RESEARCH INTO ANALOGS OF PYRAN AND RELATED COMPOUNDS

XXIX.* The Reaction of 4,4-Dichlorochromenes (4,4-Dichloro-4H-1-benzopyrans) with Derivatives of Cyanoacetic Acid**

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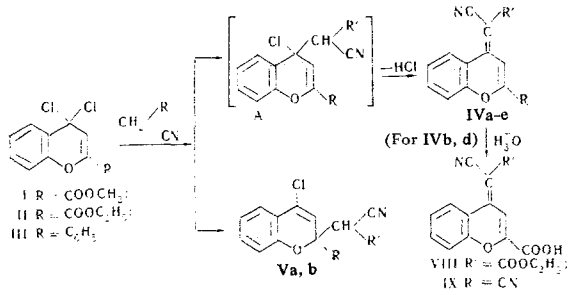
The reaction of esters of 4, 4-dichlorochromene-2-carboxylic acid and of 4, 4-dichloroflavine (4, 4-dichloro-2-phenyl-4H-1-benzopyran) with compounds containing an activated methyl group (cyanoacetic ester, cyanoacetamide, and malonodinitrile) is examined. These dichloro compounds undergo substitution in both the 2- and 4-positions of the chromene system, depending on the nature of the attacking reagent. The initially formed esters of 2-ethoxycarbonylcyanomethyl-4-chloro-3-chromene-2-carboxylic acid undergo a number of specific reactions, since the cyanoacetate group attached to the chromene system is sufficiently labile to be capable of removal of hydrolysis, and of migration to the 4-position.

It has been shown previously that 4, 4-dichlorochromenes, the halogen atoms of which are extremely reactive, are capable of undergoing attack by nucleophilic reagents (water, alcohols, and aromatic amines) at either the 2- or the 4-position, according to the nature of the nucleophile and the substituent on the carbon atom in the 2-position [1–4].

We have examined the reaction of esters of 4, 4-dichlorochromene-2-carboxylic acid (I, II) and of 4, 4-dichloroflavine (III) with ethyl cyanoacetate, cyanoacetamide, and malonodinitrile. The reaction was carried out in the absence of a condensing agent, either in the presence or absence of a solvent. As has been mentioned, nucleophilic attack by compounds with an active methylene group may occur at both the 2- and 4-positions of the dichlorochromene system:



a R=COOCH$_3$, R′=COOC$_2$H$_5$; b R=R′=COOC$_2$H$_5$; c R=COOC$_2$H$_5$, R′=CONH$_2$; d R=COOC$_2$H$_5$, R′=CN; e R=C$_6$H$_5$, R′=COOC$_2$H$_5$.

The dichlorochromene-2-carboxylic acid esters I and II reacted with cyanoacetic ester in absence of a solvent to give 38–52% of the yellow alkylidene compounds (IVa and **b**) and 12–16% of the colorless chlorine-containing 3-chromene derivatives **Va** and **b**. Reaction of the dichloroester II with cyanoacetamide in benzene gave exclusively the alkylidene compound **IVb**. Malonodinitrile behaves similarly, giving either in benzene solution or in absence of a solvent 65–80% of **IVd**. In contrast to the dichlorochromenecarboxylic acid derivatives I and II, the dichloroflavine III gives with cyanoacetic ester only the 4-substituted product **IVe**, which has been obtained previously by another route [5]. The structure of the alkylidene compounds **IVa–d** was confirmed by their elemental analyses and UV spectra. The UV spectrum of **IVb** shows a maximum at 383 nm (log ε 4.25), attributable to the development of a conjugated system. The IR spectrum of **IVb** (Fig. 1, spectrum 1) shows absorptions at 2200 cm^{-1} (conjugated C≡N group) and at 1750 and 1700 cm^{-1} (ester carbonyl groups in positions 2 and 4).

