CYANINE DYES FROM DERIVATIVES OF 4-, 5-, and 6-TRIFLUOROMETHYLINDOLENINES

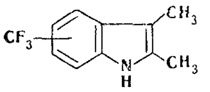
V. I. Troitskaya, I. G. Oksengendler,
S. V. Pazenok, M. S. Lyubich,
S. M. Larina, and L. M. Yagupol'skii

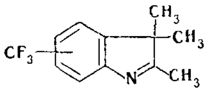
UDC 547.753.668.819.45

The synthesis of 2,3-dimethyl-5- and -6-trifluoromethylindoles and 2,3,3-trimethyl-4-, -5-, and -6-trifluoromethylindolenines, from which quaternary salts, as well as indocarbo- and di- and tricarbocyanine dyes were obtained, is described. The effect of the introduction of a trifluoromethyl group in the 4, 5, and 6 positions on the color of the indocyanine dyes is examined.

Little study has been devoted to indocyanine dyes with substituents that contain fluorine. Data on the effect of these substituents on their color and sensitizing properties have not been presented in the literature. Indole derivatives that contain fluorine in the benzene ring of the heteroring have been synthesized primarily to study their physiological activity. 5,5'-Difluoroindocarbocyanine was obtained for this purpose [1]. Information regarding dyes of various types that contain fluorinated groupings in the indole ring is limited to several patents on their application. Thus, for example, it has been proposed that styryl dyes that contain 5-CF_3 and 5-SO_2CF_3 groups be used to dye cellulose [2], that a leuco dye with a 5-SO_2CHF_2 group be used for thermographic copying of materials [3], and that a hydrazone cationic dye that contains a 5-CF_3 group be used for dyeing polyacrylonitrile fibers [4]; the bases from which the dyes were obtained were not described. In addition, a spiropyran dye that contains a fluorine atom in the 5 position is known [5].

The aim of the present research was to study the effect of trifluoromethyl groups in the 4, 5, and 6 positions of the indole ring on the color and properties of indocyanine dyes. We synthesized 5- and 6-trifluoromethylindoles I and II, as well as trifluoromethylindolenines III-V, which contain a CF_3 group in the 4, 5, and 6 positions.


I, II


III-V

I, IV 5-CF_3; II, V 6-CF_3; III 4-CF_3

Trifluoromethylindoles I and II were obtained by heating the hydrochlorides of p- and m-trifluoromethylphenylhydrazines with methyl ethyl ketone in acetic acid. Only 2,3-dimethyl-6-trifluoromethylindole (II) was isolated in the cyclization of the meta isomer, and the corresponding 4-trifluoromethyl derivative was not detected. Ring closure of methyl isopropyl ketone m-trifluoromethylphenylhydrazone in acetic acid in the presence of boron trifluoride etherate led to a mixture of isomers III and V (44 and 56%, respectively, according to the ^{19}F NMR data). After separation of the isomers, indolenine V was isolated in pure form, while base III contained ~10% indolenine V. Indolenine III was converted to a quaternary salt, viz., 2,3,3-trimethyl-4-trifluoromethylindolenine methiodide, which, after purification, did not contain isomer V. Characteristic differences are observed in the aromatic part of the PMR spectra of bases II, III, and V. The 7-H protons of indole II and indolenine V give a singlet signal (7.33 and 7.88 ppm, respectively) in the PMR spectra of its weakest field. The 5-H and 4-H protons form an AB system, which is a doublet of doublets (7.27 and 6.99 ppm for indole II and 7.61 and 7.46 ppm for base V; J_{45} = 8 and 9 Hz, respectively). In the PMR spectrum of trifluoromethylindolenine III the 5-H, 6-H, and 7-H protons give a multiplet (7.33-7.77 ppm).

Institute of Organic Chemistry, Academy of Sciences of the Ukrainian SSR, Kiev 252660. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 47-51, January, 1982. Original article submitted February 11, 1981.

