^{-1} (ester C=O), and 3400 cm^{-1} (amide NH).

Methyl α-(p-nitrobenzamido)-β-(pentafluorophenyl)acrylate (IVb) was prepared (a) by treatment of the acid **IIb** with diazomethane; yield 83%, mp 184°–186° C (from aqueous methanol). Found, %: C 49.00, 48.73; H 1.86, 2.06; F 22.82, 22.95; N 7.30, 7.50. Calculated for $C_{17}H_9F_5N_2O_5$, %: C 48.50; H 2.16; F 22.80; N 6.74. IR spectrum in CCl_4: 1350 and 1540 cm^{-1} (nitro group), 1700 cm^{-1} (amide NH); and (b) by recrystallization of the oxazolone **IIb** from methanol, yield 58%.

3-Benzamido-5,6,7,8-tetrafluorocoumarin (III). IIa (0.18g, 0.5 mmole), anhydrous KF (0.04 g, 0.7 mmole), and dry DMF (5ml) were stirred at 100° C for 5 hr. The mixture was cooled, 25 ml water added, and the precipitate removed, washed with water, and dried, to give 0.1 g of product, which was washed with methanol, sublimed in vacuo in a water-cooled vessel and recrystallized from benzene, mp 229°–231° C. Found, %: C 57.14, 56.90; H 2.01, 1.86; F 22.19, 22.16; N 4.10, 4.36. Calculated for $C_{16}H_6F_4NO_3$, %: C 57.14; H 1.78; F 22.60; N 4.17. λ_{max} 308 nm (lg ε 4.35 UV spectrum in ethanol). 0.05 g of the initial acid **IIa** was separated from the aqueous filtrate on acidification.

2-Phenyl-4-carbomethoxy-6,7,8,9-tetrafluorobenz[f]oxazepine-3 (Va). **IVa** (0.18 g, 0.5 mmole), anhydrous KF (0.04 g, 0.7 mmole and 5 ml dry DMF were stirred at 100° C for 5 hr. The mixture was cooled, 25 ml water added, the precipitate separated, washed with water, and dried to give 0.15 g (88%) of **Va**, mp 119°–120.5° C (from methanol). Found, %: C 58.34, 58.48; H 2.35, 2.44; F 21.47, 21.75; N 4.07, 3.95; M 351, 341. Calculated for $C_{17}H_9F_4NO_3$, %: C 58.10; H 2.56; F 21.65; N 3.99; M 351. UV spectrum in dioxane: $\lambda_{max\ I}$ 254 nm (lg ε 3.96).

2-(p-Nitrophenyl)-4-carbomethoxy-6,7,8,9-tetrafluorobenz[f]-oxazepine-3 (Vb). This compound was obtained from **IVb** in an analogous manner. Yield 79%, mp 168°–169° C (from chloroform). Found, %: C 51.63, 51.44; H 2.35, 2.31; F 18.45, 18.44; N 6.69, 6.86. Calculated for $C_{17}H_8F_4N_2O_5$, %: C 51.55; H 2.02; F 19.2; N 6.97. IR spectrum in CCl_4: 1250 cm^{-1} (ester C=O). UV spectrum in dioxane: $\lambda_{max\ I}$ 272 nm (lg ε 4.27); $\lambda_{max\ II}$ 346 nm (lg ε 3.95).

α-Benzamido-β-(2-hydroxy-3,4,5,6-tetrafluorophenyl)acrylic acid (VII) a) **Va** (1g, 2.8 mmole) and 25 ml of 5% aqueous KOH were stirred at 60° C for 16 hr until the solid had almost completely dissolved. Unreacted **Va** (0.04 g, mp 118°–119° C) was filtered off, the filtrate was acidified with hydrochloric acid, and the precipitate filtered, washed with water and dried to give **VII** (0.84 g, 87% based on **Va** consumed), mp 189° C (with decomposition, from aqueous methanol). Found, %: C 54.47, 54.19; H 2.90, 2.88; F 20.47, 20.61; N 4.17, 4.33. Calculated for $C_{16}H_9F_4NO_4$, %: C 54.20; H 2.54; F 21.40; N 4.16.

b) It was also obtained from **IX** in a similar manner.

Methyl α-benzamido-β-(2-hydroxy-3,4,5,6-tetrafluorophenyl) acrylate (IX). Va (0.15 g, 0.4 mmole), 3 ml acetone, 1 ml water, and 3 drops of conc. HCl were boiled for 2 hr. To the cooled mixture, 10 ml of water was added and the precipitate was filtered off to give 0.12 g (77%) of **IX**, mp 169.5°–171.5° C (from benzene). Found, %: C 55.37, 55.46; H 3.07, 3.07; F 20.59, 20.81; N 3.80, 3.90; OCH_3 7.97, 8.14. Calculated for $C_{17}H_{11}F_4NO_4$, %: C 55.30; H 2.99; F 20.60; N 3.80; OCH_3 8.30.

Methyl α-benzamido-β-(2-methoxy-3,4,5,6-tetrafluorophenyl) acrylate (VIII). a) Treatment of **VII** (0.2 g, 0.6 mmole) with diazomethane in the normal manner gave 0.21 g (97%) of **VIII**. After treatment of the reaction mixture with soda, water, and recrystallization from methanol, the product had mp 160°–161.5 C. Found, %: C 56.39, 56.47; H 3.51, 3.28; F 19.79, 19.72; N 3.87, 4.06; OCH_3 16.29, 16.41. Calculated for $C_{18}H_{13}F_4NO_4$, %: C 56.30; H 3.40; F 19.85; N 3.66; OCH_3 16.20.

b) Treatment of **IX** (0.07 g, 0.2 mmole) with diazomethane in the normal manner gave **VIII** (0.06 g, 82%) with mp 158°–161° C after treatment of the solution with soda, water and recrystallization from methanol.

N-(nitrobenzoyl)indole. To a suspension of sodium hydride (0.20 g, 8.3 mmole) in 5 ml of glyme a solution of indole (0.88 g, 7.5 mmole) in 5 ml glyme was added dropwise and with stirring. There was a vigorous evolution of hydrogen. Stirring was continued for about an hour and then p-nitrobenzoyl chloride (1.39 g, 7.5 mmole) in 5 ml of glyme was added. A precipitate formed and the mass solidified. The mixture was refluxed for 30 min, and 20 ml of water was added after the mixture had cooled. The precipitate dissolved to give a two-layered liquid, the lower layer of which solidified. The solid was removed, and washed with potassium hydroxide, water, and ethanol to give the product (1.58 g., 79%), mp 156°–157.5° C (after purification on Al_2O_3). Found, %: N 10.53, 10.40. Calculated for $C_{15}H_{10}N_2O_3$, %: N 10.52. IR spectrum in $CHCl_3$: 1345 and 1530 cm^{-1} (nitro group), 1690 cm^{-1} (amide C=O). UV spectrum in ethanol: λ_{max} 258 nm (lg ε 4.31).

N-Benzoylindole was prepared similarly from benzoyl chloride and indole. Yield 33%, mp 68°–69° C (lit [1]: mp 67°–68° C); UV spectrum in ethanol: $\lambda_{max\ I}$ 250 nm (lg ε 4.38); $\lambda_{max\ II}$ 302 nm (lg ε 3.80).

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Novosibirsk Institute of Organic Chemistry, Siberian Division, Academy of Sciences USSR