Hydrogenation of **IVb** over Pd results in uptake of 2 moles of H_2 to give the chroman derivative **VI**. The structure of the latter as a 2, 4-disubstituted chroman is confirmed by the NMR spectrum (Fig. 2, spectrum 1). In the spectrum, besides the signals due to the protons of the ethoxycarbonyl group with δ 1.25 to 4.20 ppm, a triplet is seen at 4.47 ppm (J = 6 Hz), attributable to the methine proton in position 2. No signals are seen in the 2–3-ppm region, where they would occur if the C—CH_2—CH_2—C moiety corresponding to a chroman unsubstituted in the 3- and 4-positions were present.

A multiplet of two proton units is found at 2.28 ppm which we ascribe to the nonequivalent protons of the methylene group in the 3-position which interact with the protons of the methine groups at C_2 and C_4. The NMR spectrum of a model compound (Fig. 2, spectrum 2), namely, ethyl chroman-2-carboxylate (VII) obtained by hydrogenation of the known ethyl chromanone-2-carboxylate), shows signals in the 2.18–2.70-ppm region due to the protons of the C—CH_2—CH_2—C moiety and a triplet at 4.57 ppm (J = 6 Hz) due to the methine proton in the 2-position interacting with the two neighboring protons in the 3-position. The configuration of **VI** has not been established. Compounds **IVb** and **IVd** undergo hydrolysis in acid solution to the monocarboxylic acids **VIII** and **IX**, respectively. Further acid hydrolysis is difficult. Deactivation of the nitrile and ester groups connected to the alkylidene carbon atom is no doubt brought about by the effective transfer of electron density from the oxygen heteroatom to the electrophilic centers of these groups. It is interesting to note that the 4-alkylidenechromene system is the carbon analog of the chromone system. The structure of the monoacid **VIII** was proved by methylation with diazomethane to the ester **IVa**.

*For part XXVIII, see [9].

Preliminary part, ZhOKh, **34, 1685, 1964.

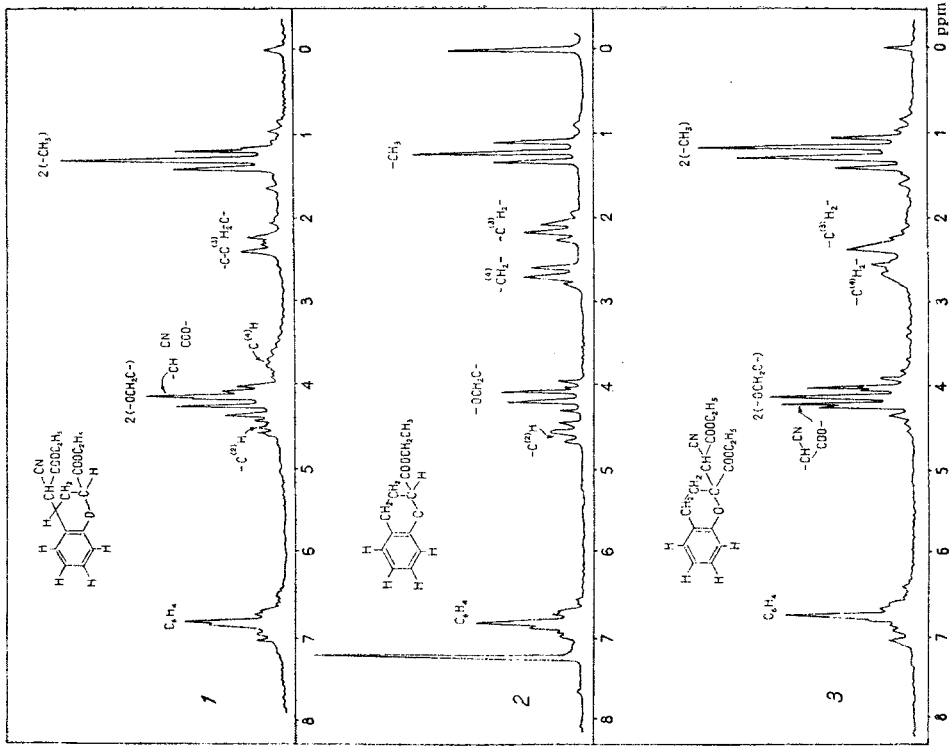


Fig. 2. NMR spectra: 1) ethyl 4-(ethoxycarbonylcyanomethyl)-chroman-2-carboxylate (VI); 2) ethyl chroman-2-carboxylate (VII); 3) ethyl 2-(ethoxycarbonylcyanomethyl)chroman-2-carboxylate (X). The spectra were recorded on an instrument with a working frequency of 60 MHz, using tetramethylsilane as internal standard, compounds VI and X being dissolved in deuterochloroform and VII in chloroform.

