RESEARCH ON PYRANES, THEIR ANALOGS, AND RELATED COMPOUNDS

XXIII. Reaction of 4,4-Dichlorochromene and 3,4,4-Trichlorochromene with Nucleophilic Reagents*

V. A. Zagorevskii, I. D. Tsvetkova, and E. K. Orlova

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 3, No. 5, 786-790, 1967

UDC 547.814.1:542.958.3'944.4'938:543.422.4

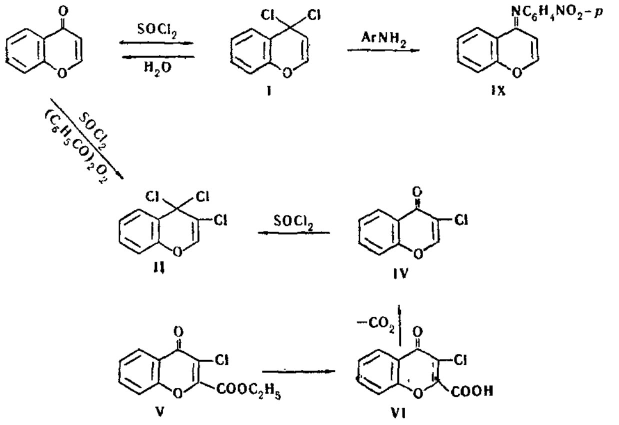
4,4-Dichorochromene (I) and 3,4,4-trichlorochromene (II) are prepared, and their reactions with nucleophilic reagents (water and aromatic amines) investigated. With water and p-nitroaniline the dichloride I gives normal reaction products: chromone and 4-(p-nitrophenylamino) chromene (IX). Compound II behaves differently, attack of water and aromatic amines occurring at position 2 in the chromene system to give respectively an ether (X) and amines (XI). Various chemical reactions of X and XI are investigated.

Continuing a study of the reaction of nucleophilic reagents with 4,4-dichlorochromene (I), we chose as subjects of investigation 4,4-dichlorochromene (I) and 3,4,4-trichlorochromene (II). If the conversion of 2-chlorocarbonyl- and 2-carbalkoxychromones to the corresponding 4,4-dichlorides takes place rather smoothly under the action of halogen carriers [$SOCl_2$, $(COCl)_2$, PCl_5] [1, 2], considerable difficulties were encountered in preparing I. The reaction of chromone with thionyl chloride is accompanied by resinification and formation of a side product, obviously trichlorochromene (II), which it is impossible to separate by distillation. As trichloride II can arise by oxidative chlorination, the reaction was run in the absence of oxygen of the air (in a current of carbon dioxide), and dichloride I was obtained in 58% yield. It is difficult to analyze and characterize this compound, as it readily reacts with moisture of the air, to give the starting chromone.

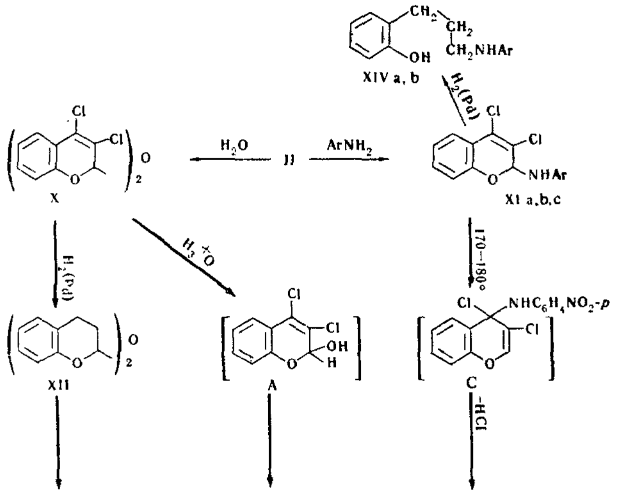
To shift the course of the reaction towards the side of formation of trichloride II, addition of benzoyl peroxide was resorted to. Under those conditions trichloride II was obtained without dichloride as impurity. The amount of benzoyl peroxide is of major importance in running the reaction successfully. The structure of the dichloride II is shown in the following way. The action of sulfuryl chloride on chromone gave 2,3-dichlorochroman-4-one (III), smoothly converted by triethylamine to 3-chlorochromone (IV). Treatment of IV with thionyl chloride gave the trichloride II. On the other hand, the structure of IV is shown by chlorinating the ethyl ester of chromone-2-carboxylic acid with sulfuryl chloride, to give the ethyl ester of 3-chlorochromone-2-carboxylic acid (V). The latter hydrolyzes to the corresponding acid (VI), further decarboxylated to IV.

