

Reactions of 3-nitro-2-trihalomethyl-2*H*-chromenes with C-nucleophiles. Synthesis of 3-nitro-4-(pyrazol-4-yl)-2-trihalomethylchromanes

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The nucleophilic addition of acetylacetone and ethyl acetoacetate at the double bond of 3-nitro-2-trihalomethyl-2*H*-chromenes in the presence of NaH affords 2,3,4-trisubstituted chromanes containing the β -dicarbonyl fragment at position 4. The *trans*–*trans* configuration and the enol structure of the reaction products were confirmed by ¹H NMR spectroscopy and X-ray diffraction. Treatment of these compounds with hydrazine gives the corresponding 3-nitro-4-(pyrazol-4-yl)-2-trihalomethylchromanes. The reactions of 3-nitro-2-trihalomethyl-2*H*-chromenes with nitromethane and nitroethane in the presence of K₂CO₃ produce 1,3-dinitro derivatives of the chromane series.

Key words: chromenes, chromanes, nitro compounds, pyrazoles, Michael reaction, diastereomers, NMR spectroscopy, X-ray diffraction study.

2*H*-Chromene (2*H*-[1]benzopyran) and its derivatives belong to an important class of oxygen-containing heterocyclic compounds, which are widespread in plants¹ and have useful properties, including high biological activity.^{2–5} In addition, 2*H*-chromenes are reactive and can be readily prepared, due to which these compounds are successfully used in the synthesis of structurally complex natural compounds, for example, of pterocarpanes and pterocarpenes.⁶ However, data on the reactions of 2*H*-chromenes with nucleophilic reagents are scarce. It is known that the reactions of 2-aryl-3-nitrochromenes with dialkyl phosphites in the presence of triethylamine are accompanied by elimination of a nitrous acid molecule to form 4-phosphorylchromenes.⁷ Recently, we have described the synthesis of 3-benzoyl- and 3-nitro-2-trihalomethyl-2*H*-chromenes⁸ and studied the reactions of the latter with a series of S- and N-nucleophiles. It was demonstrated⁹ that the reactions proceed by a mechanism of conjugated nucleophilic addition at the C(4) atom without elimination of nitrous acid to give diastereomeric mixtures (with thiols) or individual stereoisomers (with arylamines) of 2,3,4-trisubstituted chromanes. The stereochemistry of the reaction products was established by NMR spectroscopy and X-ray diffraction. In the present study, we performed the reactions of 3-nitro-2-trihalomethyl-2*H*-chromenes with C-nucleophiles, such as acetylacetone, ethyl acetoacetate, and nitroalkanes (see the preliminary communication¹⁰). Earlier, analogous reactions have been documented only for 2-aryl-3-nitro-

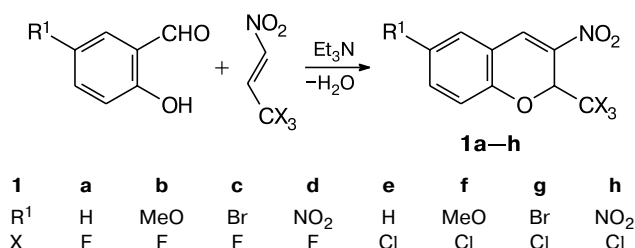
2*H*-chromenes, which react with 1-nitromethylcyclohexene¹¹ and indole¹² at the C(4) atom. By contrast, the nucleophilic addition reactions of nitroalkanes and 1,3-dicarbonyl compounds with nitroalkenes,^{13–16} including the catalytic enantioselective Michael addition,^{17–19} were studied in sufficient detail because, these reactions provide an approach to the synthesis of 1,3-dinitro compounds and other polyfunctional derivatives useful in organic synthesis.

Results and Discussion

3-Nitro-2-trihalomethyl-2*H*-chromenes **1a–h**, from which chromenes **1b,f,h** have been synthesized for the first time, were prepared by the tandem reaction (the Michael addition followed by intramolecular aldol condensation) of salicylaldehydes with 3,3,3-trifluoro(trichloro)-1-nitropropenes in the presence of triethylamine⁸ (Scheme 1).

It was demonstrated that the reactions of chromenes **1a–h** with acetylacetone and ethyl acetoacetate in THF in the presence of catalytic amounts of NaH (2–3 days, ~20 °C) proceed as the nucleophilic addition of the methylene component at the activated double bond of chromenes (Scheme 2). In all cases, after usual work-up of the reaction mixture (see the Experimental section) and recrystallization of the solid residue from a hexane–dichloromethane system, *trans*–*trans*-2,3,4-trisubstituted chromanes **2** containing the β -dicarbonyl frag-

Scheme 1

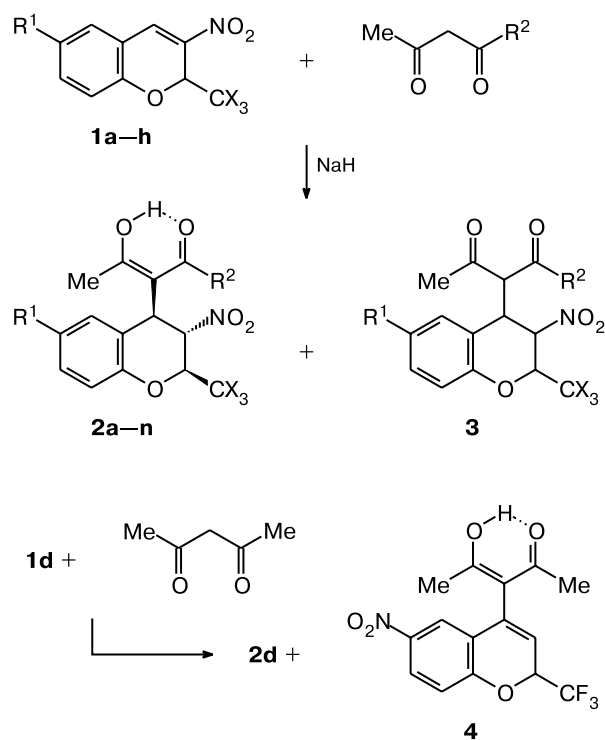


ment at position 4 were isolated in good yields (except for **2b,i**). It was found that the β -dicarbonyl fragment exists in the enol form both in a solution in CDCl₃ and in the crystalline state (X-ray diffraction data for **2i** are given below). The electron-donating MeO group at position 6 of chromenes **1** substantially decreases the reactivity of the double bond, which is manifested in low yields of products **2b** and **2i** (14 and 11%, respectively). Interestingly, the reaction of chromene **1d** is accompanied by partial elimination of a nitrous acid molecule to give a mixture of chromane **2d** and chromene **4** in a ratio of 31 : 69 (Scheme 2). Malonic and cyanoacetic esters do not react with chromenes **1c,g** under analogous conditions. Attempts to perform the reaction of ethyl acetoacetate with chromene **1e** in the presence of Et₃N by refluxing in THF for 2 h also failed.

The stereochemistry of the reaction products was assigned based on the large coupling constants ($J_{2,3} = 7.6\text{--}10.3$ Hz and $J_{3,4} = 10.4\text{--}11.5$ Hz) (Table 1), which are indicative of the axial positions of the H(2) and H(3) atoms and the pseudoaxial arrangement of the H(4) atom and, consequently, the *trans-trans* configuration of the equatorial substituents in a half-chair conformation ($J_{2,3} = 8\text{--}11$ Hz and $J_{3,4} = 10\text{--}12$ Hz were reported in the literature^{20,21} for the *trans-trans* isomers of 2,3,4-trisubstituted chromanes containing equatorial substituents).

The ¹H NMR spectroscopic study demonstrated that chromanes **2a–n** in a solution in CDCl₃ exist exclusively in the keto enol form (the presence of a narrow singlet of the enol hydroxy group at low field). As expected, the signal for the enolic proton in the spectra of adducts with ethyl acetoacetate **2i–n** is shifted upfield by approximately 4.3 ppm (from ~17.8 ppm to ~13.5 ppm) compared to that in the spectra of adducts with acetylacetone **2a–h**, which is indicative of a weakening of the intramolecular hydrogen bond in the keto enol fragment. In addition, the replacement of the methyl group with the ethoxy group causes deshielding of the H(3) and H(4) atoms by 0.31–0.40 and 0.26 ppm, respectively, and has virtually no effect on the chemical shift of the H(2) atom due, apparently, to the anisotropic and mesomeric effects of the EtO group. In the spectra of chromanes **2i–n**, the diastereotopic protons of the OCH₂Me group appear

Scheme 2



2	R ¹	R ²	X	2	R ¹	R ²	X
a	H	Me	F	h	NO ₂	Me	Cl
b	MeO	Me	F	i	H	OEt	F
c	Br	Me	F	j	Br	OEt	F
d	NO ₂	Me	F	k	H	OEt	Cl
e	H	Me	Cl	l	MeO	OEt	Cl
f	MeO	Me	Cl	m	Br	OEt	Cl
g	Br	Me	Cl	n	NO ₂	OEt	Cl

as doublets of quartets with $J = 10.8$ and 7.1 Hz at δ 4.00–4.24, and the signals of the methyl groups of compounds **2a–h** appear as singlets at δ 1.75–2.00 and 2.19–2.24.

It should be emphasized that the ¹H NMR spectra of the reaction mixtures almost always show signals of diketo form **3** (see Scheme 2), which was readily removed upon recrystallization. For example, the percentage of tautomers **3e,g** in the mother liquors obtained after purification of chromanes **2e,g** was as high as 60%; however, the configurations of these compounds were not established because of partial overlap of the signals. The ¹H NMR spectra of compounds **3e,g** in CDCl₃ are characterized by the absence of the singlet of the enol hydroxy group at low field and the presence of the doublet of the exocyclic methine proton at δ 4.44–4.46 with the constant $^3J = 10.5\text{--}10.7$ Hz, which is evidence of its *transoid* conformation with respect to the H(4) atom.