0009-3122/82/1801-0039$07.50

TABLE 1. 4-, 5-, and 6-Trifluoromethylindocyanine Dyes

Compound	Position of the CF_3 group	n	X	λ_{max}, nm (in alcohol)	mp, °C (dec.)	Found, %			Empirical formula	Calc., %			Yield, %
						C	H	F		C	H	F	
X	4	1	I	510, 540[a]	297	52,2	4,2	18,3	$C_{27}H_{27}F_6IN_2$	52,3	4,4	18,4	31
XI	5	1	I	512, 542	300	52,4	4,1	18,1	$C_{27}H_{27}F_6IN_2$	52,3	4,4	18,4	44
XII	6	1	I	509, 539	250—251	52,1	4,4	18,0	$C_{27}H_{27}F_6IN_2$	52,3	4,4	18,4	31
XIII[b]	4	2	ClO_4	635	250—251	56,6	4,8	18,4	$C_{29}H_{29}ClF_6N_2O_4$	56,3	4,7	18,4	24
XIV	5	2	ClO_4	637	262—263	56,6	4,8	18,6	$C_{29}H_{29}ClF_6N_2O_4$	56,3	4,7	18,4	26
XV[c]	6	2	ClO_4	634	255—256	56,6	4,7	18,7	$C_{29}H_{29}ClF_6N_2O_4$	56,3	4,7	18,4	29
XVI	4	3	ClO_4	738	206—207	57,8	4,9	18,0	$C_{31}H_{31}ClF_6N_2O_4$	57,3	4,8	17,7	50
XVII	5	3	ClO_4	740	192—193	57,5	4,2	18,1	$C_{31}H_{31}ClF_6N_2O_4$	57,3	4,8	17,7	55
XVIII	6	3	ClO_4	736	211—212	57,6	4,8	18,0	$C_{31}H_{31}ClF_6N_2O_4$	57,3	4,8	17,7	60

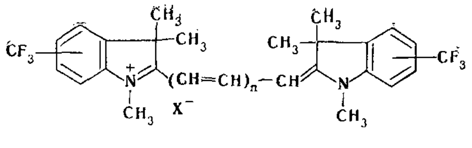
---

[a] The λ_{max} band of the corresponding unsubstituted indocarbocyanine is found at 548 nm (in alcohol). [b] ^{19}F NMR spectrum (in dimethylformamide): 7.85 ppm. [c] ^{19}F NMR spectrum (in DMF): 2 ppm.

A convenient method for the identification of indole derivatives that contain a trifluoromethyl group is the determination of the chemical shifts, which in the ^{19}F NMR spectra are singlet signals that differ for the 4 and 6 positions. Indoles, indolenines, quaternary salts, and cyanine dyes from them give a chemical shift at weak field relative to benzotrifluoride in various solvents at 6.6-8 ppm for the 4-CF_3 derivatives and at 1.9-3 ppm for the **corresponding substituted** 6-CF_3 derivatives.

Hydrolysis of the CF_3 group in indole II gave 2,3-dimethyl-6-carboxyindole (VI) [6], the structure of which has not been rigorously proved previously.

When bases I-V are heated with methyl iodide, they are converted to quaternary salts, from which indocarbo- and di- and tricarbocyanine dyes X-XVIII were synthesized. Partial oxidation of the I^- anion to the I_3^- **anion occurs** in the synthesis of di- and tricarbocyanine dyes the quaternary methiodide salts of bases III-V.



X-XII n = 1; XIII-XV n = 2; XVI-XVIII n = 3

It is apparent from the data in Table 1 that the introduction of a CF_3 group in the 4, 5, and 6 positions gives rise to a hypsochromic shift (6-9 nm) of the absorption maximum of the indocarbocyanine; as in the case of carbocyanines, an increase in the color is observed on passing from the 5- to the 4- and 6-trifluoromethyl derivatives in the indodi- and tricarbocyanine series. Lengthening of the polymethine chain by one vinylene group leads to a bathochromic shift of the absorption maximum of the dye of ~100 nm. The photographic properties of the dyes obtained will be reported later.

EXPERIMENTAL

The PMR spectra were recorded with a Tesla BS-467 spectrometer (60 MHz) with hexamethyldisiloxane (HMDS) as the external standard. The ^{19}F NMR spectra were recorded with a Tesla BS-487-B spectrometer (80 MHz); the signals at weak field were recorded relative to benzotrifluoride as the external standard. The IR spectra were obtained with a UR-20 spectrometer.