Taking account of the fact that the literature does not describe preparation of 3-chlorochromones by direct chlorination with sulfuryl chloride, we tried this method on another common chromone derivative, flavone, and readily obtained 3-chloroflavone (VII). Use of excess sulfuryl chloride led to formation of 2,2,3-trichloroflavanone (VIII).

Considerable difference is observed in the behavior of compounds I and II towards nucleophilic reagents. I and water give chromone, while p-nitroaniline gives 4-p-nitrophenylaminochromene (IX), i.e. 4-substitution products.

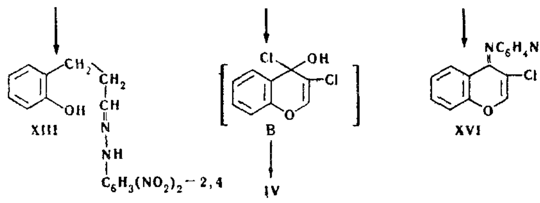


On the other hand, compound II (obtained both from chromone, and from IV) gives 2-substitution products with water and aromatic amines: the ether X and amines XIa, b, c. The structure of ether X is proved by its hydrogenation to ether XII, the latter, like an acetal, forming a 2,4-dinitrophenylhydrazone (XIII) in acid solution. Treatment of compound X with water in acid solution converts it to IV, obviously through the intermediate hydroxy derivative A, which by rearrangement gives the also unstable isomer B.



---

*For Part XXII see [4].



XI: a Ar=C_6H_5, b Ar=p-$NH_2SO_2C_6H_4$, c Ar=p-$NO_2C_6H_4$

The latter readily loses hydrogen chloride. The structure of XI is established for **XIa** by hydrogenation to compound XIVa, which is alternatively synthesized by splitting dihydrocoumarim with aniline, and reducing the resultant anilide of o-hydroxydihydrocinammic acid (XV) with $LiAlH_4$. Hydrolysis of **XIa, c** in acid solution gives **IV**. Heating **XIc** at 170–180° converts it to the imine **XVI**, probably via intermediate compound C.

EXPERIMENTAL

4,4-Dichlorochrom-2-ene (I). 20 g (0.137 mole) chromone and 50 ml $SOCl_2$ were refluxed together in a slow stream of dry CO_2 for 12 hr, excess $SOCl_2$ vacuum distilled off, and the residue distilled in the absence of moisture from the air, yield of I 16.08 g (58%), bp 150° (7 mm). Found: Cl 35.21; 34.77%, calculated for $C_9H_6Cl_2O$: Cl 35.26%.

4-(p-Nitrophenylimino)chrom-2-ene (IX). A solution of 1 g (5 mM) I in 10 ml dry benzene was mixed with a solution of 0.62 g (5 mM) p-nitroaniline in a mixture of 25 ml absolute benzene and 3 ml dry dioxane, and 1.01 g (0.01 mole) Et_3N was added over a period of 16 hr (20°). The mixture was kept for 4 hr at 20°, then refluxed for 30 min, cooled, treated with $NaHCO_3$ solution, and extracted with benzene. The benzene solution was evaporated, and the residue recrystallized from EtOH. Yield of IX 0.71 g (53%), dark yellow crystals, mp 188–188.5°. Found: C 67.33, 67.20; H 3.81, 3.74; N 10.35, 10.45%, calculated for $C_{15}H_{12}N_2O_3$: C 67.67; H 3.79; N 10.52%.

