RESEARCH INTO ANALOGS OF PYRAN AND RELATED COMPOUNDS

XXX. The Reaction of 2-Methoxycarbonyl-4,4-dichloro-2-chromene with 1-Piperidino-1-cyclohexene*

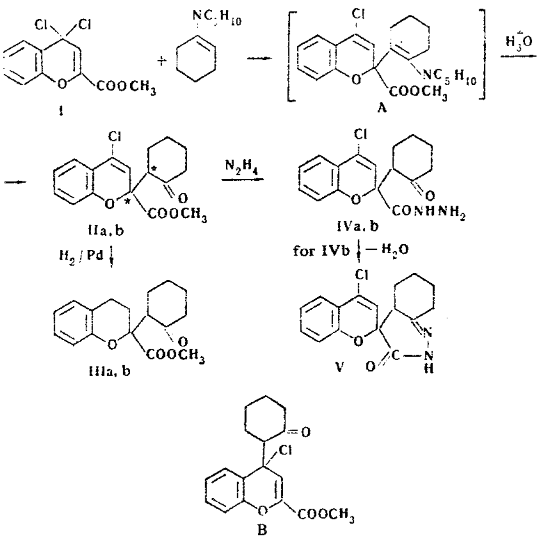
E. K. Orlova, I. D. Tsvetkova, V. S. Troitskaya, V. G. Vinokurov, and V. A. Zagorevskii

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 3, pp. 429–433, 1969

UDC 547.814.5:542.938:541.67

The reaction of 2-methoxycarbonyl-4, 4-dichloro-2-chromene with 1-piperidino-1-cyclohexene, for example, shows the high alkylating ability of 4, 4-dichlorochromenes toward enamines. In this case, the reaction is accompanied by the transfer of the reaction center in the dichloro compound from the 4- to the 2-position (allyl rearrangement), resulting (after acid hydrolysis) in the formation of 2-methoxycarbonyl-2-(2'-oxo-1'-cyclohexyl)-4-chloro-3-chromene in two diastereoisomeric pairs (**IIa** and b). The structure of compounds IIa and b is proved by hydrogenation to the diastereoisomeric 2-methoxycarbonyl-2-(2'-oxo-1'-cyclohexyl)chromans (**IIIa** and b) and examination of the NMR spectra of the latter. Hydrazides (IVa and b) were obtained from IIa and b, compound IVb then being cyclized to the intramolecular acylhydrazone V, which provides additional support for the structure **II**.

In continuation of our earlier investigation into the reaction of nucleophilic reagents with 4,4-dichlorochromenes, we have examined the reaction of 2-methoxycarbonyl-4,4-dichloro-2-chromene (I) with the tertiary enamine 1-piperidino-1-cyclohexene. The reaction was carried out with an excess of the enamine in benzene solution, without heating. Of the two possible substitution products (II or B) of the doubly reacting gem-dichloro compound, only the chromene II, containing a cyclohexanone group in the 2-position, was obtained. The reaction had therefore proceeded with allyl rearrangement of the 4,4-dichlorochromene system.



The intermediate substituted enamine (A) was not isolated in the free state, but was immediately subjected to acid hydrolysis to give the chromene **II**. Compound **II** has two asymmetric carbon atoms, and therefore probably consists of four stereoisomers. We have in fact succeeded in isolating two compounds with mp 171–171.5° C (**IIa**) and 106–107° C (**IIb**), apparently racemates. The IR spectra of **IIa** and **b** in $CHCl_3$ are clearly different from each other (figure). The UV spectral curves have a definite resemblance, but the intensities and positions of the absorption maxima do not coincide exactly. The R_f values from thin-layer chromatography are also not identical. Crystallooptic analysis shows differences in the refractive indices of **IIa** and **b**. The allocation of the 2,2-disubstituted 3-chromene structure to these compounds is supported by the NMR spectra of their hydrogenation products (**IIIa** and **b**). The NMR spectra of both **IIIa** and **b** (recorded in $CDCl_3$ relative to hexamethyldisilane on a Hitachi-H-60 apparatus with a working frequency of 60 MHz) show a broad multiplet at δ 1.5–3.2 ppm due to the protons of pyran and cyclohexane rings (the shapes of the multiplets from **IIIa** and **b** are not similar), a sharp 3-proton singlet at 3.65 ppm due to the CH_3—O group, and a multiplet between 6.7 and 7.2 ppm due to the four protons of the benzene ring. The spectrum shows no signal in the 4–5-ppm region, as would be expected from the proton in the 2-position of the chroman ring if the cyclohexyl residue were attached to the atom C_4. In the model compound, 2-ethoxycarbonylchroman, the methine proton in the 2-position is seen as a triplet at δ 4.57 ppm [1].

