CONDENSATION OF 4-AZAFLUORENONE AND 9-PHENACYLIDENE-4-AZAFLUORENE WITH ACETOPHENONE. SYNTHESIS OF 3'-OXO-spiro-[4-AZAFLUORENE-9,1'-INDANE]

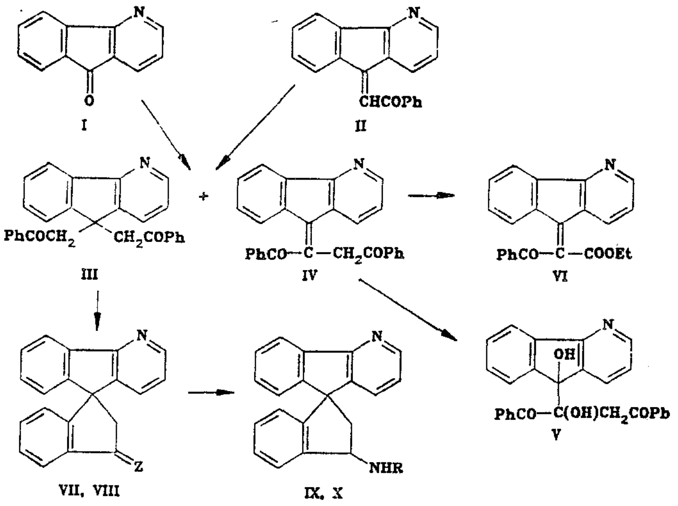
N. S. Prostakov, Mikhalis Makuli,
N. M. Mikhailova, N. D. Sergeeva,
and A. A. Obynochnyi

UDC 547.678.3'828:543.422'51

Condensation of 4-azafluorenone and 9-phenacylidene-4-azafluorene with acetophenone leads to the formation of 9,9-diphenacyl-4-azafluorene and 9-(1',2'-dibenzoylethylidene)-4-azafluorene. The structures of these products were confirmed based on their spectral and chemical data. The conversion of 9,9-diphenacyl-4-azafluorene to 3'-oxo-spiro-[4-azafluorene-9,1'-indane] represents a novel method for the preparation of this heterocycle.

Two compounds are formed upon condensation of 4-azafluorenone (I) or 9-phenacylidene-4-azafluorene (II) [1] with acetophenone in the presence of 15% ethanolic potassium hydroxide. One of the products is 9,9-diphenacyl-4-azafluorene (III), which was isolated in approximately the same yield (35%) from the two reactions. The preparation of azafluorene III by these two methods leads us to conclude that the first stage in the condensation of ketone I with acetophenone results in the formation of the phenacylidene derivative II, which then undergoes further Michael reaction and is converted to the final product III. An analogous fluorene derivative has been described previously [2].

The second product in the above reactions is 9-(1',2'-dibenzoylethylidene)-A-azafluorene (IV), which was isolated in the form of its hydrochloride in 35 and 50% yield, respectively, from the two reactions.



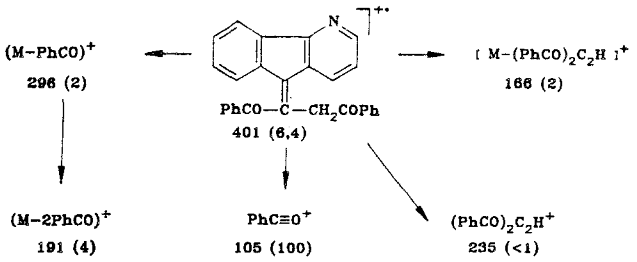
VII Z=O; VIII Z=NOH; IX R=H; X R=COMe

The IR spectrum of compound IV exhibits two very intense absorption bands at 1690 and 1660 cm^{-1}, which are assigned to carbonyl group stretching vibrations of the phenacyl and benzoyl molecular fragments. The electronic spectrum of this compound contains a band at 435 nm (log ε 4.24), which provides the basis for our assumption that there is a fulvene-like functional group arrangement in the molecule.

P. Lumumba Peoples' Friendship University, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1239-1242, September, 1988. Original article submitted February 16, 1987; revision submitted June 22, 1987.

0009-3122/88/2409-1024$12.50

The mass spectral data, which include the presence of a molecular ion peak at m/z 401 (6.4%) and characteristic fragmentation, also provide evidence for the structure of compound IV.