3,4,4-Trichlorochrom-2-ene (II). 5.84 g (0.04 mole) chromone, 40 mg benzoyl peroxide, and 20 ml $SOCl_2$ were refluxed together for 10 hr, excess $SOCl_2$ distilled off, and the residue vacuum distilled with protection against the moisture of the air. The product was left under vacuum for 40 min, then heated under vacuum for 10 min at 60–65° to remove hydrogen chloride. Yield 4.6 g (49%), bp 126° (1 mm), n_d^{20} 1.6109. Found: C 45.74, 45.75; H 2.35, 2.33; Cl 45.00, 45.08%, calculated for $C_9H_5Cl_3O$: C 45.90; H 2.12; Cl 45.28%.

Ethyl 3-chlorochromone-2-carboxylate (V). 2.18 g (0.01 mole) ethyl chromone-2-carboxylate, 6.75 g (0.05 mole) sulfuryl chloride, and 20 mg benzoyl peroxide were refluxed together for 10 hr, excess sulfuryl chloride distilled off under vacuum, and the residue recrystallized twice from EtOH, yield 1.64 g (43%), mp 91–91.5°. Found: C 56.83, 56.75; H 3.74, 3.52; Cl 14.44, 14.52%, calculated for $C_{12}H_9ClO_4$: C 57.03; H 3.60; Cl 14.04%.

3-Chlorochromone-2-carboxylic acid (VI). 2 g (8 mM) ester V and 20 ml AcOH–HCl (1 : 1), were refluxed together for 4 hr, then left for about 16 hr, evaporated, and the residue treated with saturated $NaHCO_3$ solution, which was then extracted with benzene. The bicarbonate solution was acidified, and 0.88 g (45%) acid VI filtered off, mp 206°(decomp, ex aqueous AcOH). Found: C 53.54, 53.67; H 2.33, 2.35; Cl 15.79, 15.49%, calculated for $C_{10}H_5ClO_4$: C 53.83; H 2.23; Cl 15.79%.

3-Chlorochromone (IV). Decarboxylating 0.5 g acid VI (by heating at 230° for 30 min), followed by crystallization of the reaction product from benzene–petrol ether, gave 0.24 g (61%) IV, mp 112–113°. IR spectrum (in KBr discs): 1655 cm^{-1} (C=O). Found: C 60.00, 59.92; H 2.70, 2.74; Cl 19.45, 19.45%, calculated for $C_9H_5ClO_2$: C 59.86; H 2.77; Cl 19.63%.

2-(p-Nitrophenylamino) 3,4-dichlorochrom-3-ene (XIc). A. A hot solution of a mixture of 2.02 g (0.02 mole) Et_3N and 1.47 g (11.9 mM) p-nitroaniline in 150 ml benzene was added to a solution of 2.32 g (9.9 mM) II (obtained from chromone) in 15 ml dry benzene. After 16 hr (20°) the $Et_3N \cdot HCl$ precipitate was filtered off, the benzene solution evaporated, and the oily residue rubbed with 5 ml petrol ether. The yellow crystals that formed were filtered off, washed with MeOH, and dried, yield of XIc (2.04 g (61.5%), mp 123–124°(decomp, ex petrol ether–benzene; active charcoal). IR spectrum (CHCl$_3$, c 0.05 M, d 0.166 mm): 3430 cm^{-1} (NH), unsymmetrical band at 1610 cm^{-1} (valence vibrations of C=C bonds of the benzene ring, and of the C=C bond at the 3,4 position), 1527 and 1324 cm^{-1} (NO_2). Found: C 53.44, 53.31; H 2.80, 3.00; Cl 20.53, 20.65; N 8.41, 8.32% calculated for $C_{15}H_{10}Cl_2N_2O_3$: C 53.45; H 3.00; Cl 21.02; N 8.30%.