2,3-Dimethyl-5-trifluoromethylindole (I). A mixture of 1.7 g (23 mmole) of methyl ethyl ketone with 5 g (23 mmole) of p-trifluoromethylphenylhydrazine hydrochloride [7] in 5 ml of acetic acid was heated with stirring at 100°C for 1 h, after which it was diluted with water and extracted with benzene. The benzene solution was evaporated to give 1 g (20%) of indole I with mp 110-111°C (from petroleum ether with bp 40-50°C). ^{19}F NMR spectrum (in C_6H_6): 4.18 ppm. IR spectrum (KBr pellet): 830, 900, 920, 1050, 1075, 1105, 1130, 1150, 1180, 1245, 1265, 1313, 1425, 1585, 1615, 2860, 2930, 3035, 3450 cm^{-1}. Found: F 26.6%. $C_{11}H_{10}F_3N$. **Calculated: F 26.8%.**

TABLE 2. Methiodides of 4-, 5-, and 6-Trifluoromethylindolenines

Compound	Position of the CF_3 group	mp, °C (dec.)	IR spectrum, cm^{-1} (KBr pellets)	^{19}F NMR spectrum, δ, ppm[a]	Found, %				Empirical formula	Calculated, %				Yield	
					C	H	F	I		C	H	F	I	A	B
VII	4	247—248[b]	750, 810, 985, 1050, 1080, 1120, 1170, 1195, 1270, 1300, 1430, 1620, 2970, 3030	6,61 8,04[c]	42,28	4,17		34,61	$C_{13}H_{15}F_3IN$	42,3	4,1		34,4	—	80
VIII	5	214—215	830, 920, 995, 1050, 1075, 1105, 1130, 1153, 1170, 1245, 1313, 1338, 1425, 1460, 1615, 2970, 3035	1,95	42,30	4,54		34,73	$C_{13}H_{15}F_3IN$	42,3	4,1		34,4	34	84
IX	6	247	850, 915, 990, 1050, 1080, 1120, 1135, 1180, 1265, 1310, 1350, 1425, 1600, 2970, 3010	1,92	42,32	4,16	15,78		$C_{13}H_{15}F_3IN$	42,3	4,1	15,4		50	80

---

[a] In 67% aqueous CH_3CN. [b] A mixture of this compound with salt IX had mp 236°C (dec.). [c] In DMSO.

2,3-Dimethyl-6-trifluoromethylindole (II). This compound [3 g (19%)], with mp 139-140°C (from petroleum ether with bp 40-50°C), was similarly obtained from 13 g (61 mmole) of m-trifluoromethylphenylhydrazine hydrochloride [7]. PMR spectrum (in D_6-acetone): 7.33 (1H, s, 7-H); 7.27 and 6.99 (2H, dd, 5-H, 4-H, J_{45} = 8 Hz); 2.4 (3H, s, 2-CH_3); 1.93 ppm [6H, s, (3-CH_3)$_2$]. ^{19}F NMR spectrum (in C_6H_6): 3.89 ppm. IR spectrum (KBr pellet): 817, 870, 914, 1043, 1060, 1105, 1143, 1160, 1205, 1265, 1320, 1413, 1565, 1610, 2860, 2920, 3400 cm^{-1}. Found: F 26.7%. $C_{11}H_{10}F_3N$. Calculated: F 26.8%.

2,3,3-Trimethyl-5-trifluoromethylindolenine (IV). A mixture of 12.5 g (71 mmole) of p-trifluoromethylphenylhydrazine and 6.2 g (72 mmole) of methyl isopropyl ketone was heated at 70°C for 4 h, after which it was extracted with ether. The ether solution was washed with water, dried with magnesium sulfate, and evaporated. The residual 15.7 g (64 mmole) of methyl isopropyl ketone p-trifluoromethylphenylhydrazone was refluxed with 9.2 g (65 mmole) of boron trifluoride etherate in 160 ml of acetic acid for 3 h, and the precipitate was removed by filtration and washed with acetic acid. The acetic acid filtrate was evaporated *in vacuo*, and indolenine IV was extracted with ether. The ether solution was washed with an aqueous solution of sodium bicarbonate and water, dried, and evaporated. The residue was distilled in a stream of argon to give 8.1 g (50%) of indolenine IV with bp 77-78°C (0.4 hPa). Found: C 63.2; H 5.3; F 25.0%. $C_{12}H_{12}F_3N$. Calculated: C 63.4; H 5.3; F 25.2%.