The conclusion about the keto enol structure of the β -dicarbonyl substituent in compounds **2a–n** in the crystalline state was drawn based on the IR spectra in KBr

Table 1. ^1H and ^{19}F NMR and IR spectroscopic data for chromanes **2a–n** and **7a,b**

Chro- mane	^1H NMR, CDCl_3 , δ (J/Hz)						IR, ν/cm^{-1}
	H(2)	H(3) (dd)	H(4) (d) ^a	H(5)–H(8)	OH (s)	Me (s), R ²	
2a^b	4.94 (dq, $J = 9.9$, $J = 5.1$)	5.05 ($J = 11.0$, $J = 9.9$)	4.87 ($J = 11.0$)	7.04–7.09 (m); 7.27–7.31 (m, H(7))	17.65	1.75, 2.24	1603, 1583, 1562, 1486, 1372
2b^c	4.87 (dq, $J = 9.8$, $J = 5.1$)	5.03 ($J = 11.0$, $J = 9.8$)	4.84 ($J = 11.0$)	6.55 (dd, H(5), $J = 2.9$, $J = 1.0$); 6.82 (ddd, H(7), $J = 9.0$, $J = 2.9$, $J = 0.7$); 6.99 (d, H(8), $J = 9.0$)	17.63	1.78, 2.23; 3.75 (s, MeO)	1620, 1589, 1561, 1499, 1374
2c^d	4.92 (dq, $J = 9.8$, $J = 5.0$)	5.03 ($J = 11.0$, $J = 9.8$)	4.83 ($J = 11.0$)	6.96 (d, H(8), $J = 8.7$); 7.18 (dd, H(5), $J = 2.4$, $J = 1.3$); 7.40 (ddd, H(7), $J = 8.7$, $J = 2.4$, $J = 1.0$)	17.68	1.79, 2.23	1560, 1479, 1368
2d^{e,f} (31%)	5.06–5.11 (m)	5.06 (t, ($J = 9.8$))	4.89 ($J = 9.7$)	7.23 (d, H(8), $J = 9.0$); 8.01 (dd, H(5), $J = 2.5$, $J = 1.0$); 8.21 (dd, H(7), $J = 9.0$, $J = 2.5$)	17.74	1.78, 2.27	1650, 1617, 1572, 1519, 1479, 1344
2e	5.43 (d, $J = 7.8$)	5.23 ($J = 11.5$, $J = 7.8$)	4.73 ($J = 11.5$)	7.06–7.11 (m, H(6), H(8)); 7.13 (d, H(5), $J = 8.0$); 7.31 (tm, H(7), $J = 7.8$)	17.79	1.96, 2.20	1583, 1555, 1483, 1368
2f	5.37 (d, $J = 7.6$)	5.22 ($J = 11.4$, $J = 7.6$)	4.71 ($J = 11.4$)	6.57 (dd, H(5), $J = 2.9$, $J = 1.1$); 6.83 (ddd, H(7), $J = 8.9$, $J = 2.9$, $J = 0.8$); 7.05 (d, H(8), $J = 8.9$)	17.78	2.00, 2.19; 3.75 (s, MeO)	1609, 1562, 1495, 1364
2g	5.43 (d, $J = 7.7$)	5.21 ($J = 11.5$, $J = 7.7$)	4.69 ($J = 11.5$)	7.02 (d, H(8), $J = 8.6$); 7.17 (dd, H(5), $J = 2.3$, $J = 1.3$); 7.43 (ddd, H(7), $J = 8.6$, $J = 2.3$, $J = 1.0$)	17.82	1.99, 2.19	1625, 1562, 1475, 1362
2h	5.58 (d, $J = 7.8$)	5.24 ($J = 11.6$, $J = 7.8$)	4.74 ($J = 11.6$)	7.28 (d, H(8), $J = 8.9$); 7.99 (dd, H(5), $J = 2.5$, $J = 1.2$); 8.24 (ddd, H(7), $J = 8.9$, $J = 2.5$, $J = 0.7$)	17.87	1.97, 2.21	1586, 1569, 1519, 1482, 1343
2i^g	4.87 (dq, $J = 10.3$, $J = 5.2$)	5.38 (t, $J = 10.3$)	4.61 ($J = 10.5$)	6.98–7.02 (m); 7.19–7.24 (m, H(7))	13.31	0.88 (t, $J = 7.1$); 2.13; 4.00, 4.05 (both dq, $J = 10.7$, $J = 7.1$)	1648, 1612, 1567, 1487, 1372
2j^h	4.86 (dq, $J = 10.3$, $J = 5.2$)	5.34 (t, $J = 10.2$)	4.57 ($J = 10.4$)	6.90 (d, H(8), $J = 8.7$); 7.11 (dd, H(5), $J = 2.3$, $J = 1.0$); 7.33 (ddd, H(7), $J = 8.7$, $J = 2.3$, $J = 0.7$)	13.34	0.94 (t, $J = 7.1$); 2.13; 4.08 (q, $J = 7.1$)	1649, 1615, 1559, 1479, 1374
2k	5.41 (d, $J = 7.9$)	5.63 ($J = 10.9$, $J = 7.9$)	4.47 ($J = 10.9$)	6.97 (dt, H(5), $J = 7.8$, $J = 1.0$); 7.01 (td, H(6), $J = 7.6$, $J = 0.9$); 7.07 (dd, H(8), $J = 8.1$, $J = 0.9$); 7.25 (ddd, H(7), $J = 8.1$, $J = 1.6$, $J = 0.7$)	13.52	1.01 (t, $J = 7.1$); 2.08 (d, $J = 0.5$); 4.08, 4.21 (both dq, $J = 10.8$, $J = 7.1$)	1636, 1617, 1588, 1556, 1486, 1364
2l	5.36 (d, $J = 7.7$)	5.62 ($J = 10.9$, $J = 7.7$)	4.45 ($J = 10.9$)	6.49 (dd, H(5), $J = 2.9$, $J = 1.1$); 6.78 (ddd, H(7), $J = 8.8$, $J = 2.9$, $J = 0.7$); 6.99 (d, H(8), $J = 8.8$)	13.52	1.06 (t, $J = 7.1$); 2.08; 3.74 (s, MeO); 4.10, 4.24 (both dq, $J = 10.8$, $J = 7.1$)	1648, 1602, 1559, 1495, 1371
2m	5.41 (d, $J = 7.8$)	5.58 ($J = 10.9$, $J = 7.8$)	4.43 ($J = 10.9$)	6.96 (d, H(8), $J = 8.6$); 7.07 (dd, H(5), $J = 2.3$, $J = 1.3$); 7.36 (ddd, H(7), $J = 8.6$, $J = 2.3$, $J = 0.8$)	13.55	1.06 (t, $J = 7.1$); 2.09; 4.16, 4.23 (both dq, $J = 10.7$, $J = 7.1$)	1646, 1612, 1566, 1476, 1383
2n	5.53 (d, $J = 8.0$)	5.60 ($J = 10.8$, $J = 8.0$)	4.49 ($J = 10.8$)	7.21 (d, H(8), $J = 8.9$); 7.90 (dd, H(5), $J = 2.6$, $J = 1.3$); 8.19 (ddd, H(7), $J = 8.9$, $J = 2.6$, $J = 0.8$)	13.59	1.02 (t, $J = 7.1$); 2.11; 4.13, 4.23 (both dq, $J = 10.8$, $J = 7.1$)	1650, 1610, 1589, 1567, 1522, 1484, 1340

(to be continued)

Table 1 (continued)

Chro- mane	¹ H NMR, CDCl ₃ , δ (J/Hz)						IR, ν/cm ⁻¹
	H(2)	H(3) (dd)	H(4) (d) ^a	H(5)—H(8)	OH (s)	Me (s), R ²	
7a	5.04—5.10 (m)	5.28—5.34 (m)	5.04—5.10 (m)	7.00 (dd, H(8), <i>J</i> = 8.2, <i>J</i> = 1.0); 7.03 (td, H(6), <i>J</i> = 7.5, <i>J</i> = 1.1); 7.12 (br.d, H(5), <i>J</i> = 7.5); 7.24 (td, H(7), <i>J</i> = 7.6, <i>J</i> = 1.5)	17.58	1.78, 2.29; 7.44 (s, Ph)	1608, 1580, 1552, 1482, 1373
7aⁱ (enol, 80%)	5.58 (d, <i>J</i> = 9.3)	5.45 (<i>J</i> = 10.7, <i>J</i> = 9.5)	5.16 (<i>J</i> = 10.9)	6.93—7.25 (m)	16.2—17.2 (br.s)	1.88, 2.25 (both br.s); 7.42—7.60 (m, Ph)	—
7aⁱ (keto form, 20%)	5.15 (d, <i>J</i> = 9.0)	5.51 (<i>J</i> = 9.0, <i>J</i> = 6.8)	4.51 (t, <i>J</i> = 5.9)	6.93—7.27 (m)	—	1.84, 2.11; 4.71 (d, <i>J</i> = 4.9, CH); 7.42—7.60 (m, Ph)	—
7b	5.23 (d, <i>J</i> = 9.8)	5.37 (t, <i>J</i> = 10.2)	4.82 (<i>J</i> = 10.5)	6.93—6.98 (m, H(6), H(8); 7.05 (br.d, H(5), <i>J</i> = 7.7); 7.17 (br.t, H(7), <i>J</i> = 7.7)	13.23	0.93 (t, <i>J</i> = 7.1); 2.17; 4.03 (q, <i>J</i> = 7.1); 7.42 (s, Ph)	1648, 1634, 1613, 1584, 1548, 1487, 1371

^a The doublet for H(4) is broadened due to splitting on the H(5) and H(7) atoms.