B. 0.57 g (3.15 mM) **IV** and 5 ml $SOCl_2$ were refluxed together for 10 hr, excess $SOCl_2$ distilled off, the residue rubbed with 20 ml benzene, and 0.48 g (3.5 mM) p-nitroaniline and 0.7 g Et_3N in 20 ml benzene added, and the products worked up as described in the preceeding experiment, to give 1.04 g (98%), compound **XIc** (identified by mixed mp and IR spectrum).

C. 1 g aminochromene **XIc** in 40 ml EtOH and 10 ml conc HCl were refluxed together for 15 min, the products diluted with an equal volume of water, and then repeatedly extracted with benzene. Crystallization from MeOH gave 0.24 g (38.6%) compound whose mp (mixed mp) and R_f in thin-layer chromatography on Al_2O_3 were identical with that of known **IV** prepared as above.

3-Chloro-4-(p-nitrophenylamino)chrom-2-ene (XVI). 1.5 g (4.45 mM) aminochromene **XIc** was heated, in an oil bath to 170° (at 130° the compound melted, then solidified, and at 170° melted again). The products were ground in a mortar with a saturated solution of Na_2CO_3, the solid filtered off, washed with water, dried, and treated with cold benzene (2 × 150 ml), the insoluble residue filtered off, the benzene solution evaporated, and the residue recrystallized from benzene–petrol ether. Yield of **XVI** 0.34 g (25%), dark orange crystals, mp 191–192° (ex benzene). Found: C 59.90; H 3.14; Cl 11.72, 11.89 N 9.36, 9.43%, calculated for $C_{15}H_9ClN_2O_3$: C 59.92; H 3.02; Cl 11.80; N 9.32%.

2-Phenylamino-3,4-dichlorochrom-3-ene (XIa). Compound **II** prepared from 3.6 g (0.02 mole) **IV** in 20 ml dry benzene, was mixed with 1.86 g (0.02 mole) aniline and 4.04 g (0.04 mole) Et_3N in 100 ml dry benzene, the $Et_3N \cdot HCl$ filtered off, the solution evaporated, the oily residue rubbed with a small amount of petrol ether, the product filtered off and recrystallized from MeOH to give 2.9 g colorless crystals of compound **XIa**. A further 0.7 g material was isolated from the mother liquors. Total yield 3.6 g (61.5%), mp 92–92.5°. IR spectrum CHCl$_3$, c 0.1 M, d 0.166 mm) 3430 cm^{-1} (NH), 1605 cm^{-1} (unsymmetrical band, valence vibrations of C=C bonds in the benzene ring, and of the C=C bond at the 3,4 position). Found: C 61.94; 62.06; H 3.77, 3.74; Cl 24.38, 24.65; N 4.95, 5.02%, calculated for $C_{15}H_{11}Cl_2NO$: C 61.67; H 3.80; Cl 24.26; N 4.80.

0.3 g **XIa** in 10 ml EtOH and 8 ml conc HCl were refluxed together for 4 hr, the solution evaporated, and the residue washed with 2 N HCl and water, to give 0.18 g (95%) **IV**, identical with a known specimen with respect to mp (mixed mp) and R_f for thin layer chromatography on Al_2O_3.

3-(o-Hydroxyphenyl)propylphenylamine (XIVa). A. 0.8 g (2.73 mM) **XIa** was hydrogenated in 70 ml absolute MeOH in the presence of 0.5 g 5% Pd/BaSO$_4$ and 1.01 g (0.01 mole) Et_3N for 30 min, under ordinary conditions, until 4 molecules of H_2 had been absorbed. The catalyst was filtered off, the filtrate diluted with an equal volume of water, when a colorless precipitate of **XIVa** formed, yield 0.55 g (88.7%), mp 123–124°(ex petrol ether-benzene, then from aqueous MeOH). Found: C 78.98, 79.05; H 7.49, 7.66; N 6.26; 6.40%, calculated for $C_{15}H_{17}NO$: C 79.27; H 7.54; N 6.16%.