Based on the integrated intensity ratio of the methylene group proton singlets (at 4.76 and 4.83 ppm) in the PMR spectrum of compound IV, this material consists of a mixture of E- and Z-isomers (1:1.5) with respect to the position of the benzoyl group relative to the pyridine ring in the azafluorene fragment. The proton signals for the pyridine ring are also doubled: 7.76 (1-H), 7.08 (2-H), 8.53 ppm (3-H) (for the E-isomer), and 7.32 (1-H), 6.83 (2-H), and 8.39 ppm (3-H) (for the Z-isomer). Comparison of these values with the chemical shift data for 4-azafluorene [7.64 (1-H); 7.04 (2-H), and 8.47 ppm (3-H)] [3] indicates that in the E-isomer these chemical shift values remain practically unchanged. Apparently, therefore, the pyridine ring protons in this isomer are separated from the magnetic anisotropy of the benzoyl group. All of the pyridine ring protons in the Z-isomer, in contrast, have undergone significant chemical shift changes.

In order to establish the structure of compound IV it was oxidized under phase transfer catalysis conditions at room temperature. One of the possible reaction pathways under these conditions involves Wagner-type oxidation of the exo-double bond, which leads to 9-hydroxy-9-(1'-hydroxy-1',2'-dibenzoylethyl-1')-4-azafluorene (V) (in ca. 40% yield). The second possible oxidation pathway for compound IV involves oxidation of the double bond in the enol form of the phenacyl radical. The acid generated in this manner was not isolated, but rather subjected to esterification in the form of its salt. 9-(α-Ethoxycarbonylphenacylidene)-4-azafluorene (VI) was obtained from this reaction in ca. 24% yield. Benzoic acid (in ca. 30% yield) was also isolated in these experiments, which provides further evidence for the oxidation of the enol form of compound IV.

The formation of compounds III and IV from 9-phenacyl-4-azafluorene (II) can be explained by assuming that under Michael reaction conditions polarization of the exocyclic double bond results in the formation of zwitterions, with the carbocationic centers localized in the $C_{(9)}$ position of the azafluorene fragment and on the methine carbon atom. In the latter case stabilization analogous to that observed in the cyclopentadienyl cation is possible. Reaction of the first of these two possible zwitterions with phenacyl anion leads to compound III, while the second ion gives 9-(1',2'-dibenzoylethyl)-4-azafluorene, which is further oxidized under the reaction conditions to compound IV. There is apparently an analogy between these intermediate reaction products and 9-arylaminofluorenes [4] and 9-arylaminoazafluorenes [5]. These secondary amines are intramolecular charge transfer complexes, which explains their rapid oxidation to 9-aryliminofluorenes and 9-aryliminoazafluorenes.

When the diphenacyl derivative III was heated in sulfuric acid 3'-oxo-spiro-[4-azafluorene-9,1'-indane] (VII) [1] was obtained in 46% yield; this is formed via cyclization of the phenacylidene derivative II, which is generated from compound III under the reaction conditions.

We have also prepared several functional derivatives of the spiro compound VII, including the oxime VIII, amine IX, and acetylamino derivative X, which may be of interest as physiologically active substances.

EXPERIMENTAL

PMR spectra were recorded on Bruker WP-80 (80 MHz) and WM-250 (250 MHz) spectrometers using solutions in $CDCl_3$ vs. TMS as internal standard. Multiplets were analyzed based on first order approximations. The IR spectra of compounds III, and VII-X were obtained on a UR-20 spectrophotometer (using KBr pellets), while that of compound IV was obtained on a

Specord IR-71 spectrophotometer; electronic absorption spectra were measured on a Specord UV-Vis spectrophotometer. Mass spectra were measured on an MX-1303 mass spectrometer (at 70 eV) by direct introduction of the sample into the ion source.

9,9-Diphenacyl-4-azafluorene (III) and 9-(1',2'-Dibenzoylethylidene)-4-azafluorene (IV). A. To a green solution of 1 g (5.5 mmole) 4-azafluorenone I in 20 ml 15% ethanolic KOH solution was added with stirring 5 g (40 mmole) acetophenone. The reaction mixture, which turned dark red in color, was maintained at 20°C for 20 h. The precipitate was filtered and washed with 30 ml water and then 10 ml of ether. Yield 0.76 g (34%) of compound III. Colorless crystals, mp 235-236°C (from a mixture of alcohol—acetone, 1:1). IR spectrum: 1697 cm^{-1} (CO). In the mass spectrum peaks at m/z 298 (20%) and 284 (100%) are assigned to cleavage of PhCO and $PhCOCH_2$, particles, respectively, from the M^+ ion. Found, %: C 83.2, H 5.2, N 3.7. M^+ 40.3. $C_{28}H_{21}NO_2$. Calculated, %: C 83.4, H 5.2, N 3.5. M 403.