^b ¹⁹F NMR: 84.73 (d, CF₃, *J* = 5.1 Hz).

^c ¹⁹F NMR: 84.79 (d, CF₃, *J* = 5.1 Hz).

^d ¹⁹F NMR: 84.77 (d, CF₃, *J* = 5.0 Hz).

^e ¹⁹F NMR: 84.81 (d, CF₃, *J* = 4.6 Hz).

^f A mixture with 3-(6-nitro-2-trifluoromethyl-2*H*-chromen-4-yl)pentane-2,4-dione (**4**); ¹H NMR (δ) of **4** (69%): 1.97 and 2.04 (both s, 3 H each, Me); 5.45 (qd, 1 H, H(2), *J*_{H,F} = 6.4 Hz, *J* = 4.1 Hz); 5.80 (d, 1 H, H(3), *J* = 4.1 Hz); 7.08 (d, 1 H, H(8), *J* = 8.9 Hz); 7.90 (d, 1 H, H(5), *J* = 2.6 Hz); 8.16 (dd, 1 H, H(7), *J* = 8.9 Hz, *J* = 2.6 Hz); 16.77 (s, 1 H, OH); ¹⁹F NMR: 82.59 (d, CF₃, *J* = 6.4 Hz).

^g ¹⁹F NMR: 84.54 (d, CF₃, *J* = 5.2 Hz).

^h ¹⁹F NMR: 84.56 (d, CF₃, *J* = 5.2 Hz).

ⁱ In DMSO-*d*₆.

pellets. In the spectra of chromanes **2a—h**, the ν(C=O) band at ~1700 cm⁻¹ is absent and a broad (sometimes with several shoulders) band at 1570—1560 cm⁻¹ characteristic of the enol form of β-diketone is observed. In the spectra of chromanes **2i—n**, the signal of the carbonyl group of the ester fragment involved in intramolecular hydrogen bonding with the enol hydroxy group appears as an intense band at 1650—1640 cm⁻¹ with a weak shoulder at ~1720 cm⁻¹ (is not given in Table 1), which is, apparently, attributed to the presence of the unconjugated COOEt group.

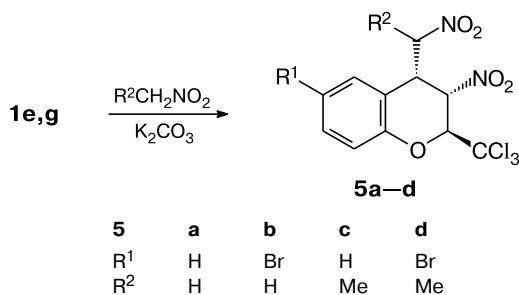
The use of DMSO-*d*₆ instead of CDCl₃ in the case of chromane **2a** generated from chromene **1a** and acetylacetone leads to the appearance of the second set of signals in the ¹H NMR spectrum, which was assigned to diketone form **3a** (19%, δ: 2.00 and 2.05 (both s, 3 H each, Me); 4.40 (dd, 1 H, H(4), *J* = 6.6 Hz, *J* = 5.0 Hz); 4.67 (d, 1 H, CH, *J* = 6.6 Hz); 5.35—5.42 (m, 1 H, H(2)); 5.51 (dd, 1 H, H(3), *J* = 7.8 Hz, *J* = 5.0 Hz); 7.10—7.17 (m, 2 H, H(8), H(6)); 7.29—7.37 (m, 2 H, H(7), H(5))). The protons of enol form **2a** appear in the spectrum in DMSO-*d*₆ as broadened signals due to partial destruction of the intramolecular hydrogen bond and the formation

of an intermolecular hydrogen bond with the basic solvent molecules (81%, δ: 1.94 and 2.21 (both br.s, 3 H each, Me); 5.01 (br.d, 1 H, H(4), *J* ≈ 8.0 Hz); 5.38—5.46 (br.s, 1 H, H(2)); 5.70 (br.s, 1 H, H(3)); 7.00—7.08 (br.m, 3 H, H(5), H(6), H(8)); 7.20—7.27 (br.m, 1 H, H(7)); 10.50—11.50 (br.s, 0.2 H, OH (intermolecular H bond)); 15.20 (br.s, 0.8 H, OH (intramolecular H bond))). An analogous but an even more complex spectral pattern is observed in DMSO-*d*₆ for adduct with ethyl acetoacetate **2i**. In this case, the enol tautomer with an intermolecular hydrogen bond predominates. The chemical shifts of this tautomer differ from those of the corresponding protons of the enol form with an intramolecular hydrogen bond. Diketo form **3i** contains an additional exocyclic chiral center, resulting in the appearance of four sets of signals in the spectra. Two main sets were assigned to enol with an intermolecular hydrogen bond (53%, δ: 0.88 (br.s, 3 H, MeCH₂); 2.39 (s, 3 H, Me); 3.90 (br.s, 2 H, CH₂); 5.22 (br.s, 1 H, H(4)); 5.45 (t, 1 H, H(3), *J* = 10.3 Hz); 5.64—5.72 (m, 1 H, H(2)); 6.95—7.20 (m, 4 H, arom.); 10.97 (s, 1 H, OH)) and enol with an intramolecular hydrogen bond (31%, δ: 0.78 (t, 3 H, MeCH₂, *J* = 7.1 Hz); 2.12 (s, 3 H, Me); 3.90—4.07 (m,

2 H, CH₂); 4.94 (d, 1 H, H(4), $J = 10.7$ Hz); 5.34 (t, 1 H, H(3), $J = 10.4$ Hz); 5.63–5.70 (m, 1 H, H(2)); 7.05–7.30 (m, 4 H, arom.); 13.18 (s, 1 H, OH)). Diketo form **3i** exists as two diastereomers in a ratio of 1 : 1 in equilibrium with the above enols (16%, δ : 0.99 and 1.01 (both t, 3 H, MeCH₂, $J = 7.1$ Hz); 2.15 and 2.17 (both s, 3 H each, Me); 4.37 (d, 1 H, CH, $J = 5.5$ Hz); 4.41–4.43 (m, 2 H, H(4), CH); 4.45 (t, 1 H, H(4), $J = 5.5$ Hz), other protons are not observed due to overlap of their signals). The validity of the assignment of the signals in the ¹H NMR spectra of compounds **2a** and **2i** in DMSO-*d*₆ was confirmed by the ¹⁹F NMR spectroscopic data for the same samples recorded after 3 days for **2a** and after 2 days for **2i**. ¹⁹F NMR for **2a**: 81%, 86.41 (br.s, 0.2 CF₃, enol with an intermolecular H bond), 86.79 (br.s, 0.8 CF₃, enol with an intramolecular H bond); 19%, 87.46 (d, CF₃, diketo form **3a**, $J = 6.5$ Hz). ¹⁹F NMR for **2i**: 84%, 86.33 (d, 0.4 CF₃, enol with an intramolecular H bond, $J = 5.7$ Hz), 86.36 (d, 0.6 CF₃, enol with an intermolecular H bond, $J = 5.6$ Hz); 16%, 87.22 (d, CF₃, diketo form **3i**, $J = 6.2$ Hz), 87.42 (d, CF₃, diketo form **3i**, $J = 6.3$ Hz). In addition, both spectra show a doublet at δ 85.90 with $J = 6.8$ Hz belonging to the CF₃ group of the starting chromene **1a** (23% for **2a** and 6% for **2i**), which is indicative of instability of chromanes **2** in a solution of dimethyl sulfide.

We studied the reactions of 2-CCl₃-chromenes **1e,g** with nitromethane and nitroethane and found that these CH-acids are also readily added to the nitroalkene fragment in the presence of K₂CO₃ (2–3 days, ~20 °C) to form 3-nitro-4-nitroalkyl-2-(trichloromethyl)chromanes **5a–d** (Scheme 3). Attempts to perform the reaction of chromene **1e** with 2-nitropropane either in the presence of K₂CO₃ or by heating in an ethanolic solution in the presence of a catalytic amount of piperidine failed,²² which is apparently attributed to the steric factor manifested in unfavorable interactions between the *peri*-H(5) atom and the substituents at the exocyclic carbon atom.

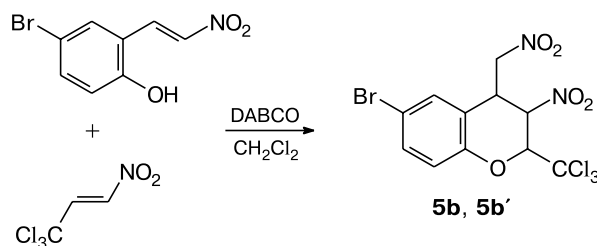
Scheme 3



Chromanes **5a–d** were prepared in 50–61% yields after recrystallization of the reaction mixture from hexane or a hexane–dichloromethane mixture. The stereo-

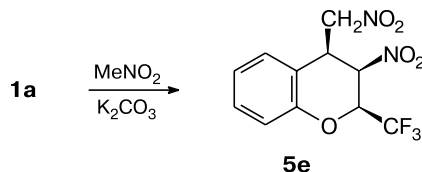
chemistry of these compounds (except for the configuration of the exocyclic carbon atom in **5c,d**) was established based on analysis of the spin-spin coupling constants and the 2D NOESY experiment (Table 2). The moderate coupling constants ($J_{2,3} = 4.7$ – 6.3 Hz and $J_{3,4} = 4.6$ – 5.4 Hz) for chromanes **5a–d** are indicative of their *trans*–*cis* configuration.⁹ This is confirmed by the 2D NOESY spectrum of compound **5b**, in which the cross-peak is observed only between the H(3) and H(4) protons. It should be noted that the reaction of chromene **1g** and nitromethane produced a mixture of two diastereomers, *viz.*, *trans*–*cis* diastereomer **5b** (73%) and **5b'** (27%, the stereochemistry was not determined) with $J_{2,3} = 6.1$ Hz and $J_{3,4} = 3.8$ Hz. From this mixture, isomer **5b** was isolated by recrystallization. A mixture of the same compounds in the **5b** : **5b'** ratio of 53 : 47 was prepared in 40% yield by the reaction of *trans*-4-bromo-2-(2-nitrovinyl)phenol with 3,3,3-trichloro-1-nitropropene in the presence of DABCO according to a known procedure²³ (CH₂Cl₂, ~20 °C, 2 days) (Scheme 4).