2,3,3-Trimethyl-4- and -6-trifluoromethylindolenines (III and V). As in the case of base IV, from 42.8 g (0.24 mole) of m-trifluoromethylphenylhydrazine, after vacuum distillation, we obtained 36.3 g (0.16 mole) of a mixture of indolenines III and V, which was dissolved in 120 ml of anhydrous benzene and mixed with a solution of 45 g (0.21 mole) of picric acid in 230 ml of benzene. After crystallization from methanol, 58.3 g (80%) of a mixture of picrates of bases III and V was obtained. A 28-g sample of this mixture was heated with ammonium hydroxide, and the mixture was extracted with ether. The ether solution was washed with water and evaporated to give 13 g (81%) of a mixture of isomers, which, according to the ^{19}F NMR data, consisted of 44% of base III and 56% of V. A 13-g sample of the mixture of isomers was dissolved in hot petroleum ether with bp 40-50°C, the solution was cooled, and the precipitate was removed by filtration to give 2.66 g of indolenine V. The mother liquor was evaporated, and the residue was allowed to stand at 3-5°C for 24 h. The precipitate was removed by filtration and washed with petroleum ether to give another 2.64 g of isomer V. The liquid obtained after separation of indolenine V was distilled to give 4 g of III with bp 89-90°C (0.4 hPa) and 1.5 g of base V with bp 90-92°C (0.4 hPa). By separation of the mixture of isomers we were able to isolate a total of 6.64 g (52%) of base V and 4 g (31%) of indolenine III containing ~10% of isomer V.

Indolenine III (characterized in the mixture with 10% of base V) was obtained as a viscous oil with bp 89-90°C (0.4 hPa). PMR spectrum (in CCl_4): 7.33-7.77 ppm (3H, m, 5-H, 6-H, 7-H); 2.42 (3H, s, 2-CH_3); 1.55 ppm [6H, s, (3-CH_3)$_2$]. ^{19}F NMR spectrum: 6.6 (C_6H_6), 6.64 (DMF), and 7.44 ppm (DMSO). IR spectrum (pure substance): 755, 815, 930, 1050, 1090, 1120, 1160, 1240, 1250, 1310, 1380, 1415, 1450, 1490, 1650, 2860, 2930, 3070 cm^{-1}. Found: F 24.7; N 6.2%. $C_{12}H_{12}F_3N$. Calculated: F 25.1; N 6.2%. The picrate had mp 177°C (dec., from methanol). Found: F 12.7; N 12.3%. $C_{12}H_{12}F_3N \cdot C_6H_3N_3O_7$. Calculated: F 12.5; N 12.3%.

Indolenine V had mp 79-80°C (from petroleum ether with bp 40-50°C) and bp 90-92°C (0.4 hPa). PMR spectrum (in CCl_4): 7.88 (1H, s, 7-H); 7.61 and 7.46 (2H, dd, 5-H, 4-H, J_{45} = 9 Hz); 2.53 (3H, s, 2-CH_3); 1.53 ppm [6H, s, (3-CH_3)$_2$]. ^{19}F NMR spectrum: 2.05 (C_6H_6), 2.1 (DMF), and 3.09 ppm (DMSO). IR spectrum (pure substance): 830, 900, 920, 1048, 1080, 1110, 1158, 1190, 1230, 1285, 1310, 1330, 1370, 1415, 1450, 1560, 1610, 2860, 2930, 2965, 3040 cm^{-1}. Found: F 24.8; N 6.3%. $C_{12}H_{12}F_3N$. Calculated: F 25.1; N 6.2%. The picrate had mp 210°C (dec., from methanol). Found: F 12.6; N 12.3%. $C_{12}H_{12}F_3N \cdot C_6H_3N_3O_7$. Calculated: F 12.5; N 12.3%.