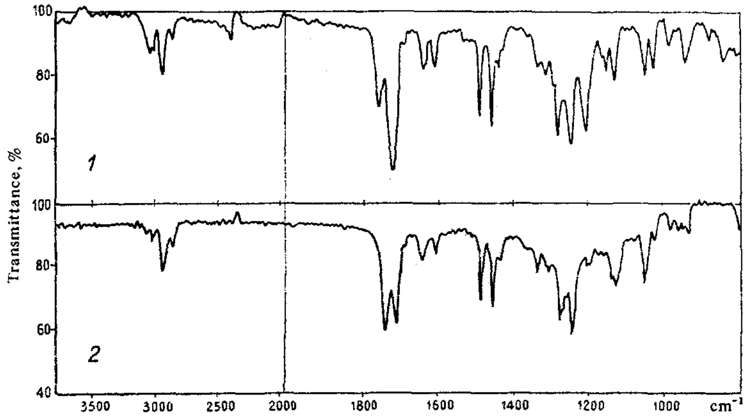
The nuclear quadrupole resonance spectrum (NQR) of **IIa** also corresponds with this structure. The chlorine atom gives a signal at 35.502 MHz, which is in the same region as that observed for the known 4-chlorocoumarin (35.455 MHz), which may be considered as approximating a model compound for compound **IIa** (the authors are very grateful to G. K. Semin and T. A. Babushkina for recording and interpreting the NQR spectra).

The esters **IIa** and **b** were converted into the corresponding hydrazides (IVa and **b**). The hydrazide **IVb**, for example, undergoes cyclization to the intramolecular acylhydrazone (V). This conversion also supports the validity of the structure indicated in formula II, since study of the Stuart-Briegleb molecular models shows that structure B could not undergo this cyclization.

The detailed structure of 4,4-dichlorochromenes presents an interesting problem. In our opinion, notwithstanding the resemblance to the pyrylium salts in

---

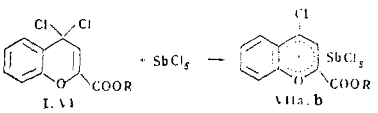
*For part XXIX, see [1].



The IR spectra of the diastereoisomeric 2-methoxycarbonyl-2-(2'-oxo-1'-cyclohexyl)-4-chloro-3-chromenes (**IIa** and **b**) in $CHCl_3$: 1) **IIa**, c 0.005 mole, d 0.133 mm; 2) **IIb**, c 0.005 mole, d 0.109 mm.

reactivity, the 4,4-dichlorochromenes clearly possess a covalent C—Cl bond, although this is strongly polarized. The covalent character of the bond is to a certain extent confirmed by the fact that these compounds are colorless or pale yellow in color, are soluble in nonpolar solvents, have fairly low melting points, and some of those without heavy substituents can be distilled in vacuo. In the allyl system of the dichlorochromenes in the crystalline state, both chlorine atoms are clearly in the 4-position, i.e., are geminal, as is shown by the NQR spectra. Thus in the NQR spectra of the dichloro compound **I** and of 2-chlorocarbonyl-4,4-dichlorochromene, there are seen only single signals in the 33–38-MHz region due to the two equivalent chlorine atoms at 36.043 and 36.995 MHz, respectively, as is also the case with 9,9-dichloroxanthene (36.316 MHz).

Pyrylium salts may be obtained from 4,4-dichlorochromenes. For example, the dichloro compound **I** and 2-ethoxycarbonyl-4,4-dichlorochromene (**VI**) react with $SbCl_5$ to give 2-methoxycarbonyl- and 2-ethoxycarbonyl-4-chlorobenzopyrylium hexachloroantimonates (**VIIa** and **b**).



I, VI

VIIa, b

I, VIIa R = CH_3; VI, VIIb R = C_2H_5

The IR spectra of **VIIa** and **b** show the ester carbonyl absorption bands at 1760 cm^{-1}, thereby excluding the possible structure where the $SbCl_5$ forms an adduct with the carbonyl oxygen. The salts **VIIa** and **b** are yellow in color, and are soluble in fairly polar, inert solvents, but insoluble in water. They are much more stable toward water and enamines than are the parent dichloro compounds.