Scheme 4



Interestingly, the reaction of 3-nitro-2-trifluoromethyl-2*H*-chromene (**1a**) with nitromethane under the conditions used for 2-CCl₃-chromenes **1e,g** produced chromane **5e** in 56% yield as the *cis*–*cis* diastereomer with $J_{2,3} = 2.7$ Hz and $J_{3,4} = 3.5$ Hz. In this case, the conclusion about the *cis*–*cis* configuration was drawn based on the chemical shifts of the H(3) and H(2) protons, which differ by 0.74 ppm (earlier,⁹ we have reported $\Delta\delta = \delta_{H(3)} - \delta_{H(2)} = 0.7$ – 1.1 ppm for 2-CF₃-substituted *cis*–*cis*-chromanes) (Scheme 5).

Scheme 5



Due to the presence of the β -dicarbonyl fragment, compounds **2a–n** are of interest as polyfunctional substrates for the synthesis of more complex molecules, in

Table 2. ^1H NMR and IR spectroscopic data for chromanes **5a–e**

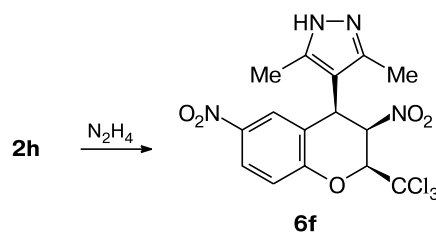
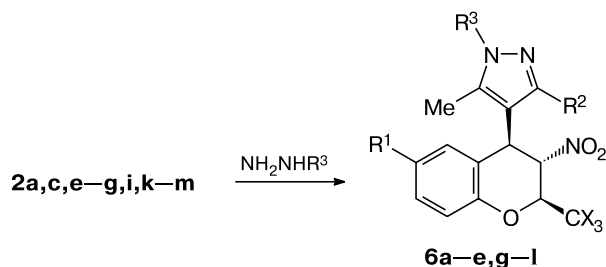
Chro- mane	^1H NMR, CDCl_3 , δ (J/Hz)					IR, ν/cm^{-1}
	H(2) (d)	H(3)	H(4)	H(5)–H(8)	CH(R ²)	
5a	5.58 ($J = 6.5$)	5.39 (dd, $J = 6.5$, $J = 5.3$)	4.50 (dt, $J = 9.3$, $J = 5.4$)	7.12 (td, H(6), $J = 7.5$, $J = 1.1$); 7.16 (d, H(8), $J = 8.2$); 7.17 (dd, H(5), $J = 7.8$, $J = 1.7$); 7.37 (ddd, H(7), $J = 8.2$, $J = 7.3$, $J = 1.7$)	4.68 (dd, CHH , $J = 13.8$, $J = 5.4$); 4.81 (dd, CHH , $J = 13.8$, $J = 9.3$)	1555, 1487, 1377
5b (73%)	5.56 ($J = 6.3$)	5.38 (dd, $J = 6.3$, $J = 5.4$)	4.47 (dt, $J = 9.0$, $J = 5.4$)	7.06 (d, H(8), $J = 8.6$); 7.31 (d, H(5), $J = 2.2$); 7.49 (dd, H(7), $J = 8.6$, $J = 2.2$)	4.68 (dd, CHH , $J = 14.1$, $J = 5.5$); 4.80 (dd, CHH , $J = 14.1$, $J = 9.0$)	1553, 1481, 1376
5b' (27%)	5.30 ($J = 6.1$)	5.43 (dd, $J = 6.1$, $J = 3.8$)	4.27 (td, $J = 6.9$, $J = 3.8$)	7.11 (d, H(8), $J = 8.6$); 7.37 (d, H(5), $J = 2.2$); 7.51 (dd, H(7), $J = 8.6$, $J = 2.2$)	4.62 (dd, CHH , $J = 14.6$, $J = 6.7$); 4.87 (dd, CHH , $J = 14.6$, $J = 7.0$)	—
5c	5.56 ($J = 4.8$)	5.39 (t, $J = 4.7$)	4.18 (dd, $J = 8.7$, $J = 4.6$)	7.08–7.16 (m); 7.34 (ddd, H(7), $J = 8.4$, $J = 7.2$, $J = 1.7$)	1.81 (d, Me, $J = 6.7$); 5.20 (dq, CHMe , $J = 8.7$, $J = 6.7$)	1562, 1547, 1489, 1360
5d	5.55 ($J = 4.7$)	5.37 (t, $J = 4.7$)	4.15 (dd, $J = 8.3$, $J = 4.7$)	7.03 (d, H(8), $J = 8.6$); 7.26 (d, H(5), $J = 2.2$); 7.46 (dd, H(7), $J = 8.6$, $J = 2.2$)	1.80 (d, Me, $J = 6.7$); 5.16 (dq, CHMe , $J = 8.3$, $J = 6.7$)	1557, 1480, 1360
5e*	4.69 (qd, $J = 5.9$, $J = 2.7$)	5.43 (t, $J = 2.9$)	4.28 (dt, $J = 9.5$, $J = 3.5$)	7.09 (dd, H(8), $J = 8.3$, $J = 1.1$); 7.15 (td, H(6), $J = 7.5$, $J = 1.1$); 7.25–7.27 (m, H(5)); 7.34 (dddd, H(7), $J = 8.2$, $J = 7.3$, $J = 1.6$, $J = 0.6$)	4.70 (dd, CHH , $J = 14.3$, $J = 9.5$); 4.86 (dd, CHH , $J = 14.3$, $J = 3.6$)	1566, 1490, 1376

* ^{19}F NMR (CDCl_3): 87.67 (d, CF_3 , $J = 5.9$ Hz).

particular, of various chromane derivatives containing a heterocyclic substituent at position 4. In recent years, such structures have attracted increasing attention because some of these compounds have high pharmacological activity (for example, the calcium channel activator cromakalim, *viz.*, 3-hydroxy-2,2-dimethyl-4-(2-oxopyrrolidin-1-yl)chromane-6-carbonitrile, has antihypertensive activity).^{3–5}

In the present study, we examined the reactions of compounds **2** with hydrazines in ethanol at $\sim 20^\circ\text{C}$ with the aim of developing a new method for the synthesis of 4-heterylchromanes with potential biological activity. The reactions with hydrazine hydrate and methylhydrazine produced *trans-trans*-4-pyrazolylchromanes **6a–e,g–l** (in 30–84% yields, Scheme 6) with the constants $J_{2,3} = 7.6$ –9.8 Hz and $J_{3,4} = 11.1$ –11.7 Hz. These constants are virtually equal both in $\text{DMSO}-d_6$ and CDCl_3 (Table 3), which indicates that, in these solvents, 4-pyrazolylchromanes **6** adopt a half-chair conformation the containing substituents in equatorial positions. Under the conditions examined in the present study, the reactions of compounds **2a,e** with phenylhydrazine and hydroxylamine proceed ambiguously to give unidentifiable mixtures of products.

Therefore, heterocyclization of the β -dicarbonyl group with hydrazine or methylhydrazine does not lead to a change in stereochemistry of the pyran ring. The only exception is *trans-trans*-3,6-dinitrochromane **2h**, whose

Scheme 6

6	R ¹	R ²	R ³	X	6	R ¹	R ²	R ³	X
a	H	Me	H	F	g	H	Me	Me	F
b	Br	Me	H	F	h	Br	Me	Me	Cl
c	H	Me	H	Cl	i	H	OH	H	F
d	MeO	Me	H	Cl	j	H	OH	H	Cl
e	Br	Me	H	Cl	k	MeO	OH	H	Cl
f	NO ₂	Me	H	Cl	l	Br	OH	H	Cl

reaction with hydrazine hydrate is accompanied by a change in the configuration at the C(3) atom to give

Table 3. ^1H and ^{19}F NMR and IR spectroscopic data for pyrazolylchromanes **6a–l** and **8a,b**