2,3-Dimethyl-6-carboxyindole (VI). A 0.1-g (4.7 mmole) sample of indole II was heated with 2 ml of H_2SO_4 (sp. gr. 1.83) at 110°C for 1-1.5 h until the evolution of gas bubbles ceased. The mixture was then diluted with water, and the precipitate was removed by centrifugation, transferred to a filter, and washed on the filter with water to give 0.08 g (90%) of indole VI with mp 278-280°C (from methanol with water) (mp 275-280°C [6]).

Quaternary Salts (VII-IX, Table 2). A) A 0.5-g (2.4 mmole) sample of base I or II was heated in a sealed ampul with 1.2 g (8.5 mmole) of methyl iodide in 2 ml of anhydrous alcohol at 110°C for 20 h, after which the precipitated salt was washed with ether and reprecipitated from acetone by the addition of ether.

B) A 3.5-g (15.4 mmole) sample of indolenine III-V was heated in a sealed ampul with 12 ml of methyl iodide at 100°C for 4 h. The salt was precipitated and washed with ether and reprecipitated from acetone by the addition of ether. The salts obtained from bases I and II did not depress the melting points of the salts obtained from indolenines IV and V, respectively.

Carbocyanines X-XII (Table 1). A 0.5-g (1.35 mmole) sample of the corresponding quaternary salt was refluxed for 4 h with 1 ml of ethyl orthoformate in 5 ml of pyridine. The dye was removed by filtration, washed with ether and hot water, and crystallized from alcohol or alcohol with water.

Dicarbocyanines XIII-XV. A 0.5-g (1.35 mmole) sample of the quaternary salt was refluxed with 1 ml of tetraethoxypropane in 6 ml of pyridine containing three drops of acetic anhydride for 3 h. The dye was precipitated with hexane and washed with hexane, ether, hot water, Na_2SO_3 solution, and water. It was then dissolved in alcohol, and $NaClO_4$ solution was added. The dye was crystallized twice from alcohol with water.

Tricarbocyanines XVI-XVIII. A 0.08-g (0.3 mmole) sample of glutaconic aldehyde dianil hydrochloride was added to a heated (to 30°C) suspension of 0.28 g (0.75 mmole) of the quaternary salt in 12 ml of freshly distilled acetic anhydride, after which a solution of 0.06 g (0.6 mmole) of triethylamine in 6 ml of acetic anhydride was added dropwise. A blue coloration developed after 30-40 min. The mixture was allowed to stand for 24 h, after which the dye was precipitated by the addition of an aqueous solution of Na_2SO_3. The precipitate was removed by filtration, washed with water, and dissolved in alcohol. The product was converted to the perchlorate by the addition of an aqueous solution of sodium perchlorate. The precipitate was removed by filtration and washed with water, alcohol with water (1:4 and 1:2), benzene, a mixture of benzene with ether, and ether.

LITERATURE CITED

1. M. F. Moreau, F. Lapalus, and G. Meyniel, Eur. J. Med. Chem., 9, 274 (1974).
2. I. G. Ferbenindustrie, Akt.-Ges., French Patent No. 886294; Chem. Zentralblatt, 1, 600 (1944).
3. R. G. Lemahieu, W. Janssens, and D. A. Claeys, West German Patent No. 2363453; Chem. Abstr., 81, 144255 (1975).
4. E. Schmitt and R. Raue, West German Patent No. 2039492; Chem. Abstr., 77, 7290 (1972).
5. M. A. Gal'bershtam, L. M. Mikheeva, and N. P. Samoilova, Khim. Geterotsikl. Soedin., No. 11, 1534 (1972).
6. P. E. Verkade and L. Lieste, Rec. Trav. Chim., 65, 912 (1946).
7. E. J. Forbes, M. Stacey, J. C. Tatlow, and R. T. Wragg, Tetrahedron, 8, 67 (1960).