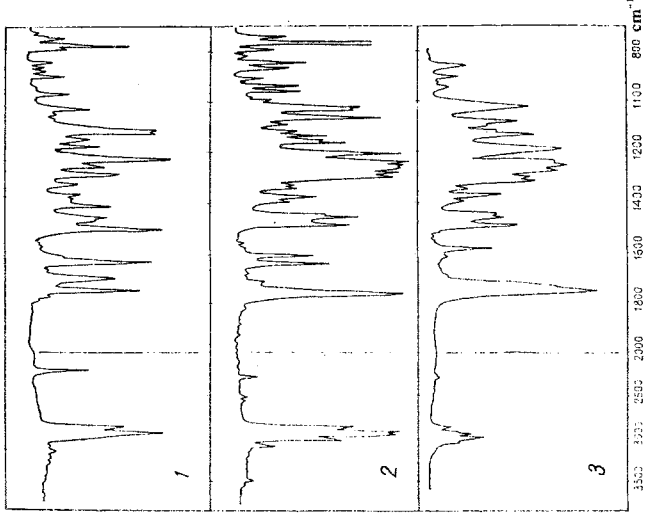
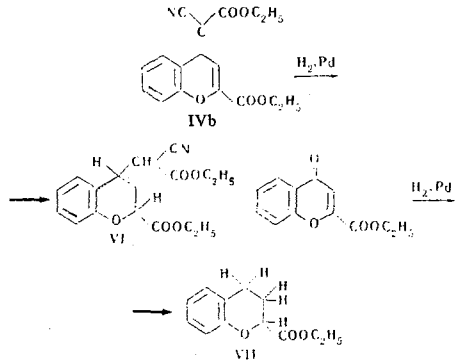


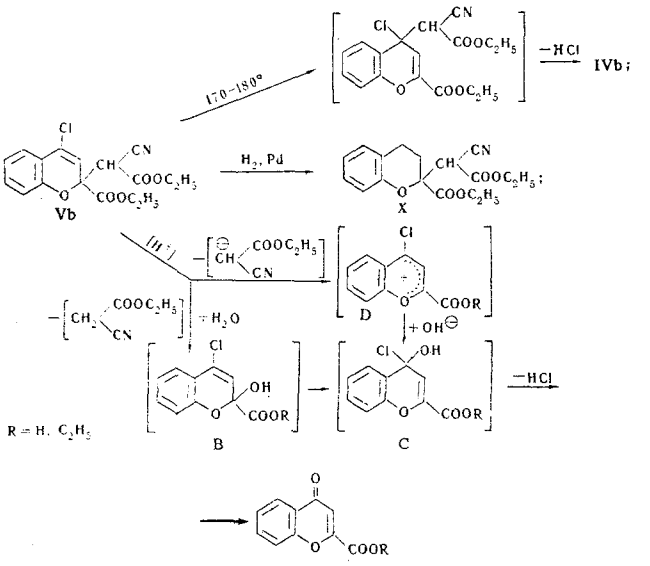
Fig. 1. IR spectra: 1) ethyl 4-(ethoxycarbonylcyanomethylene)-2-chromene-2-carboxylate (IVb); 2) ethyl 2-ethoxycarbonylcyanomethyl-4-chloro-3-chromene-2-carboxylate (Vb); 3) ethyl 2-(ethoxycarbonylcyanomethyl)chroman-2-carboxylate (X). The spectra of IVb and Vb were taken in vaseline oil, and that of X in chloroform (c 0.1 M, d = 0.168 mm).