Chro- mane	¹ H NMR, δ (J/Hz)						IR, ν/cm^{-1}
	H(2) (d)	H(3) (dd)	H(4) (d) ^a	H(5)—H(8)	R ³	Me (br.s), R ²	
6a ^{b,c}	5.79 (dq, <i>J</i> = 9.7, <i>J</i> = 5.5	5.09 (<i>J</i> = 11.2, <i>J</i> = 9.7)	4.98 (<i>J</i> = 11.2)	6.77 (d, H(5), <i>J</i> = 7.7); 7.01 (t, H(6), <i>J</i> = 7.6); 7.07 (d, H(8), <i>J</i> = 8.2); 7.28 (t, H(7), <i>J</i> = 7.7)	12.36 (s)	1.83, 1.99	3247, 1587, 1563, 1486, 1368
6a ^{d,e}	4.94—5.00 (m)		4.81 (<i>J</i> = 11.1)	6.84 (dt, H(5), <i>J</i> = 7.8, <i>J</i> = 1.2); 6.99 (td, H(6), <i>J</i> = 7.7, <i>J</i> = 1.2); 7.05 (dd, H(8), <i>J</i> = 8.2, <i>J</i> = 1.2); 7.26 (m, H(7))	3.70—4.70 (br.s)	2.07	—
6b ^{b,f}	5.81 (dq, <i>J</i> = 9.8, <i>J</i> = 5.1)	5.13 (<i>J</i> = 11.2, <i>J</i> = 9.9)	5.01 (<i>J</i> = 11.2)	6.85 (dd, H(5), <i>J</i> = 2.0, <i>J</i> = 1.0); 7.08 (d, H(8), <i>J</i> = 8.7); 7.46 (dd, H(7), <i>J</i> = 8.7, <i>J</i> = 1.8)	12.41 (s)	1.84, 2.01	3207, 3146, 1564, 1479, 1367
6c ^b	5.80 (<i>J</i> = 8.2)	5.05 (<i>J</i> = 11.3, <i>J</i> = 8.3)	4.90 (<i>J</i> = 11.4)	6.75 (d, H(5), <i>J</i> = 7.6); 7.03 (t, H(6), <i>J</i> = 7.5); 7.09 (d, H(8), <i>J</i> = 8.0); 7.31 (t, H(7), <i>J</i> = 7.6)	12.40 (br.s)	1.90, 2.06	3231, 1590, 1561, 1515, 1485, 1363
6c ^d	5.48 (<i>J</i> = 7.7)	5.16 (<i>J</i> = 11.4, <i>J</i> = 7.7)	4.68 (<i>J</i> = 11.4)	6.84 (dt, H(5), <i>J</i> = 7.7, <i>J</i> = 1.2); 7.01 (td, H(6), <i>J</i> = 7.6, <i>J</i> = 1.2); 7.12 (dd, H(8), <i>J</i> = 8.2, <i>J</i> = 1.2); 7.29 (dm, H(7), <i>J</i> = 7.8)	4.60—5.50 (br.s)	2.17	—
6d ^b	5.72 (<i>J</i> = 7.9)	5.03 (<i>J</i> = 11.3, <i>J</i> = 8.0)	4.84 (<i>J</i> = 11.3)	6.23 (d, H(5), <i>J</i> = 2.9); 6.89 (dd, H(7), <i>J</i> = 8.8, <i>J</i> = 2.9); 7.04 (d, H(8), <i>J</i> = 8.8)	12.42 (s)	1.94, 2.05, 3.62 (s, MeO)	3190, 3136, 1611, 1564, 1496, 1365
6e ^b	5.84 (<i>J</i> = 8.0)	5.03 (<i>J</i> = 11.4, <i>J</i> = 8.0)	4.94 (<i>J</i> = 11.4)	6.81 (dd, H(5), <i>J</i> = 2.3, <i>J</i> = 1.1); 7.09 (d, H(8), <i>J</i> = 8.7); 7.49 (ddd, H(7), <i>J</i> = 8.7, <i>J</i> = 2.3, <i>J</i> = 0.8)	11.70—13.30 (br.s)	1.92, 2.05	3200, 3139, 1589, 1565, 1475, 1361
6e ^d	5.48 (<i>J</i> = 7.6)	5.14 (<i>J</i> = 11.5, <i>J</i> = 7.6)	4.63 (<i>J</i> = 11.5)	6.95 (dd, H(5), <i>J</i> = 2.2, <i>J</i> = 1.2); 7.01 (d, H(8), <i>J</i> = 8.6); 7.40 (ddd, H(7), <i>J</i> = 8.6, <i>J</i> = 2.2, <i>J</i> = 0.9)	4.60—6.40 (br.s)	2.17	—
6f ^b	5.06—5.09 (m)	6.06 (t, <i>J</i> = 4.0)	5.06—5.09 (m)	7.37 (d, H(8), <i>J</i> = 9.0); 7.54 (d, H(5), <i>J</i> = 2.0); 8.22 (dd, H(7), <i>J</i> = 9.0, <i>J</i> = 2.3)	12.54 (s)	1.87, 2.12	3205, 1618, 1587, 1565, 1519, 1480, 1342
6g ^b	5.78 (dq, <i>J</i> = 9.8, <i>J</i> = 5.2)	5.10 (<i>J</i> = 11.2, <i>J</i> = 9.8)	4.98 (<i>J</i> = 11.2)	6.77 (d, H(5), <i>J</i> = 7.7); 7.01 (t, H(6), <i>J</i> = 7.6); 7.07 (d, H(8), <i>J</i> = 8.0); 7.28 (t, H(7), <i>J</i> = 7.7)	3.65 (s)	1.69, 2.12	1575, 1564, 1552, 1487, 1370
6g ^{d,g}	4.92—5.00 (m)		4.76 (br.s)	6.87 (d, H(5), <i>J</i> = 7.7); 6.97 (t, H(6), <i>J</i> = 7.6); 7.04 (d, H(8), <i>J</i> = 8.2); 7.25 (t, H(7), <i>J</i> = 7.7)	3.74 (s)	1.83, 2.13	—
6h ^{b,h}	5.83 (<i>J</i> = 7.8)	5.03 (br.s)	4.95 (<i>J</i> = 11.3)	6.83 (br.s, H(5)); 7.09 (d, H(8), <i>J</i> = 8.7); 7.49 (dd, H(7), <i>J</i> = 8.7, <i>J</i> = 2.4)	3.69 (s)	1.82, 2.13	1558, 1473, 1364
6h ^{d,i}	5.46 (<i>J</i> = 7.6)	5.15 (<i>J</i> = 11.7, <i>J</i> = 7.6)	4.55 (<i>J</i> = 11.7)	6.97 (br.s, H(5)); 7.01 (d, H(8), <i>J</i> = 8.6); 7.39 (ddd, H(7), <i>J</i> = 8.6, <i>J</i> = 2.3, <i>J</i> = 0.8)	3.78 (s)	2.06, 2.14 (both s)	—
6i ^{b,j}	5.73 (<i>J</i> = 9.8, <i>J</i> = 5.9)	5.35 (<i>J</i> = 11.1, <i>J</i> = 9.8)	4.76 (<i>J</i> = 11.1)	6.82 (dt, H(5), <i>J</i> = 7.7, <i>J</i> = 1.2); 6.97—7.04 (m, H(6), H(8)); 7.24 (br.t, H(7), <i>J</i> = 7.8)	9.00—12.30 (br.s)	2.06 (s), 9.00—12.30 (br.s)	3400, 1613, 1586, 1561, 1538, 1485, 1375
6j ^b	5.72 (<i>J</i> = 8.3)	5.39 (<i>J</i> = 11.2, <i>J</i> = 8.3)	4.67 (<i>J</i> = 11.2)	6.79 (d, H(5), <i>J</i> = 7.6); 7.00 (t, H(6), <i>J</i> = 7.5); 7.03 (d, H(8), <i>J</i> = 8.1); 7.26 (t, H(7), <i>J</i> = 7.7)	11.20—11.80 (br.s)	2.05 (s), 9.50—10.20 (br.s)	3391, 1612, 1588, 1558, 1534, 1486, 1369

(to be continued)

Table 3 (continued)

Chro- mane	¹ H NMR, δ (J/Hz)						IR, ν/cm ⁻¹
	H(2) (d)	H(3) (dd)	H(4) (d) ^a	H(5)—H(8)	R ³	Me (br.s), R ²	
6k^b	5.64 (<i>J</i> = 8.0)	5.36 (<i>J</i> = 11.1, <i>J</i> = 8.0)	4.62 (<i>J</i> = 11.1)	6.29 (dd, H(5), <i>J</i> = 2.9, <i>J</i> = 0.9); 6.85 (dd, H(7), <i>J</i> = 8.8, <i>J</i> = 2.9); 6.99 (d, H(8), <i>J</i> = 8.8)	11.40—11.70 (br.s)	2.04 (s), 3.63 (s, MeO), 9.70—10.10 (br.s)	3393, 1605, 1564, 1541, 1488, 1364
6l^b	5.77 (<i>J</i> = 8.3)	5.36 (<i>J</i> = 11.2, <i>J</i> = 8.3)	4.71 (<i>J</i> = 11.2)	6.86 (dd, H(5), <i>J</i> = 2.3, <i>J</i> = 1.1); 7.03 (d, H(8), <i>J</i> = 8.6); 7.45 (ddd, H(7), <i>J</i> = 8.6, <i>J</i> = 2.3, <i>J</i> = 0.7)	11.40—11.70 (br.s)	2.06 (s), 9.70—10.30 (br.s)	3414, 3364, 1609, 1564, 1539, 1475, 1366
8a^b	5.59 (<i>J</i> = 9.5)	5.25 (t, <i>J</i> = 10.4)	5.03 (<i>J</i> = 11.3)	6.80 (d, H(5), <i>J</i> = 7.4); 6.92—6.98 (m, H(6), H(8)); 7.22 (t, H(7), <i>J</i> = 7.5); 7.40—7.62 (m, Ph)	12.24 (s)	1.77, 2.07	3198, 1610, 1582, 1554, 1485, 1368
8b^b	5.54 (<i>J</i> = 9.8)	5.40 (t, <i>J</i> = 10.4)	4.85 (<i>J</i> = 10.9)	6.86 (d, H(5), <i>J</i> = 7.6); 6.92 (d, H(8), <i>J</i> = 8.2); 6.94 (t, H(6), <i>J</i> = 7.5); 7.18 (t, H(7), <i>J</i> = 7.5); 7.42—7.52 (m, Ph)	10.60—11.80 (br.s)	2.05 (s), 9.20—10.40 (br.s)	3428, 1610, 1580, 1556, 1533, 1483, 1375

^a The doublet for H(4) is broadened due to splitting on the H(5) and H(7) atoms.

^b In DMSO-*d*₆.

^c ¹⁹F NMR (DMSO-*d*₆): 86.67 (d, CF₃, *J* = 5.5 Hz).

^d In CDCl₃.

^e ¹⁹F NMR (CDCl₃): 84.68 (d, CF₃, *J* = 5.0 Hz).

^f ¹⁹F NMR (DMSO-*d*₆): 86.87 (d, CF₃, *J* = 5.1 Hz).

^g ¹⁹F NMR (CDCl₃): 84.67 (d, CF₃, *J* = 5.2 Hz).