In addition to this investigation, bearing in mind the extreme ease of hydrolysis of 4,4-dichlorochromenes in quantitative yields, we have utilized this reaction for labeling the carbonyl oxygen of benzopyrones. Thus, decomposition of the dichloro compound **I** with H_2O^{18} containing 55% of O^{18} afforded 2-methoxychromone, the IR spectrum of which in CCl_4 solution showed clearly the vibration bands of the pyrone carbonyl with O^{16} and O^{18} at 1663 and 1650 cm^{-1}, respectively. We expect that the ability to obtain pyrones labeled at the carbonyl group will assist in the solution of several problems connected with, for example, the kinetics of carbonyl oxygen exchange in acid media, the structure of pyrone derivatives (such as 4-hydroxycoumarin) which are capable of tautomeric conversion, etc.

EXPERIMENTAL

The authors express their sincere thanks to E. I. Fedin for the NMR spectra and to V. I. Sokol for carrying out the crystallographic examinations.

Thin-layer chromatography was carried out on grade II alumina with chloroform in the cases of compounds **IIa**, **b** and **IIIa**, **b**, and with grade VI activity using a mixture of chloroform and ethyl acetate (10 : 1) for compounds **IVa** and **b**.

2-Methoxycarbonyl-2-(2'-oxo-1'-cyclohexyl)-4-chloro-3-chromenes (IIa and b). To a solution of the dichloro compound **I** [1], obtained from 4.08 g (0.02 mole) of 2-methoxycarbonylchromone in 80 ml of dry benzene was added a solution of 8.26 g (0.05 mole) of 1-piperidino-1-cyclohexene in 10 ml of benzene, and the mixture was kept for ~18 hr. Then 250 ml of 2 N HCl was added, and the mixture was kept for a further 2 hr with occasional shaking. The acid layer (**A**) was separated and the benzene layer washed with water and evaporated in vacuo. The residue was treated with a mixture of methanol and light petroleum (1 : 4), and the resulting crystals were filtered off and washed with a small amount of methanol, giving 1.04 g of a mixture of compounds **IIa** and **b** (fraction 1) with a satisfactory elemental analysis that showed only two spots with thin-layer chromatography on Al_2O_3. The filtrate and washings yielded a further 0.94 g of the mixture of **IIa** and **b** (fraction 2). Benzene was added to acid solution **A**; the organic layer separated after 3 hr and a further 0.96 g of the mixture of **IIa** and **b** (fraction 3) separated as above. This operation was repeated once more, and the benzene layer separated after ~18 hr to give another 0.54 g of the mixture (fraction 4). Fractions 2, 3, and 4 were combined and crystallized from the minimum amount of methanol to give 2.34 g of a mixture of **IIa** and **b** (fraction 5), with a satisfactory analysis and chromatogram. The total yield of the mixture of **IIa** and **IIb** was 3.38 g (52.6%). Recrystallization of fraction 1 from ethanol gave **IIa**, mp 171–171.5° C, R_f 0.63; UV spectrum (in heptane, c $1 \cdot 10^{-4}$ to $1 \cdot 10^{-3}$): λ_{max} 224, 270 and 319 nm (log ε 4.45, 3.66, and 3.48); IR spectrum (chloroform): 1760 cm^{-1} (ester carbonyl), 1723 cm^{-1} (ketone carbonyl), N_p 1.519, N_m ~ 1.670, N_g 1.702. Found, %: C 63.68, 63.57; H 5.47, 5.44; Cl 11.19, 11.24. Calculated for $C_{17}H_{17}ClO_4$, %: C 63.65; H 5.33; Cl 11.05. Fraction 5 (2.34 g), twice recrystallized from 70% methanol (the first time with charcoal) gave 1.5 g of **IIb** (the recrystallization was best carried out by seeding and cooling to about 40° C for about 15 min), mp 106–107° C, R_f 0.8; UV spectrum (heptane, c $1 \cdot 10^{-4}$ to $1 \cdot 10^{-3}$): λ_{max} 222, 268, and 312 nm (log ε 4.54, 3.58, and 3.48); IR spectrum ($CHCl_3$): 1740 cm^{-1} (ester carbonyl), 1710 cm^{-1} (ketone carbonyl). N_p 1.561, $N_m \sim$ 1.600, N_g 1.736. Found, %: C 63.69, 63.52; H 5.36, 5.36; Cl 11.10, 10.89. Calculated for $C_{17}H_{17}ClO_4$, %: C 63.65; H 5.33; Cl 11.05.