The mother liquor was treated with 100 ml water and then with conc. HCl to an acidic reaction. The resulting precipitate was filtered and washed with 20 ml water followed by ether. Yield 0.74 g (35%) of the hydrochloride of compound IV. Dark red crystals, mp 276-279°C (from acetone). Found, %: C 76.7, H 4.8, Cl 7.8, N 3.0; M^+ 401. $C_{28}H_{19}NO_2 \cdot HCl$. Calculated, %: C 76.9, H 4.6, Cl 8.1, N 3.2. [M − HCl] 401. Free base IV. Orange crystals, mp 92-98°C (from 1:1 benzene—heptane). Found, %: N 3.6, M^+ 401. Calculated, %: N 3.5; M 401.

B. To a solution of 0.5 g (1.7 mmole) compound II in 10 ml of 15% ethanolic KOH was added 1 g (8.3 mmole) acetophenone. The reaction mixture, whose color changed from yellow to red, was treated for 20 h. The reaction products were isolated as described above in method A. Yield 0.25 g (35%) compound III and 0.35 g (50%) of the hydrochloride of compound IV, both of which were identical with the compounds described above.

9-Hydroxy-9-(1'-hydroxy-1',2'-dibenzoylethyl-1')-4-azafluorene (V). To a solution of 2.6 g (5.9 mmole) of the compound IV hydrochloride in 130 ml benzene was added 0.15 g (0.7 mmole) TEBA and 50 ml water, followed by portions of 2 g (12.7 mmole) potassium permanganate. The mixture was stirred for 12 h at 20°C, ethanol (3 ml) was added until the purple color had dissipated, and the manganese dioxide precipitate was removed by filtration and washed with benzene and water. The benzene solution was dried over magnesium sulfate. The residue remaining after solvent removal (1.2 g) was crystallized from heptane. Yield 1.14 g (40.7%) of compound V. Yellow crystals, mp 243-245°C. IR spectrum: 3600-3200 (OH), 1720 and 1680 cm^{-1} (CO). Found, %: N 3.4. $C_{28}H_{21}NO_4$. Calculated, %: N 3.2. The aqueous solution, after treatment with hydrochloric acid, yielded 0.29 g (36.7%) of benzoic acid.

9-(α-Ethoxycarbonylphenacylidene)-4-azafluorene (VI). A mixture of 1.2 g (2.7 mmole) of the hydrochloride salt of compound IV, 0.068 g (0.3 mmole) TEBA, 0.95 g (6 mmole) potassium permanganate, 130 ml benzene, and 30 ml water was stirred for 24 h. After removal of the manganese dioxide precipitate the aqueous layer was worked up with hydrochloric acid and 0.1 g (30%) of benzoic acid was obtained. The benzene layer was shaken with 50 ml of 5% KOH solution. The basic aqueous solution was then evaporated on a water bath under vacuum. The residue (0.25 g) was dried over phosphorus pentoxide and then dissolved in 25 ml absolute alcohol and refluxed for 3 h under a continuous stream of dry hydrogen chloride. The alcohol was evaporated, 10% aqueous sodium bicarbonate was added to give a pH of 8, and the mixture was extracted with 100 ml ether. Yield 0.23 g (23.7%) of compound VI, mp 158-160°C (from benzine solvent). IR spectrum: 1665 (CO), 1250 cm^{-1} (C—O—C). Found, %: N 4.1. $C_{23}H_{17}NO_3$. Calculated, %: N 3.9.

3'-Oxo-spiro-[4-azafluorene-9,1'-indane] (VII). A solution of 0.2 g (0.5 mmole) compound III in 10 ml sulfuric acid (monohydrate) was stored for 0.5 h at 50°C. After cooling the solution was neutralized with 25% ammonia solution to pH 8 and extracted with 70 ml ether; the ether extract was then dried over sodium sulfate. The residue (0.11 g) after ether evaporation was crystallized from heptane. Yield 0.065 g (46%), mp 183-184°C; a mixed probe with an authentic sample [1] melted without a mp depression. IR spectrum: 1715 cm^{-1} (CO). Found, %: N 4.6; M^+ 283. $C_{20}H_{13}NO$. Calculated, %: N 4.6; M 283.

