

# PYRANS, THEIR ANALOGS, AND RELATED COMPOUNDS.

## XLIII\*. SYNTHESIS OF 2,3,3,4,4-PENTACHLOROFLAVAN AND INVESTIGATION OF SOME OF ITS REACTIONS

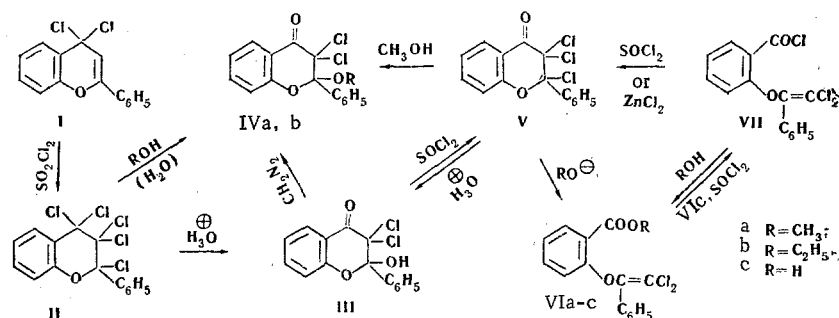
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UDC 547.814:542.938

Reaction of 4, 4-dichloroflavine (I) with sulfurylchloride affords 2, 3, 3, 4, 4-pentachloro-flavan (II). Hydrolysis of II gives 2-hydroxy-3, 3-dichloro-4-flavanone (III), while alcoholysis with aqueous alcohols yields 2-alkoxy-3,3-dichloro-4-flavanones (IVa, b). Treatment of III with  $\text{SOCl}_2$  gives 2,3,3-trichloro-4-flavanone (V), which with caustic alkali or sodium ethoxide is converted into o-(1-phenyl-2, 2-dichlorovinyl)benzoic acid (VIc) or its ethyl ester (VIb), respectively.

Although reactions of 4, 4-dichloropyrans involving replacement of one or both halogen atoms have been fairly widely investigated, reactions of these dichlorides in which both chlorine atoms are unaffected have not been examined.

We have obtained 2, 3, 3, 4, 4-pentachloroflavan (II) in 66% yield by treatment of 4, 4-dichloroflavine (I) [1] with sulfuryl chloride. This compound undergoes a variety of reactions. Hydrolysis of II gives 2-hydroxy-3, 3-dichloro-4-flavanone (III), and reaction with aqueous alcohols (sometimes with the addition of hydrochloric acid) affords 2-alkoxy-3, 3-dichloro-4-flavanones (IVa and b). The methyl ether IVa was also obtained by treatment of III with diazomethane.



Alkaline hydrolysis of the dichloride III removes two chloride ions. This shows that all the chlorine atoms in III, and consequently also in II, occur in the pyran ring. The hydroxyl group in III is not replaced by methoxyl on treatment with methanol in the presence of conc. HCl. Reaction of III with thionyl chloride afforded 2, 3, 3-trichloro-4-flavanone (V). Passing hydrogen chloride through a benzene solution of III did not give the trichloro-compound V, even on addition of anhydrous zinc chloride. Compound V is hydrolyzed in acid solution back to the carbinol III. Reaction of V with methanol (best in presence of hydrochloric acid)

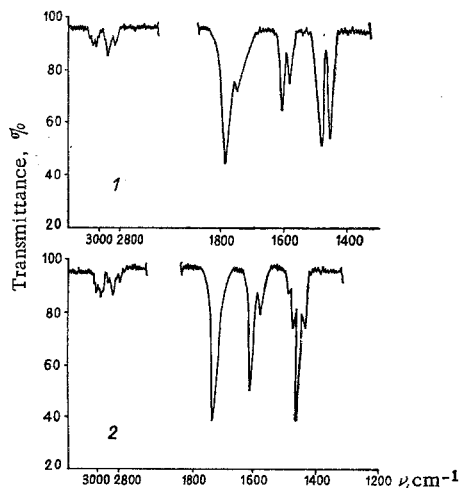
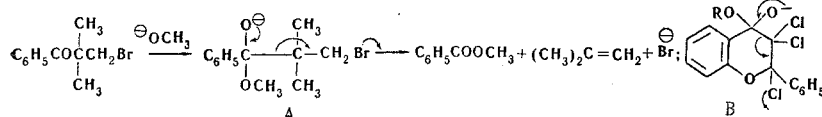
\*For Part XLII, see [7].

Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Translated from *Khimiya Geterotsiklicheskikh Soedinenii*, No. 9, pp. 1167-1170, September, 1970. Original article submitted July 7, 1969.

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gives IVa. Treatment of V with caustic alkali or with sodium ethoxide affords o-(1-phenyl-2, 2-dichlorovinyl)oxybenzoic acid (VIc), or its ethyl ester (VIb), respectively. In the presence of tertiary amines, the trichlorocompound V loses a molecule of chlorine with the formation of 3-chloro-4-flavone. The acid VIc gives the methyl ester (VIa) on acidic esterification or on treatment with diazomethane. The structure of VIa was confirmed by its IR spectrum ( $1728\text{ cm}^{-1}$ ,  $\text{C}=\text{O}$ ), and by hydrogenolysis to methyl salicylate (VIII) which was identified by conversion into the known crystalline benzoate (IX). Reaction of the acid VIc with thionyl chloride afforded the acid chloride (VII), which could be converted into the acid (VIc) or the esters (VIa and b). Moreover, reaction of VII with benzylamine gives the benzylamide of VIc (X), which on hydrogenation afforded the known benzylamide of salicylic acid (XI).

Compounds VII and V are isomeric, and a doubt therefore arises as to whether they might be conformers of cyclic structures of the V type. A thorough examination of the chemical properties and of some physicochemical characteristics showed that VII is, however, an acid chloride, while V is a substituted flavanone. VII reacts much more readily than V with solutions of silver nitrate to give silver chloride. The IR spectrum of VII (see Fig.) exhibits strong acid chloride carbonyl absorption at  $1785\text{ cm}^{-1}$  (together with a low intensity band at  $1750\text{ cm}^{-1}$ ). In the IR spectrum of V (see figure), the carbonyl adsorption appears at  $1730\text{ cm}^{-1}$ . The IR spectral curves of V and VII differ. The nuclear quadrupole resonance (NQR) spectrum of V shows signals at 38.248 and 39.060 MHz attributed to the two geminal chlorine atoms in the 3-position and a signal at 34.986 MHz arising from the Cl in the 2-position. The NQR spectrum of VII exhibits signals at 37.590 and 37.954 MHz (two geminal chlorine atoms at the double bond), and at 30.264 MHz (Cl in the  $\text{COCl}$  group). (The NQR spectra were obtained by T. A. Babushkina, for which the authors are extremely grateful.) We were unable to convert V into VII, whereas the reverse process was accomplished by heating V with thionyl chloride (the reaction proceeded much better if small quantities of water were added at intervals, resulting in the liberation of hydrogen chloride), or in benzene in the presence of anhydrous zinc chloride. The conversion of VII into V is probably a modified Kondakov reaction, with clear evidence for the possibility of the addition of the elements of the acid chloride group to the carbon-carbon double bond. This example, in our view, is of interest in view of the current interest in the mechanism of the Kondakov reaction. We have observed that the acid VIb is not converted into the carbinol III or the chloride V on treatment with hydrogen chloride. The mechanism of the conversion of the  $\beta$ -chloroketone V into VI under the influence of alkaline reagents would appear to be similar to that of the corresponding fragmentation reaction of open-chain  $\beta$ -haloketones [2, 3]:



IR Spectra (in  $\text{CHCl}_3$ ,  $c\ 0.1\text{ M}$ ,  $d\ 0.1\text{ mm}$ ). 1) o-(1-phenyl-2, 2-dichlorovinyl)benzoyl chloride (VII), 2) 2, 2, 3-trichloro-4-flavanone (V).

In the case of open-chain ketones, fragmentation of the molecule occurs via the intermediate compound A, with the formation of an ester and an unsaturated compound. In our case, the intermediate addition product of the nucleophile with the carbonyl compound is assigned the structure B, and this on fission of the single C-C bond does not give two molecules, since the acid and olefin fragments remain in the same molecule.