^h The signals of the second rotamer: 1.94 and 2.02 (both br.s, Me).

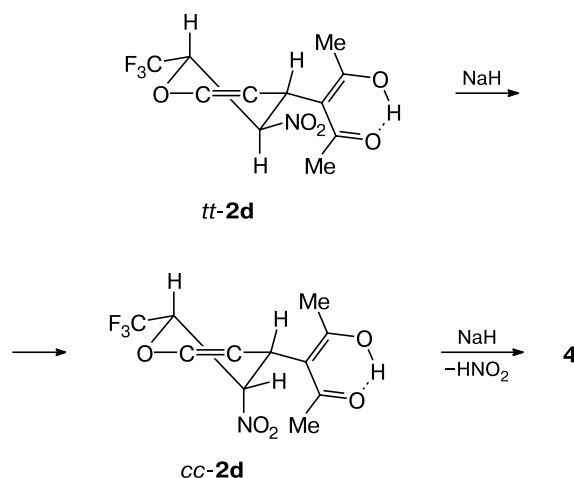
ⁱ The signals of the second rotamer: 5.04 (br.t, H(3), *J* ≈ 8.0 Hz); 4.65 (d, H(4), *J* = 11.7 Hz).

^j ¹⁹F NMR (DMSO-*d*₆): 86.38 (d, CF₃, *J* = 5.9 Hz).

cis—*cis*-3,5-dimethyl-4-(3,6-dinitro-2-trichloromethyl-3,4-dihydro-2*H*-chromen-4-yl)-1*H*-pyrazole (**6f**) in 77% yield. In the ¹H NMR spectrum of this compound, the H(3) proton appears as a triplet with *J*_{2,3} ≈ *J*_{3,4} = 4.0 Hz at δ 6.06, and Δδ = δ_{H(3)} − δ_{H(2)} = 1.0 ppm, which is indicative of the *cis*—*cis* structure.⁹ Apparently, this fact is attributed to the presence of the 6-NO₂ group, which increases the acidity of the hydrogen atoms of the pyran ring, in particular, of the H(3) atom, thus facilitating epimerization. It is also possible that the formation of chromene **4** in a mixture with *trans*—*trans*-chromane **2d** (*tt*) (see above) proceeds through epimerization of the latter to give *cis*—*cis* isomer **2d** (*cc*), in which elimination of the HNO₂ molecule is facilitated due to the anticoplanar arrangement of the 3-NO₂ group and the H(4) atom (Scheme 7).

It should be noted that the signals for the H(2) and H(4) atoms in the NMR spectra of 2-CCl₃-chromanes **6c,e,h** in CDCl₃ are shifted upfield by 0.2–0.4 ppm, whereas the signal for the H(3) atom is shifted downfield by ~0.1 ppm compared to the corresponding signals in the spectra in DMSO-*d*₆. In the spectra of 2-CF₃-chromanes **6a,g** in CDCl₃, all protons are shielded (the H(2) atom is shielded most substantially and is shifted upfield by ~0.8 ppm). The presence of the Me group at the nitro-

Scheme 7

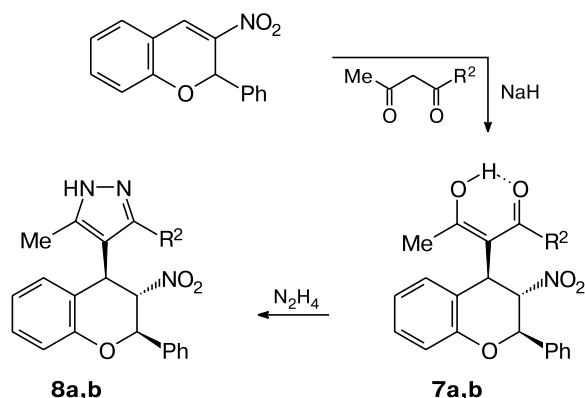


gen atom in the pyrazole ring has no effect on the chemical shifts of the H(2)—H(4) protons, whereas the replacement of the Me group at the C(3') atom by the hydroxy group (a more stable tautomeric form compared to the pyrazolone form²⁴) leads to changes in the chemical shifts analogous to those observed in going from **2a**—**h** to **2i**—**n** (see above). The singlets of the methyl groups at the C(3')

and C(5') atoms are broadened, which may be associated with a hindered rotation of the pyrazole fragment about the C(4)—C(4') bond (see Table 3).

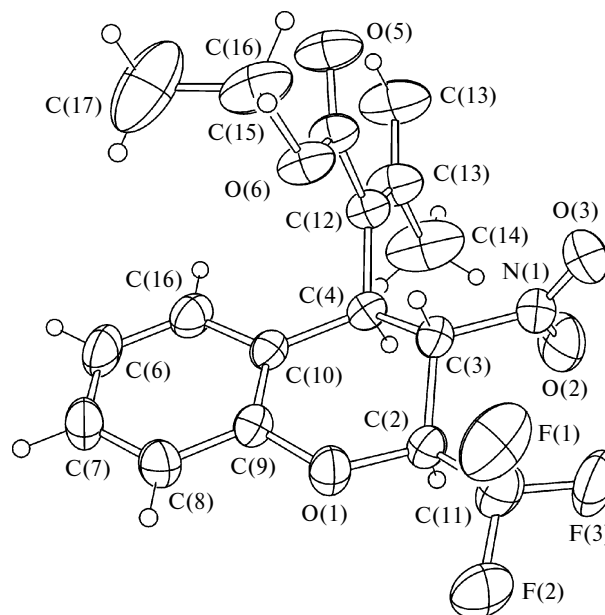
Data on the reactions of 2-aryl-3-nitro-2*H*-chromenes with 1,3-dicarbonyl compounds are lacking in the literature. Earlier, attempts to add thiols and arylamines to 3-nitro-2-phenyl-2*H*-chromene²⁵ have failed.⁹ We found that the latter compound reacts with acetylacetone and ethyl acetoacetate in the presence of NaH to give *trans-trans*-chromanes **7a,b** ($J_{2,3} = 9.3$ – 9.8 Hz, $J_{3,4} = 10.5$ – 10.9 Hz) in 56 and 18% yields, respectively. Like the above-described 2-CX₃-chromanes **2a–h**, compounds **7a,b** are transformed into the corresponding 4-pyrazolylchromanes **8a,b** with retention of the configuration of the pyran ring ($J_{2,3} = 9.5$ – 9.8 Hz and $J_{3,4} = 10.9$ – 11.3 Hz) in the reactions with hydrazine hydrate (Scheme 8).

Scheme 8



R² = Me (**7a**, **8a**), OEt (**7b**), OH (**8b**)

To finally confirm the conclusion about the *trans-trans* structure of chromanes **2**, which was drawn based on analysis of the spin-spin coupling constants, and to prove the fact that these compounds exist in the solid state as keto enols, we studied the crystal structure of chromane **2i** by X-ray diffraction. The molecular structure of **2i** (Fig. 1) confirms its *trans-trans* configuration. The pyran ring adopts a distorted half-chain conformation with the C(2) and C(3) atoms deviating from the plane through the other atoms by $-0.295(3)$ and $0.497(3)$ Å, respectively. The same conformation of the heterocycle was found in structurally similar chromane¹¹ containing the nitro group at position 3. It should be noted that the substituents in the pyran ring are in equatorial positions, and the nitro group and the substituent at the C(4) atom are eclipsed relative to the corresponding C—H bonds. The strong intramolecular O(4)—H...O(5) hydrogen bond in the keto enol fragment is characterized by the following parameters: O—H, $1.00(3)$ Å; H...O, $1.62(3)$ Å; O...O, $2.515(2)$ Å, O—H...O, $147(3)^\circ$. Interestingly, the same

Fig. 1. Overall molecular view of *trans-trans* isomer **2i**.

hydroxy group is involved in the weak O(4)—H...O(3) hydrogen bond (the corresponding parameters are $1.00(3)$ Å, $2.44(3)$ Å, $2.878(2)$ Å, and $106(2)^\circ$), through which the molecules are linked to each other to form centrosymmetric dimers. Among other intermolecular interactions, the C(2)—H... π (H...centroid, 2.62 Å) and C(16)—H...O(4) (H...O, 2.48 Å; C—H...O, 150°) interactions are worthy of note.

To summarize, 3-nitro-2-trihalomethyl-2*H*-chromenes accept acetylacetone and ethyl acetoacetate at the activated double bond to form *trans-trans*-2,3,4-trisubstituted chromanes containing the keto enol fragment at position 4. These compounds can be used for the synthesis of 4-heterylchromanes with potential biological activity. Analogous reactions with nitroalkanes produce *trans-cis*-3-nitro-4-nitroalkyl-2-(trichloromethyl)chromanes, which are of interest for the further diversity of compounds of the chromane series.

Experimental

The IR spectra were recorded on a Perkin—Elmer Spectrum BX-II instrument in KBr pellets. The ¹H and ¹⁹F NMR spectra were measured on a Bruker DRX-400 spectrometer in CDCl₃ or DMSO-*d*₆ operating at 400.1 MHz (¹H) and 376.5 MHz (¹⁹F) with Me₄Si and C₆F₆, respectively, as the internal standard. The 2D NOESY experiment was performed with the use of standard pulse sequences incorporated in the Bruker Xwin-NMR Suite 3.5 software; the mixing time was 1.7 s.