In establishing the structures of compounds V, we bore in mind that one cannot exclude a priori the probable occurrence of structures isomeric with V, for example A (Scheme 1). Structure V was chosen on the basis of several properties and chemical reactions. The IR spectrum of **Vb** (Fig. 1, spectrum 2) has bands at 2270 cm^{-1} (nonconjugated C≡N group), and a broad, intense band at 1760 cm^{-1} (C=O of two ester groups). In the NMR spectrum of **Vb**, apart from the signals due to the protons of the aromatic ring and to the two O—CH_2CH_3 groups, there are two singlets with δ 5.98 ppm (the vinyl proton at C_3) and 4.45 ppm (the methine proton in —CH(CN)$COOC_2H_5$). At the temperature of its formation, **Vb** in presence of hydrogen chloride is not converted into the alkylidene compound **IVb**, which is a strong argument against **Vb** having the structure A.

Specific properties of **Vb** are in large measure determined by the possession of the —CH(CN)$COOC_2H_5$ group, which is rather labile by virtue of its electron-acceptor properties. Thus, for example, at 170–180° C, **Vb** is converted into **IVb** by migration of the cyanoacetic ester residue to the 4-position, followed by loss of hydrogen chloride via an intermediate of type A (Scheme 3). Work on the migration of alkyl (benzyl) groups in the pyran system has recently been reported by other workers [6]. Heating **Vb** with hydrochloric acid in ethanol gives chromone-2-carboxylic acid and its ester (Scheme 3). The reaction probably proceeds by hydrolytic fission of the cyanoacetic acid residue, followed by rearrangement of the intermediate compound **B** to **C** (which may also arise from the pyrylium cation **D**), and elimination of hydrogen chloride from **C**. A similar case of hydrolytic fission of a C—C bond has been reported with cycloheptatriene derivatives in acid solution [7].

Compound **Vb** has two asymmetric carbon atoms. However, to judge from the fairly sharp melting point (which is unchanged on recrystallization), thin-layer chromatography, and crystallooptic analysis by the immersion method (for which the authors thank V. I. Sokol) demonstrating the homogeneity of the crystals, we are dealing with a single racemate, apparently the most stable one of the two possibilities, which may be in equilibrium with the other as a result of the mobility of the methine hydrogen atom in the cyanoacetic ester group.



Hydrogenation of **Vb** over Pd gives the 2,2-disubstituted chroman (**X**) as the racemate (Scheme 3). The IR spectrum of **X** (Fig. 1, spectrum 3) is in agreement with this structure. The NMR spectrum (Fig. 2, spectrum 3) fully confirms the structure of **X**. In the region from 1.06 to 1.40 ppm there are two overlapping triplets of intensity six proton units due to the two terminal methyl groups of the two nonequivalent ethoxycarbonyl groups. A poorly resolved multiplet is found in the 2.15–2.80-ppm region; it consists of two groups of signals totaling four proton units, possibly due to the C—CH_2—CH_2—C fragment, where the methylene group at position 3 corresponds to the peaks at high field. Signals due to the methylene protons of the ethoxycarbonyl groups and the methine proton (CN—CH—COO—) of intensity five proton units are found in the region 3.90–4.35 ppm.

EXPERIMENTAL

Methyl 4-(ethoxycarbonylcyanomethylene)-2-chromene-2-carboxylate (IVa) and methyl 2-ethoxycarbonylcyanomethyl-4-chloro-3-chromene-2-carboxylate (Va). A 4.08-g (0.02 mole) quantity of methyl chromone-2-carboxylate was converted into the dichloro compound I [3] by boiling for 10 hr with 15 ml of $SOCl_2$ followed by removal of the excess $SOCl_2$ in vacuo (finally with addition and subsequent distillation of dry benzene). To the residue, containing **I**, was added 4.5 g (0.04 mole) of ethyl cyanoacetate, and after 16 hr at 20° C the mixture was treated with a mixture of 40 ml of light petroleum and 10 ml of methanol. The yellow crystals were filtered off, giving 2.3 g (38%) of **IVa**, mp 153–154° C (from ethanol). Found, %: C 64.15, 64.08; H 4.24, 4.25. Calculated for $C_{16}H_{13}NO_5$, %: C 64.21; H 4.38. The petroleum-methanol solution, on evaporation and then treatment with a small amount of methanol–light petroleum mixture and finally with ether, gave 0.82 g (12%) of colorless crystals of **Va**, 115–117° C. Found, %: C 57.46, 57.54; H 4.23, 4.28; Cl 10.33, 10.53. Calculated for $C_{16}H_{14}ClNO_5$, %: C 57.25; H 4.20; Cl 10.56.