## EXPERIMENTAL

2, 3, 3, 4, 4-Pentachloroflavan (II). Dichloroflavan [1] (I), obtained from 4.44 g (0.02 mole) of flavone, was boiled with 10 ml of  $\text{SO}_2\text{Cl}_2$  for 1 hr 30 min. The excess of  $\text{SO}_2\text{Cl}_2$  was distilled off in vacuo, and the residue was washed with light petroleum and recrystallized from the minimum amount of benzene to give 5 g (66%) of II, mp  $143-144^\circ$  (from a mixture of benzene and light petroleum). Found: C 47.2; H 2.6; Cl 46.0.  $\text{C}_{15}\text{H}_9\text{Cl}_5\text{O}$ . Calculated: C 47.1; H 2.4; Cl 46.4%.

2-Hydroxy-3, 3-dichloro-4-flavanone (III). A portion of II [0.77 g (2 mmole)] in 30 ml of 60% acetic acid was boiled for 7 h, and evaporated to dryness. The residue was washed repeatedly with

water and recrystallized from  $\text{CCl}_4$  to give 0.5 g (80%) of III, mp 164-165° (from  $\text{CCl}_4$ ). Found: C 58.6; H 3.3; Cl 22.9%.  $\text{C}_{15}\text{H}_{10}\text{Cl}_2\text{O}_3$ . Calculated: C 58.3; H 3.3; Cl 22.9%. The compound gave no coloration with ferric chloride. IR spectrum (in  $\text{CCl}_4$ , c 0.01 M, d 1 mm),  $\text{cm}^{-1}$ : 3600 (OH), 1732 (C=O), 1614, 1590, 1480, 1465, 1455. UV spectrum (in alcohol, c  $1.10^{-5}$ - $1.10^{-2}$  M)  $\lambda_{\text{max}}$ , nm (log  $\epsilon$ ): 245 (4.28) and 312 (3.17).

2-Methoxy-3, 3-dichloro-4-flavanone (IVa). A portion of II [0.7 g (1.8 mole)] was boiled in a mixture of 20 ml of methanol and 5 ml of water, cooled, and 0.5 g (86%) of IVa, mp 141-141.5° (from methanol) was filtered off. Found: C 59.7; H 3.8; Cl 21.7%.  $\text{C}_{16}\text{H}_{12}\text{Cl}_2\text{O}_3$ . Calculated: C 59.5; H 3.7; Cl 21.9%. IR spectrum (here and below, the IR spectra are given in solution at c 0.1 M, d 0.1-1.0 mm) (in  $\text{CHCl}_3$ ),  $\text{cm}^{-1}$ : 1723 (C=O), 1612, 1590, 1480, 1467, 1455. Carrying out the reaction in the presence of hydrochloric acid had virtually no effect on the results. IVa was also obtained by the reaction of ethereal diazomethane with III, in 20% yield, mp 140-141°. Both samples were identical by their IR spectra and their  $R_f$  values on thin layer chromatography on alumina.

2-Ethoxy-3, 3-dichloro-4-flavanone (IVb). Obtained as for IVa, from 0.77 g (2 mmole) of II by boiling for 7 h in a mixture of 10 ml of alcohol and 5 ml of 2N HCl. Yield 0.4 g (60%), mp 108-109° (from 80% methanol). Found: C 60.7; H 4.1; Cl 20.9%.  $\text{C}_{17}\text{H}_{14}\text{Cl}_2\text{O}_3$ . Calculated: C 60.5; H 4.2; Cl 21.0%. IR spectrum (in  $\text{CHCl}_3$ ),  $\text{cm}^{-1}$ : 1725 (C=O), 1615, 1590, 1480, 1465, 1455.