B. A suspension of 5.2 g anilide **XV** in dry ether, was added with stirring, over a period of 20 min, to 0.9 g $LiAlH_4$ in 200 ml dry ether, the whole refluxed for 6 hr, decomposed with water, and acidified with 2 N HCl. The aqueous solution was separated off, the ether solution repeatedly extracted with 2 N HCl. 3 g starting anilide **XV** was isolated from the ether solution. The combined hydrochloric acid solutions were neutralized with K_2CO_3 and extracted with benzene, the extract dried and evaporated to give 1.9 g amine **XIVa** (92% on the anilide reacted), mp 122–123.5°(ex aqueous MeOH, active charcoal). Undepressed mixed mp with a specimen prepared by method A.

o-Hydroxycinnamanilide (XV). 7.4 g (0.05 mole) dihydrocoumarin (obtained in quantitative yield by hydrogenating coumarin in EtOH using Pd/$BaSO_4$ in the presence of conc HCl) and 15 g (0.16 mole) aniline were refluxed together for 6 hr. After 16 hr (20°) the product was filtered off and washed with ether, yield 10 g (83.2%), mp 137.5–138° (ex benzene). Found: C 74.60, 74.65; H 6.34, 6.35; N 5.92, 5.88%, calculated for $C_{15}H_{15}NO_2$: C 74.68; H 6.27; N 5.81%.

2-(p-Sulfamidophenylamino)-3,4-dichlorochrom-3-ene (XIb). A solution of 0.87 g (5.08 mM) 4-aminobenzenesulfamide and 1.5 g (0.015 mole) Et_3N in 50 ml dry dioxane was added to a solution of 1.20 g (5.08 mM) **II** in 20 ml dry dioxane. After 2 days the products were diluted with twice their volume of water, and the precipitate filtered off and recrystallized repeatedly from aqueous EtOH. Yield 1.44 g (76.5%). On heating it decomposed without melting. Found: C 48.56, 43.38; H 3.24, 3.11; Cl 19.35, 19.53; S 8.98, 8.82%, calculated for $C_{15}H_{12}Cl_2N_2O_3S$: C 48.55; H 3.26; Cl 19.09; S 8.64%.

3-(o-Hydroxyphenyl)propyl(p-sulfamidophenyl)amine (XIVb). 0.62 g (1.67 mM) compound **XIb** was hydrogenated in 100 ml MeOH in the presence of 0.5 g 5% Pd/$BaSO_4$ and 1.01 g (0.01 mole) Et_3N, for 1 hr under ordinary conditions, until 4 moles of hydrogen had been absorbed. The catalyst was filtered off, the solution evaporated, and the residue treated with water and extracted with ether. The extract was dried and evaporated. Yield 0.34 g (66.5%) amine **XIVb**, mp 159–160° (ex aqueous EtOH, active charcoal). Found: N 9.04; S 10.53, 10.62%, calculated for $C_{15}H_{18}N_2O_3S$: N 9.15; S 10.46%.

Di(3,4-dichlorocoumar-3-ene-2-yl) ether (X). Compound **II**, prepared from 1.80 g (0.01 mole) **IV**, was treated with a saturated solution of $NaHCO_3$. The crystalline product was filtered off, washed with water, boiled with 5 ml MeOH, and the solid separated off and dried, yield 1.76 g (84.5%) **X**, mp 168–169° (ex toluene–hexane, active charcoal). Found: C 51.83, 51.84; H 2.42, 2.30; Cl 33.76, 33.92%, calculated for $C_{18}H_{10}Cl_4O_3$: C 51.96; H 2.43; Cl 34.07%.

On keeping in air, the ether **X** was quantitatively hydrolyzed to **IV**.

Dicoumarin ether (XII). A suspension of 1.55 g (3.76 mM) ether **X** in 175 ml absolute MeOH was hydrogenated in the presence of 2.02 g (0.02 mole) Et_3N and 1 g 5% Pd/$BaSO_4$ for 4 hr under ordinary conditions until 6.2 moles of hydrogen had been absorbed. The catalyst was filtered off, the solution evaporated, the residue treated with water, and extracted with ether. The extract was then dried over Na_2SO_4, the ether distilled off, and the residue rubbed with 5 ml cold MeOH 0.47 g (44%) colorless crystals of **XII** were filtered off rapidly, mp 95–96° (ex EtOH). Found: C 76.61, 76.46; H 6.52, 6.52%, calculated for $C_{18}H_{18}O_3$: C 76.60; H 6.41%.