Ethyl 4-(ethoxycarbonylcyanomethylene)-2-chromene-2-carboxylate (IVb) and ethyl 2-ethoxycarbonylcyanomethyl-4-chloro-3-chromene-2-carboxylate (Vb). A 10.9-g (0.05 mole) quantity of ethyl chromonecarboxylate was converted as before into the dichloro compound **II**; to this was added 11.3 g (0.1 mole) of ethyl cyanoacetate, and the mixture heated for 1 hr at 100° C. After 16 hr, the precipitate was filtered off, washed several times with a mixture of light petrol-

eum and benzene (4 : 1), and treated with 150 ml of cold benzene; the insoluble portion was filtered off to give 2.60 g (16%) of colorless **Vb**, mp 140–141° C (from ethanol). Refractive indices: N_p 1.570, N_m 1.582, N_q 1.618. Found, %: Cl 10.31, 10.21; C 58.53, 58.59; H 4.64, 4.56. Calculated for $C_{17}H_{16}ClNO_5$, %: Cl 10.14; C 58.37; H 4.60. The benzene solution was evaporated, giving 8.1 g (52%) of yellow **IVb**, mp 141–141.5° C (from ethanol). UV spectrum, λ_{max}, nm (log ε): 225 (4.40), 258 (3.90), 282 (3.96), 383 (4.25). Found, %: C 65.55, 65.27; H 4.56, 4.71; N 4.90, 4.72. Calculated for $C_{17}H_{15}NO_5$, %: H 4.82; N 4.47. When the reaction was carried out in boiling benzene (longer heating), approximately the same results were obtained. In a finely divided state, **Vb** dissolved in sodium carbonate with the development of red color. Treatment with alcoholic silver nitrate in the cold for several minutes did not result in removal of halogen. Heating **Vb** with ethyl cyanoacetate for 10 hr at 100° C in the absence of hydrogen chloride, or with passage of the latter, did not give the alkylidene derivative **IVb**.

By heating 0.5 g of **Vb** for 1 hr at 170–180° C (evolution of hydrogen chloride and much resinification), followed by chromatography on an alumina column (grade 2 activity, eluted with chloroform), there was obtained 50 mg of yellow **IVb**, mp 139–141° C. The product gave no depression of melting point with the sample obtained above and was identical with it according to the R_f values on thin-layer chromatography on alumina.

A solution of 2.2 g (0.0063 mole) of **Vb** in 100 ml of ethanol and 20 ml of conc. HCl was boiled for 7 hr and evaporated and the residue was treated with bicarbonate solution and extracted with dichloroethane. The dichloroethane was removed to give 0.34 g (45%) of ethyl chromonecarboxylate, mp 75° C (from ethanol), which gave no depression of mp with an authentic sample. Acidification of the bicarbonate solution gave 0.2 g (31%) of chromone-2-carboxylic acid, mp 260° C (decomp., from aqueous dioxane).

Ethyl 4-(carbamoylcyanomethylene)-2-chromene-2-carboxylate (IVc). To the dichloro compound **II**, obtained as before from 2.18 g (0.01 mole) of ethyl chromone-2-carboxylate, was added a solution of 0.84 g (0.012 mole) of cyanoacetamide in 15 ml of dry benzene. After 16 hr at 20° C, the mixture was boiled for 30 min, cooled, the precipitate filtered off, and the product washed with dry ether to give 1.7 g (60%) of yellow **IVc**, mp 229–230° C (from a mixture of ethanol and dimethylformamide); product dried in vacuo over P_2O_5 for 2 hr at 85° C. Found, %: C 63.63, 63.34; H 4.35, 4.35; N 10.04, 10.08. Calculated for $C_{15}H_{12}N_2O_4$, %: C 63.39; H 4.26; N 9.85.