2, 3, 3-Trichloro-4-flavanone (V). A portion of III [0.12 g (0.38 mmole)] in 5 ml of  $\text{SOCl}_2$  was boiled for 1 h 30 min, the excess of thionyl chloride removed in vacuo, and the residue triturated with 2 ml of alcohol. Crystallization from absolute alcohol afforded 0.1 g (76%) of V, mp 110-110.5°. IR spectrum (in  $\text{CHCl}_3$ ),  $\text{cm}^{-1}$ : 1730 (C=O), 1615, 1590, 1480, 1452. The sample gave no depression of mp on admixture with an authentic sample [4], and was identical with the latter by its IR spectrum and  $R_f$  value by thin layer chromatography on alumina. UV spectrum (in heptane, c  $1.10^{-5}$ - $1.10^{-2}$  M),  $\lambda_{\text{max}}$ , nm (log  $\epsilon$ ): 255 (3.97, 3.12 (3.39)).

Reactions of 2, 3, 3-trichloro-4-flavanone (V). a) On boiling 0.5 g (1.5 mmole) of V in a mixture of 10 ml of acetic acid and 5 ml of conc. HCl, there was obtained 0.3 g (64%) of III, mp 164-165.5° (from  $\text{CCl}_4$ ).

b) 0.5 g (1.5 mmole) of V was boiled for 10 h with a mixture of 10 ml of methanol and 1 ml of conc. HCl and evaporated to about  $\frac{1}{4}$  of its volume. The precipitate was filtered off and recrystallized from methanol to give 0.3 g (60%) of IVa, mp 140-141°. Without hydrochloric acid, the reaction proceeded differently.

c) To a solution of 1.31 g (4 mmole) of V in 45 ml of dioxane was added at  $\sim 50^\circ$  a solution of 0.52 g (13 mmole) of NaOH in 30 ml of water. The mixture was boiled for 30 min, evaporated rapidly in vacuo at  $50^\circ$  to  $\frac{1}{5}$  of its volume, 30 ml of water added, filtered, acidified with dilute (1:3)  $\text{HNO}_3$ , and extracted with ethyl acetate. The extract was evaporated in vacuo, and the residual oil was treated with 100 ml of boiling light petroleum ( $5 \times 20$  ml) with decantation, and recrystallized from a mixture of benzene and light petroleum to give 0.85 g (77%) of o-(1-phenyl-2, 2-dichlorovinyl)oxy)benzoic acid (VIc), mp 139.5-140.5°. Found: C 58.3; H 3.3; Cl 22.8%.  $\text{C}_{15}\text{H}_{10}\text{Cl}_2\text{O}_3$ . Calculated: C 58.3; H 3.3; Cl 22.9%. IR spectrum (in  $\text{CCl}_4$ ),  $\text{cm}^{-1}$ : 2400-3400 (wide bands, hydroxyl in COOH), 1760 and 7007 (weak and very strong, respectively, doublet due to C=O in COOH), 1610, 1490. UV spectrum (in alcohol, c  $1.10^{-5}$ - $1.10^{-2}$  M),  $\lambda_{\text{max}}$ , nm (log  $\epsilon$ ): 260 (4.11), inflexion at 286 (3.7).

d) To a solution of 1.64 g (5 mmole) of V in 20 ml of absolute alcohol was added at  $\sim 50^\circ$  a solution of sodium ethoxide (from 0.12 g of sodium and 5 ml of absolute alcohol), and the mixture was boiled for 6 h. The solid which separated on cooling was filtered off, and washed thoroughly with water to give 0.65 g (40%) of VIc ethyl ester (VIb), mp 117.5-118° (from alcohol). Found: C 60.6; H 4.1; Cl 21.2%.  $\text{C}_{17}\text{H}_{14}\text{Cl}_2\text{O}_3$ . Calculated: C 60.5; H 4.2; Cl 21.0%. IR spectrum (in  $\text{CCl}_4$ ),  $\text{cm}^{-1}$ : 1728 (C=O), 1610, 1585, 1490, 1460. The alcoholic solution, after removal of VIb, was evaporated, and the residue extracted with sodium carbonate solution to give 0.22 g (14%) of VIc, mp 139-140°.