The oxime VIII was prepared in 87% yield by refluxing ketone VII with hydroxylamine in pyridine for 12 h, mp 215-217°C (from 3:1 hexane—ethyl acetate). IR spectrum: 3200 cm^{-1} (OH). Found, %: N 9.4; M^+ 298. $C_{20}H_{14}N_{20}$. Calculated, %: N 9.4; M 298.

3'-Amino-spiro-[4-azafluorene-9,1'-indane] (IX). A solution of 0.18 g (0.6 mmole) oxime VIII and 1 ml hydrazine hydrate in 10 ml ethanol was stirred for 72 h in the presence of a catalytic quantity of Raney nickel. After the catalyst was removed 20 ml water was added to the solution and the precipitate was removed by filtration. Yield 0.12 g (70.6%) of amine IX, mp 202-204°C (from heptane). IR spectrum: 3365 cm^{-1} (NH_2). Found, %: N 9.6, M^+ 284. $C_{20}H_{16}N_2$. Calculated, %: N 9.9, M 284.

3'-Acetylamino-spiro-[4-azafluorene-9,1'-indane] (X). A mixture of 0.05 g (0.18 mmole) amine IX and 5 ml acetic anhydride was heated for 20 min at 60°C. The reaction mixture was poured into water (20 ml) and neutralized with sodium bicarbonate. the precipitate was filtered and washed with 30 ml water and 5 ml ether and then dried over phosphorus pentoxide. Yield 0.025 g (44%), mp 277-279°C. IR spectrum: 3210, 3110 (NH), 1685 cm^{-1} (CO). Found, %: N 8.8, M^+ 326. $C_{22}H_{18}N_2O$. Calculated, %: N 8.6, M 326.

LITERATURE CITED

1. N. S. Prostakov Makuli Mikhalis, N. M. Mikhailova, and N. D. Sergeeva, Khim. Geterotsikl. Soedin., No. 4, 510 (1984).
2. C. Dufraisse and A. P. Carvalno, Bull. Soc. Chim., 3(5), 882 (1936).
3. A. A. Fomichov, S. O. Lawani-Edogiawerie, and N. S. Prostakov, Org. Magn. Reson., 21, No. 5, 310 (1983).
4. Ya. F. Freimanis, A. R. Voron'ko, and V. A. Usov, Izv. Akad. Nauk Latv SSR, Ser. Khim., No. 1, 94 (1977).
5. N. S. Prostakov, V. P. Shalimov, B. Montenegro Kordova Galo, and N. I. Leonova, Khim. Geterotsikl. Soedin., No. 11, 1527 (1983).

---

^{13}C-^{13}C SPIN-SPIN COUPLING CONSTANTS IN SIX-MEMBERED RING AZAAROMATIC COMPOUNDS

A. Yu. Denisov, V. I. Mamatyuk,
and O. P. Shkurko

UDC 543.422.25:547.853.4'823'821.411

The ^{13}C-{^1H} NMR spectra of monomethyl substituted diazines, protonated at the picoline and 2-methylopyrimidine nitrogen atoms,have been analyzed, along with that of pyridine N-oxide and its 2-methyl derivatives protonated at the oxygen atom. Direct and vicinal ^{13}C-^{13}C spin-spin coupling constants (SSCC) have been measured. It was found that the ^{13}C-^{13}C SSCC in diazines follow additivity rules which are based on consideration of the number and mutual orientation or distribution of nitrogen atoms in the ring. It has also been demonstrated that increased direct $^1J_{CC}$ values involving methyl group carbon atoms in α-positions to nitrogen atoms in the aromatic ring are due to effects associated with unshared electron pairs.

The recent development of pulse NMR techniques has made the measurement of ^{13}C-^{13}C SSCC values practical and convenient; these SSCC values, in turn, can provide valuable information concerning the structure, both three-dimensional and electronic, of organic compounds [1-4]. We have previously analyzed [5] the ^{13}C-^{13}C SSCC in monosubstituted pyridines and have established linear correlations between the corresponding direct and vicinal constants in monosubstituted pyridines and benzenes (changes in these parameters are determined primarily by the electronegativities of substituents). These results, together with data concerning additivity effects of substituents on both direct and vicinal coupling constant values in benzenes [6], can be used to predict the ^{13}C-^{13}C SSCC values in six-membered

---

Novosibirsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Novosibirsk. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1243-1250, September, 1988. Original article submitted March 20, 1987.

0009-3122/88/2409-1027$12.50