Ethyl 4-(dicyanomethylene)-2-chromene-2-carboxylate (IVd). To the dichloro compound II, prepared from 4.36 g (0.02 mole) of ethyl chromonecarboxylate, was added 1.36 g (0.02 mole) of malonodinitrile (a vigorous evolution of hydrogen chloride was noted), and after 16 hr at 20° C the mixture was treated with a small amount of ethanol. The solid was filtered off to give 4.32 g (81%) of yellow **IVd**, mp 145–146° C (from ethanol). Found, %: C 67.69, 67.75; H 3.90, 3.99; N 10.61, 10.71. Calculated for $C_{15}H_{10}N_2O_3$, %: C 67.66; H 3.79; N 10.52. On carrying out the reaction in dry benzene, the yield of **IVd** was 65%. In no case was the presence of chlorine-containing compounds in the reaction mixture observed.

4-(Cyanoethoxycarbonylmethylene)flavine (IVe). To 4,4-dichloroflavine (III) (from 1.1 g (0.005 mole) of flavone and 5 ml of $SOCl_2$, boiled for 10 hr) was added 5.85 g (0.05 mole) of ethyl cyanoacetate, and the mixture was heated for 1 hr at 110° C. After 16 hr (~20°) the solid was filtered off and washed with a mixture of light petroleum and methanol (4 : 1) to afford 1.5 g (79%) of yellow **IVe**, mp 160–161° C (from ethanol) [5].

4-(Ethoxycarbonylcyanomethylene)-2-chromene-2-carboxylic acid (VIII). Two grams (0.0064 mole) of **IVb**, 50 ml of 2 N hydrochloric acid, and 50 ml of ethanol were boiled for 7 hr, evaporated, treated with sodium bicarbonate solution, and 1.03 g of the starting ester filtered off. Acidification of the bicarbonate solution with conc. HCl precipitated 0.5 g (57% allowing for recovered ester) of the acid VIII, mp 261–262° C (decomp., from aqueous dioxane). Found, %: C 62.93, 63.10; H 3.86, 3.88; N 4.93, 4.99. Calculated for $C_{15}H_{11}NO_5$, %: C 63.14; H 3.89; N 4.91. Hydrolysis in a mixture of ethanol and conc. HCl (5 : 1) gave the same results. Hydrolysis with 70% sulfuric acid for 16 hr at 100° C also gave **VIII**. Methylation of **VIII** with diazomethane in ether afforded the ester **IVa**, mp 151–152° C, identical with that previously described, in quantitative yield.

4-(Dicyanomethylene)-2-chromene-2-carboxylic acid (IX). A 0.65-g (0.0024 mole) quantity of **IVd**, 10 ml of conc. HCl, and 10 ml of acetic acid were boiled for 8 hr. The solution was evaporated, the residue treated with sodium bicarbonate solution, the precipitate of the sodium salt of the acid filtered off, treated with 2 N HCl, washed with water, and dried over P_2O_5, giving 0.46 g (79%) of the acid **IX**, mp 239° C (decomp., from a mixture of acetic and hydrochloric acids, 2 : 1, and dried in vacuo over caustic alkali for 3 days at 120–130° C). Found, %: C 65.18, 65.34; H 2.65, 2.54; N 11.99, 11.85. Calculated for $C_{12}H_6N_2O_3$, %: C 65.54; H 2.54; N 11.76.