The starting chromenes **1a–h** and 3-nitro-2-phenyl-2*H*-chromene were synthesized according to known procedures.^{8,25}

6-Methoxy-3-nitro-2-trifluoromethyl-2*H*-chromene (1b). The yield was 55%, m.p. 72 – 73 °C (from hexane), orange needle-like crystals. Found (%): C, 47.95; H, 2.88; N, 4.97. C₁₁H₈F₃NO₄. Calculated (%): C, 48.01; H 2.93; N, 5.09. IR,

ν/cm^{-1} : 1650, 1613, 1582, 1521, 1491, 1335. ^1H NMR, δ : 3.81 (s, 3 H, MeO); 6.04 (q, 1 H, H(2), $J = 6.4$ Hz); 6.84–6.86 (m, 1 H, H(5)); 6.99–7.01 (m, 2 H, H(7), H(8)); 8.08 (s, 1 H, H(4)). ^{19}F NMR, δ : 84.11 (d, CF_3 , $J = 6.4$ Hz).

6-Methoxy-3-nitro-2-trichloromethyl-2H-chromene (1f).

The yield was 61%, m.p. 125–126 °C (from ethanol), orange needle-like crystals. Found (%): C, 40.67; H, 2.41; N, 4.25. $\text{C}_{11}\text{H}_8\text{Cl}_3\text{NO}_4$. Calculated (%): C, 40.71; H 2.48; N, 4.32. IR, ν/cm^{-1} : 1644, 1612, 1579, 1518, 1488, 1341, 1323. ^1H NMR, δ : 3.81 (s, 3 H, MeO); 6.27 (s, 1 H, H(2)); 6.84 (d, 1 H, H(5), $J = 2.5$ Hz); 6.99–7.05 (m, 2 H, H(7), H(8)); 8.08 (s, 1 H, H(4)).

3,6-Dinitro-2-trichloromethyl-2H-chromene (1h). The yield was 78%, m.p. 171–172 °C (from ethanol), pale-yellow powder. Found (%): C, 35.25; H, 1.23; N, 8.11. $\text{C}_{10}\text{H}_5\text{Cl}_3\text{N}_2\text{O}_5$. Calculated (%): C, 35.18; H 1.48; N, 8.25. IR, ν/cm^{-1} : 1651, 1621, 1581, 1521, 1478, 1342. ^1H NMR, δ : 6.43 (s, 1 H, H(2)); 7.27 (d, 1 H, H(8), $J = 8.9$ Hz); 8.15 (s, 1 H, H(4)); 8.32 (d, 1 H, H(5), $J = 2.6$ Hz); 8.35 (dd, 1 H, H(7), $J = 8.9$ Hz, $J = 2.6$ Hz).

Reactions of 3-nitrochromenes 1a–h with acetylacetone and ethyl acetoacetate (general procedure). A solution of acetylacetone or ethyl acetoacetate (1.5 mmol) in anhydrous THF (2 mL) was added dropwise with stirring to a suspension of NaH (0.03 g, 0.12 mmol) in anhydrous THF (6 mL). The reaction mixture was stirred at ~ 20 °C for 1 h. Then a solution of 3-nitrochromene **1** (1.0 mmol) in anhydrous THF (2 mL) was added dropwise. The reaction mixture was stirred for 2 days (for **1a–d**) or 3 days (for **1e–h**), washed with a saturated NH_4Cl solution (2 mL), extracted with diethyl ether (2×2 mL), washed with H_2O (2 mL), and dried with anhydrous Na_2SO_4 . The solvent was removed *in vacuo*, and the residue was recrystallized from a dichloromethane–hexane system. Compounds **2a–n** were synthesized: 3-(3-nitro-2-trifluoromethyl-3,4-dihydro-2H-chromen-4-yl)pentane-2,4-dione (**2a**), 3-(6-methoxy-3-nitro-2-trifluoromethyl-3,4-dihydro-2H-chromen-4-yl)pentane-2,4-dione (**2b**), 3-(6-bromo-3-nitro-2-trifluoromethyl-3,4-dihydro-2H-chromen-4-yl)pentane-2,4-dione (**2c**), 3-(3-nitro-2-trichloromethyl-3,4-dihydro-2H-chromen-4-yl)pentane-2,4-dione (**2e**), 3-(6-methoxy-3-nitro-2-trichloromethyl-3,4-dihydro-2H-chromen-4-yl)pentane-2,4-dione (**2f**), 3-(6-bromo-3-nitro-2-trichloromethyl-3,4-dihydro-2H-chromen-4-yl)pentane-2,4-dione (**2g**), 3-(3,6-dinitro-2-trichloromethyl-3,4-dihydro-2H-chromen-4-yl)pentane-2,4-dione (**2h**), ethyl 2-(3-nitro-2-trifluoromethyl-3,4-dihydro-2H-chromen-4-yl)-3-oxobutanoate (**2i**), ethyl 2-(6-bromo-3-nitro-2-trifluoromethyl-3,4-dihydro-2H-chromen-4-yl)-3-oxobutanoate (**2j**), ethyl 2-(3-nitro-2-trichloromethyl-3,4-dihydro-2H-chromen-4-yl)-3-oxobutanoate (**2k**), ethyl 2-(6-methoxy-3-nitro-2-trichloromethyl-3,4-dihydro-2H-chromen-4-yl)-3-oxobutanoate (**2l**), ethyl 2-(6-bromo-3-nitro-2-trichloromethyl-3,4-dihydro-2H-chromen-4-yl)-3-oxobutanoate (**2m**), and ethyl 2-(3,6-dinitro-2-trichloromethyl-3,4-dihydro-2H-chromen-4-yl)-3-oxobutanoate (**2n**).

Reactions with 3-nitro-2-phenyl-2H-chromene were carried out under analogous conditions. Compounds **7a,b** were synthesized: 3-(3-nitro-2-phenyl-3,4-dihydro-2H-chromen-4-yl)pentane-2,4-dione (**7a**) and ethyl 2-(3-nitro-2-phenyl-3,4-dihydro-2H-chromen-4-yl)-3-oxobutanoate (**7b**).

The ^1H and ^{19}F NMR and IR spectroscopic data for chromanes **2a–n** and **7a,b** are given in Table 1. The yields, the melting points, and elemental analysis data are listed in Table 4.

Table 4. Yields, physicochemical properties, and elemental compositions of chromanes **2a–c,e–n** and **7a,b**

Chromane	Yield (%)	M.p. /°C	Found (%)			Molecular formula
			Calculated	C	H	
2a	50	156–157	52.21 52.18	4.31 4.09	4.07 4.06	$\text{C}_{15}\text{H}_{14}\text{F}_3\text{NO}_5$
2b	14	127–128	51.22 51.21	4.03 4.30	3.70 3.73	$\text{C}_{16}\text{H}_{16}\text{F}_3\text{NO}_6$
2c	32	141–142	42.27 42.47	2.90 3.09	3.24 3.30	$\text{C}_{15}\text{H}_{13}\text{BrF}_3\text{NO}_5$
2e	50	176–177	45.47 45.65	3.58 3.58	3.33 3.55	$\text{C}_{15}\text{H}_{14}\text{Cl}_3\text{NO}_5$
2f	59	146–147	45.18 45.25	3.71 3.80	3.31 3.30	$\text{C}_{16}\text{H}_{16}\text{Cl}_3\text{NO}_6$
2g	56	187–189	38.25 38.05	2.79 2.77	2.94 2.77	$\text{C}_{15}\text{H}_{13}\text{BrCl}_3\text{NO}_5$
2h	40	195–196	40.91 40.98	2.93 2.98	6.35 6.37	$\text{C}_{15}\text{H}_{13}\text{Cl}_3\text{N}_2\text{O}_7$
2i	52	91–92	51.14 51.21	4.27 4.30	3.69 3.73	$\text{C}_{16}\text{H}_{16}\text{F}_3\text{NO}_6$
2j	37	111–112	42.54 42.31	3.30 3.33	2.93 3.08	$\text{C}_{16}\text{H}_{15}\text{BrF}_3\text{NO}_6$
2k	74	137–138	45.28 45.25	3.68 3.80	3.20 3.30	$\text{C}_{16}\text{H}_{16}\text{Cl}_3\text{NO}_6$
2l	11	104–105	44.86 44.91	3.80 3.99	2.99 3.08	$\text{C}_{17}\text{H}_{18}\text{Cl}_3\text{NO}_7$
2m	67	125–126	38.13 38.16	3.03 3.00	2.61 2.78	$\text{C}_{16}\text{H}_{15}\text{BrCl}_3\text{NO}_6$
2n	54	160–161	40.99 40.92	3.16 3.22	5.96 5.96	$\text{C}_{16}\text{H}_{15}\text{Cl}_3\text{N}_2\text{O}_8$
7a	56	185–186	67.83 67.98	5.24 5.42	3.98 3.96	$\text{C}_{20}\text{H}_{19}\text{NO}_5$
7b	18	102–103	65.71 65.79	5.47 5.52	3.68 3.65	$\text{C}_{21}\text{H}_{21}\text{NO}_6$

A mixture of *trans*–*trans*-3-(3,6-dinitro-2-trifluoromethyl-3,4-dihydro-2H-chromen-4-yl)pentane-2,4-dione (**2d**, 31%) and 3-(6-nitro-2-trifluoromethyl-2H-chromen-4-yl)pentane-2,4-dione (**4**, 69%). The yield was 11%, m.p. 125–127 °C. Found (%): C, 50.20; H, 3.21, N, 5.02. $0.31(\text{C}_{15}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_7) + 0.69(\text{C}_{15}\text{H}_{12}\text{F}_3\text{NO}_5)$. Calculated (%): C, 50.35; H, 3.47, N, 5.13.

Reactions of 3-nitrochromenes 1e,g with nitroalkanes. A solution of the corresponding chromene **1** (1.2 mmol) in nitromethane or nitroethane (2 mL) in the presence of K_2CO_3 (0.03 g, 0.2 mmol) was stirred at ~ 20 °C for 2 days. Then 10% HCl (5 mL) was added, the mixture was extracted with dichloromethane (2×2 mL) and dried with anhydrous Na_2SO_4 , the solvent was removed, and the residue was recrystallized from a 1 : 3 dichloromethane–hexane system. Compounds **5a–e** were synthesized: 3-nitro-4-nitromethyl-2-(trichloromethyl)chromane (**5a**), 6-bromo-3-nitro-4-nitromethyl-2-(trichloromethyl)chromane (**5b**), 3-nitro-4-(1-nitroethyl)-2-(trichloromethyl)chromane (**5c**), 6-bromo-3-nitro-4-(1-nitroethyl)-2-(trichloromethyl)chromane (**5d**), and 3-nitro-4-nitromethyl-2-(trifluoromethyl)chromane (**5e**).