o-(1-Phenyl-2, 2-dichlorovinyl)benzoyl Chloride (VII). A mixture of 1.78 g 15.7 mmole) of VIc and 15 ml of  $\text{SOCl}_2$  was boiled for 1 h, evaporated in vacuo, and the residue recrystallized from light petroleum to give 1.56 g (83%) of VII, mp 74-75° (from light petroleum, with charcoal). Found: C 55.1; H 3.1; Cl 32.5%.  $\text{C}_{15}\text{H}_9\text{Cl}_3\text{O}_2$ . Calculated: C 55.0; H 2.8; Cl 32.5%. IR spectrum (in  $\text{CHCl}_3$ ),  $\text{cm}^{-1}$ : 1785 and 1750 (strong and weak, respectively, doublet due to C=O in COCl), 1605, 1585, 1480, 1455. UV spectrum (in heptane, c  $1.10^{-5}$ - $1.10^{-2}$  M),  $\lambda_{\text{max}}$ , nm (log  $\epsilon$ ): 249 (4.25), 303 (3.59).

Reactions of VII. a) A portion of VII (0.1 g) and 4 ml of water were boiled for 4 h, to give 0.08 g (85%) of VIc, mp 139-140°.

b) A portion of VII (0.5 g) and 15 ml of methanol were boiled for 1 h, and the mixture evaporated to 1/4 its volume and 0.44 g (90%) of the methyl ester of VIc (VIa) was filtered off, mp 126.5-127° (from methanol). Found: C 59.7; H 3.8; Cl 22.0%.  $C_{16}H_{12}Cl_2O_3$ . Calculated: C 59.5; H 3.7; Cl 21.9%. Reaction of VII with the equivalent amount of sodium methoxide in methanol gave 81% of VIa, also obtained in 96% yield by treatment of VIc with diazomethane, or in 80% yield by esterification of VIc with methanol in the presence of conc. HCl. IR spectrum (in  $CHCl_3$ ),  $cm^{-1}$ : 1728, 1610, 1585, 1490, 1457. Hydrogenation of VIa in methanol over 10% Pd/BaSO<sub>4</sub> under the usual conditions until 4 moles of hydrogen had been taken up afforded the oily salicylic acid methyl ether (VIII), which was benzoylated by the Schotten-Baumann method without purification to give 41% of VIII benzoate (IX), mp 81-82° (from alcohol, with charcoal), identical with an authentic specimen [5].

c) Similarly, 0.5 g of VII on boiling for 30 min in alcohol gave 0.5 g (92%) of VIb.

d) To a solution of 0.33 g (1 mmole) of VII in 20 ml of absolute benzene was added a solution of 0.21 g (2 mmole) of benzylamine. After 2 h, the mixture was filtered, the benzene solution concentrated to 2 ml, and 20 ml of light petroleum added to give 0.35 g (87.5%) of VIc (X) benzylamide, mp 109.5-110° (from a mixture of benzene and light petroleum). Found: C 66.3; H 4.4; Cl 17.7%.  $C_{22}H_{17}NCl_2O_3$ . Calculated: C 66.3; H 4.3; N 3.5; Cl 17.8%. IR spectrum (in  $CHCl_3$ ),  $cm^{-1}$ : 3440 (narrow band, amide NH), 1650 (amide I), 1600, 1530 (amide II), 1480, 1450. Hydrogenation of X in alcohol over 10% Pd/BaSO<sub>4</sub> under the usual conditions until absorption of hydrogen ceased gave salicylic acid benzylamide (XI), yield 87%, mp 133.5-134.5°, giving no depression of mp on admixture with an authentic sample [6].

e) A portion of VII [0.2 g (0.6 mmole)] was boiled with 5 ml of SOCl<sub>2</sub> for 10 h, 2 drops of water being added each hour. The excess of SOCl<sub>2</sub> was distilled off in vacuo, and the residue was treated with light petroleum and twice recrystallized from alcohol with charcoal, to give 0.1 g (50%) of V, mp 110.5-111°. The compound was identical with an authentic sample (by mixed mp and IR spectrum). Cyclization of VII to V also occurred on boiling in dry benzene in the presence of a catalytic amount of calcined zinc chloride, for 1 h 30 min.

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