Ethyl 4-(ethoxycarbonylcyanomethyl)chroman-2-carboxylate (VI). A 5.5-g quantity (0.0175 mole) of **IVb** in 300 ml of ethyl acetate was hydrogenated over 3 g of 5% Pd/$BaSO_4$ for three days under normal conditions until 2 moles of H_2 had been taken up. The catalyst was filtered off, the filtrate evaporated, and the oily residue treated repeatedly with light petroleum with decantation. Then 15 ml of a mixture of ether and light petroleum (1 : 5) was added, and after 16 hr at 0° C the resulting colorless crystals were filtered off, washed with cold ether, the mother liquors evaporated, and the treatment was repeated. In all there was obtained 1.2 g (22%) of **VI**, mp 87.5–88.5° C. Found, %: C 64.50, 64.34; H 6.18, 6.11. Calculated for $C_{17}H_{19}NO_5$, %: C 64.32; H 6.05.

Ethyl 2-(ethoxycarbonylcyanomethyl)chroman-2-carboxylate (X). A 1.75-g quantity (0.005 mole) of **Vb** in 100 ml of desulfurized absolute ethanol was hydrogenated over 1 g of 5% Pd/$BaSO_4$ until 2.6 moles of hydrogen had been taken up (20° C, 1.5 hr), with occasional heating to 70–80° C. The catalyst was filtered off, the solution evaporated, and the residue kept for 16 hr at 0° C, treated with 50 ml of ether, and 0.14 g of starting material **Vb** filtered off. The solution was evaporated, the residue triturated with 4 ml of ether while cooling to −70° C, and 0.48 g (33% calculated on recovered starting material) of **X**, mp 92.5–93.5° C (from a mixture of ether and light petroleum at −70° C) was filtered off. Found, %: C 64.60, 64.24; H 6.08, 6.01; N 4.57, 4.41. Calculated for $C_{17}H_{19}NO_5$, %: C 64.32; H 6.05; N 4.41. In one experiment, a crystalline modification mp 82–83.5° C was obtained. This gave no depression of mp on admixture with the material mp 92.5–93.5° C, and gave identical analytical results (IR spectrum (in $CHCl_3$), and R_f value by thin-layer chromatography on Al_2O_3).

Ethyl chroman-2-carboxylate (VII). A 3.27-g quantity (0.015 mole) of ethyl chroman-2-carboxylate in 50 ml of absolute ethanol and 0.5 ml of conc. HCl was hydrogenated for 12 hr over 0.8 g of Pd/$BaSO_4$, 3.2 moles of hydrogen being taken up. The catalyst was filtered off, the filtrate treated with an equal volume of water, the mixture extracted with benzene, the benzene extract washed with sodium bicarbonate solution and water, and dried over calcined sodium sulfate. Distillation afforded 2.30 g (75%) of **VII**, bp 124–125° C (1 mm), n_D^{20} 1.5228. The literature bp is 156–159° C (6 mm) [8] (obtained by esterifying chroman-2-carboxylic acid). Found, %: C 70.00, 70.04; H 6.93, 6.94. Calculated for $C_{12}H_{14}O_3$, %: C 69.88; H 6.84.

REFERENCES

1. V. A. Zagorevskii and D. A. Zykov, ZhOKh, **30**, 1378, 1960.

2. V. A. Zagorevskii and D. A. Zykov, ZhOKh, **30**, 3100, 1960.

3. V. A. Zagorevskii, ZhOKh, **32**, 3770, 1962.

4. V. A. Zagorevskii, I. D. Tsvetkova, and E. K. Orlova, ZhOKh, **34**, 1911, 1964.

5. F. Kröhnke and K. Dickore, Ber., **92**, 46, 1959.

6. K. Dimroth, K. Wolf, and H. Kroke, Ann., **678**, 183, 1964.

7. M. E. Vol'pin and I. S. Akhrem, DAN, **161**, 597, 1965.

8. Sekio Mitski, Akira Kasahara, Tetsko Oike, and Kaoru Hanaya, Nippon Kagaku Zasshi, **83**, 581, 1962; C. A., **59**, 3727, 1963.

9. N. M. Sharkova, N. F. Kucherova, and V. A. Zagorevskii, KhGS [Chemistry of Heterocyclic Compounds], 88, 1969.

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