Table 5. Yields, physicochemical properties, and elemental compositions of chromanes **5a–e**

Chro- mane	Yield (%)	M.p. /°C	Found (%)			Molecular formula
			Calculated			
			C	H	N	
5a	50	72–73	<u>37.30</u> 37.16	<u>2.54</u> 2.55	<u>7.84</u> 7.88	C ₁₁ H ₉ Cl ₃ N ₂ O ₅
5b	51	100–102	<u>30.62</u> 30.41	<u>1.85</u> 1.86	<u>6.52</u> 6.45	C ₁₁ H ₈ BrCl ₃ N ₂ O ₅
5c	61	193–195	<u>38.92</u> 39.00	<u>2.97</u> 3.00	<u>7.59</u> 7.58	C ₁₂ H ₁₁ Cl ₃ N ₂ O ₅
5d	57	198–200	<u>32.36</u> 32.14	<u>2.26</u> 2.25	<u>6.27</u> 6.25	C ₁₂ H ₁₀ BrCl ₃ N ₂ O ₅
5e	56	92–93	<u>43.24</u> 43.15	<u>2.93</u> 2.96	<u>9.10</u> 9.15	C ₁₁ H ₉ F ₃ N ₂ O ₅

The ¹H and ¹⁹F NMR and IR spectroscopic data for chromanes **5a–e** are given in Table 2. The yields, the melting points, and elemental analysis data are listed in Table 5.

Reactions of chromanes 2 and 7 with hydrazines (general procedure). A 60% hydrazine hydrate solution (0.2 mL) or a 60% methylhydrazine solution (0.1 mL) was added to a suspension of chromane **2** or **7** (1.0 mmol) in ethanol (7 mL). The reaction mixture was kept at ~20 °C for 10 h. Then the reaction mixture was concentrated to one-half on the initial volume, and water (2 mL) was added. The precipitate that formed was filtered off, washed with water, dried, and recrystallized from 75% ethanol or hexane. Compounds **6a–l** (see Scheme 6) and **8a,b** (see Scheme 8) were synthesized: 3,5-dimethyl-4-(3-nitro-2-trifluoromethyl-3,4-dihydro-2H-chromen-4-yl)-1H-pyrazole (**6a**), 4-(6-bromo-3-nitro-2-trifluoromethyl-3,4-dihydro-2H-chromen-4-yl)-3,5-dimethyl-1H-pyrazole (**6b**), 3,5-dimethyl-4-(3-nitro-2-trichloromethyl-3,4-dihydro-2H-chromen-4-yl)-1H-pyrazole (**6c**), 4-(6-methoxy-3-nitro-2-trichloromethyl-3,4-dihydro-2H-chromen-4-yl)-3,5-dimethyl-1H-pyrazole (**6d**), 4-(6-bromo-3-nitro-2-trichloromethyl-3,4-dihydro-2H-chromen-4-yl)-3,5-dimethyl-1H-pyrazole (**6e**), 3,5-dimethyl-4-(3,6-dinitro-2-trichloromethyl-3,4-dihydro-2H-chromen-4-yl)-1H-pyrazole (**6f**), 1,3,5-trimethyl-4-(3-nitro-2-trifluoromethyl-3,4-dihydro-2H-chromen-4-yl)-1H-pyrazole (**6g**), 4-(6-bromo-3-nitro-2-trichloromethyl-3,4-dihydro-2H-chromen-4-yl)-1,3,5-trimethyl-1H-pyrazole (**6h**), 5-methyl-4-(3-nitro-2-trifluoromethyl-3,4-dihydro-2H-chromen-4-yl)-1H-pyrazol-3-ol (**6i**), 5-methyl-4-(3-nitro-2-trichloromethyl-3,4-dihydro-2H-chromen-4-yl)-1H-pyrazol-3-ol (**6j**), 4-(6-methoxy-3-nitro-2-trichloromethyl-3,4-dihydro-2H-chromen-4-yl)-5-methyl-1H-pyrazol-3-ol (**6k**), 4-(6-bromo-3-nitro-2-trichloromethyl-3,4-dihydro-2H-chromen-4-yl)-5-methyl-1H-pyrazol-3-ol (**6l**), 3,5-dimethyl-4-(3-nitro-2-phenyl-3,4-dihydro-2H-chromen-4-yl)-1H-pyrazole (**8a**), and 5-methyl-4-(3-nitro-2-phenyl-3,4-dihydro-2H-chromen-4-yl)-1H-pyrazol-3-ol (**8b**).

The ¹H and ¹⁹F NMR and IR spectroscopic data for chromanes **6a–l** and **8a,b** are given in Table 3. The yields, the melting points, and elemental analysis data are listed in Table 6.

X-ray diffraction study of compound *n*-2i was performed on a Bruker P4 diffractometer (Mo-Kα radiation, graphite monochromator, 2θ/θ-scanning technique, angle range 2θ < 54°). The X-ray data were collected from a crystal of compound *n*-2i

Table 6. Yields, physicochemical properties, and elemental compositions of pyrazolyl chromanes **6a–l** and **8a,b**

Chro- mane	Yield (%)	M.p. /°C	Found (%)			Molecular formula
			Calculated			
			C	H	N	
6a	78	167–168	<u>52.77</u> 52.79	<u>3.99</u> 4.13	<u>12.25</u> 12.31	C ₁₅ H ₁₄ F ₃ N ₃ O ₃
6b	73	163–164	<u>42.87</u> 42.88	<u>3.26</u> 3.12	<u>10.02</u> 10.00	C ₁₅ H ₁₃ BrF ₃ N ₃ O ₃
6c	82	252–253	<u>45.99</u> 46.12	<u>3.69</u> 3.61	<u>10.85</u> 10.76	C ₁₅ H ₁₄ Cl ₃ N ₃ O ₃
6d	84	202–203	<u>45.67</u> 45.68	<u>3.79</u> 3.83	<u>10.02</u> 9.99	C ₁₆ H ₁₆ Cl ₃ N ₃ O ₄
6e	69	204–205	<u>38.64</u> 38.37	<u>2.78</u> 2.79	<u>9.01</u> 8.95	C ₁₅ H ₁₃ BrCl ₃ N ₃ O ₃
6f	77	143–144	<u>41.27</u> 41.36	<u>3.22</u> 3.01	<u>12.75</u> 12.86	C ₁₅ H ₁₃ Cl ₃ N ₄ O ₅
6g	83	92–93	<u>53.95</u> 54.09	<u>4.37</u> 4.54	<u>11.81</u> 11.83	C ₁₆ H ₁₆ F ₃ N ₃ O ₃
6h	77	176–177	<u>39.93</u> 39.74	<u>3.05</u> 3.13	<u>8.71</u> 8.69	C ₁₆ H ₁₅ BrCl ₃ N ₃ O ₃
6i	58 (decomp.)	244–245	<u>49.10</u> 48.99	<u>3.49</u> 3.52	<u>12.10</u> 12.24	C ₁₄ H ₁₂ F ₃ N ₃ O ₄
6j	47 (decomp.)	254–255	<u>42.81</u> 42.83	<u>2.91</u> 3.08	<u>10.88</u> 10.70	C ₁₄ H ₁₂ Cl ₃ N ₃ O ₄
6k	42	255–256	<u>42.64</u> 42.63	<u>3.15</u> 3.34	<u>9.70</u> 9.94	C ₁₅ H ₁₄ Cl ₃ N ₃ O ₅
6l	30 (decomp.)	264–265	<u>35.73</u> 35.66	<u>2.40</u> 2.35	<u>8.76</u> 8.91	C ₁₄ H ₁₁ BrCl ₃ N ₃ O ₄
8a	79	210–211	<u>68.47</u> 68.75	<u>5.40</u> 5.48	<u>12.04</u> 12.03	C ₂₀ H ₁₈ N ₃ O ₄
8b	80	272–273	<u>64.77</u> 64.95	<u>4.95</u> 4.88	<u>11.90</u> 11.96	C ₁₉ H ₁₇ N ₃ O ₄

of dimensions 0.3×0.4×0.7 mm. Crystals are triclinic: *a* = 8.177(1), *b* = 10.287(2), *c* = 11.493(2) Å, α = 109.27(1), β = 95.81(1), γ = 102.15(1)°, *V* = 876.7(2) Å³, space group *P* $\bar{1}$, *Z* = 2, C₁₆H₁₆F₃NO₆, *d*_{calc} = 1.422 g cm^{−3}, μ = 0.128 mm^{−1}. The intensities of 4015 reflections were measured, of which 3752 reflections were independent (*R*_{int} = 0.0209). An empirical absorption correction was applied (the transmission was 0.6789–0.9578). The structure was solved by direct methods with the use of the SHELXS-97 program package.²⁶ The structure was refined by the full-matrix least-squares method with anisotropic displacement parameters using the SHELXL-97 program package.²⁶ The parameters of the H atoms were calculated in each refinement cycle from the coordinates of the corresponding carbon atoms (a riding model). The hydrogen atom of the hydroxy group was located in a difference electron density map and refined isotropically. The final refinement was performed based on all *F*² to *wR*₂ = 0.1587, *S* = 1.029, 239 parameters were refined (*R* = 0.0530 for 2878 reflections with *F* > 4σ). The details of the X-ray diffraction study were deposited with the Cambridge Structural Database (CCDC 612713).

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