3-(o-Hydroxyphenyl)propionaldehyde 2,4-dinitrophenylhydrazone (XIII). 0.2 g (0.71 mM) ether **XII**, 10 ml MeOH, 0.14 g (0.71 mM) 2,4-dinitrophenylhydrazine, and 0.5 ml conc HCl were refluxed together for 2 hr. Cooling precipitated 0.22 g (94% calculated on the 2,4-dinitrophenylhydrazine) orange crystals of **XIII**, mp 178–179° (ex MeOH).* Found: C 54.55, 54.83; H 4.49, 4.40; N 16.93, 16.89%, calculated for $C_{15}H_{14}N_4O_5$: C 54.55; H 4.27; N 16.96%.

2,3-Dichlorochromanone-4 (III). 2.92 G (0.02 mole) chromone and 3.34 g (0.025 mole) sulfuryl chloride were mixed with cooling, kept for about 16 hr at 20°, excess sulfuryl chloride vacuum distilled off, and the residue recrystallized from absolute EtOH. Yield of **III** 2.4 g (56%), mp 91–91.5°. IR spectrum (in KBr discs): 1700 cm^{-1} (C=O). Found: C 49.96, 50.14; H 2.80, 2.69; Cl 32.91, 32.65%, calculated for $C_9H_6Cl_2O_2$: C 49.81; H 2.76; Cl 32.67%.

0.88 g (8.8 mM) Et_3N was added to a solution of 1.90 g (8.8 mM) **III** in 20 ml dry benzene, the $Et_3N \cdot HCl$ filtered off, the solution evaporated, and the residue recrystallized from EtOH. Yield 1.24 g (78.5%) **IV**, mp 112–113°.

3-Chloroflavone (VII). A solution of 1.11 g (5 mM) flavone in 15 ml dry $CHCl_3$ and 0.75 g (5.6 mM) sulfuryl chloride were refluxed together for 1 hr, the products vacuum evaporated, the residue washed with water, dried, and recrystallized from EtOH to give 0.82 g (65%) compound **VII**, mp 119.5–120.5°. Found: C 70.27, 70.15; H 3.56, 3.59; Cl 14.06, 14.11%, calculated for $C_{15}H_9ClO_2$: C 70.18; H 3.54; Cl 13.81%.

2,3,3-Trichloroflavanone (VIII). A mixture of 1.11 g (5 mM) flavone, 1.67 g (12.5 mM) sulfuryl chloride, and 10 mg benzoyl peroxide (the mixture boiled on mixing) was allowed to stand for 16 hr at about 20°. The precipitate was filtered off, washed with aqueous MeOH (1:1), and crystallized from absolute EtOH, to give 1.07 g (67%, allowing for the material isolated from the mother liquors) **VIII**, mp 110.5–111°. Found: C 54.92, 54.94; H 2.80, 2.80; Cl 32.44, 32.49%, calculated for $C_{15}H_9Cl_3O_2$: C 55.00; H 2.78; Cl 32.48%.

---

*The literature [3] gives mp 182–183°.

REFERENCES

1. V. A. Zagorevskii and D. A. Zykov, ZhOKh, 30, 1378, 1960.
2. V. A. Zagorevskii, ZhOKh, 32, 770, 1962.
3. W. Parham and L. Huestis, J. Am. Chem. Soc., 84, 813, 1962.
4. V. A. Zagorevskii, Sh. M. Glozman, V. G. Vinokurov, and V. S. Troitskaya, KhGS [Chemistry of Heterocyclic Compounds], 782, 1967.

13 December 1965

Institute of Pharmacology
and Chemotherapy, AMS
USSR, Moscow