2-Methoxycarbonyl-2-(2'-oxo-1'-cyclohexyl)chroman (IIIa). 1.25 g (3.9 mM) of IIa in alcohol was hydrogenated over 0.2 g of 5% Pd/$BaSO_4$ in presence of 0.4 g of triethylamine under the usual conditions until 8.2 mM of H_2 had been taken up. The catalyst was filtered off, the solution evaporated in vacuo, and the residue washed repeatedly by decantation with water and recrystallized from 70% methanol, giving 0.76 g (67.6%) of IIIa, mp 110–111°C (from alcohol); R_f 0.55. Found, %: C 70.96, 71.17; H 7.05, 7.25. Calculated for $C_{17}H_{20}O_4$, %: C 70.81; H 6.99.

2-Methoxycarbonyl-2-(2'-oxo-1-cyclohexyl)chroman (IIIb). 0.32 g (1 mM) of the ester IIb in methanol was hydrogenated in the presence of 0.22 g of triethylamine as for IIIa, and the residue remaining after evaporation of the solution was washed with water and extracted with a mixture of ether and ethyl acetate. The combined extracts were evaporated, the residual oil was crystallized by rubbing, and the overall yield of residue was induced to crystallize by scratching and was treated with light petroleum to give 0.28 g (48.3%) of **IIIb**, mp 109–110° C (from 70% methanol). R_f 0.43. Found, %: C 70.82, 70.92; H 7.12, 7.08. Calculated for $C_{17}H_{20}O_4$, %: C 70.81; H 6.99. The melting point of a mixture of IIIa and b was depressed (95–105° C).

2-(2'-Oxo-1'-cyclohexyl)-4-chloro-3-chromene-2-carbonohydrazide (IVa). A 0.64-g quantity (2 mM) of IIa and 0.11 g of hydrazine hydrate in 150 ml of methanol was kept at 20° C for about 18 hr, the methanol distilled off quickly in vacuo at about 45° C, and the residue triturated with dry ether, after which the crystals were filtered off, washed with ether and recrystallized from absolute ethanol to give 0.26 g (40.5%) of the hydrazide IVa, decomp. 123° C. R_f 0.14; IR spectrum (KBr disk): 3500, 3325, 3280 cm^{-1} ($NHNH_2$ group), 1708 cm^{-1} (broad, very intense unsymmetrical band due to two carbonyl groups). Found, %: C 60.05, 59.99; H 5.40, 5.19; N 8.88, 8.87. Calculated for $C_{16}H_{17}ClN_2O_3$, %: C 59.91; H 5.34; N 8.73.

2-(2'-Oxo-1'-cyclohexyl)-4-chloro-3-chromene-2-carbonohydrazide (IVb). The reaction between 0.64 g of the ester IIb and 0.11 g of hydrazine hydrate in 100 ml of methanol was carried out as above, and the product treated with ethanol to give 0.46 g (71.8%) of the hydrazide IVb, decomp. above 100° C, R_f 0.23. Found, %: C 60.28, 60.29; H 5.53, 5.28; N 8.48, 8.55. Calculated for $C_{16}H_{17}ClN_2O_3$, %: H 5.34; N 8.73.

Intramolecular hydrazidohydrazone (V). A solution of 0.2 g (0.62 mM) of the hydrazide **IVb** in dry toluene was boiled for 1 hr, water being removed by means of a Dean and Stark apparatus containing barium oxide. The solution was filtered hot and kept for about 16 hr. The precipitate which separated was filtered off and washed with toluene to yield 0.1 g (53 %) of V, mp 156° C (decomp., from toluene), IR spectrum (KBr disk): 3345, 3290 (NH), 1739 C=O), 1702 (C=N), 1645, 1610 and 1580 cm^{-1} (pyran and benzene double bonds). Found, %: C 63.11; H 5.01; Cl 11.52. Calculated for $C_{16}H_{15}ClN_2O_2$, %: C 63.48; H 5.00; Cl 11.77.

2-Methoxycarbonyl-4-chlorobenzopyrylium hexachloroantimonate (VIIa). To a solution of the dichloro compound **I** (from 2.04 g of 2-methoxycarbonylchromone) in 100 ml of dry benzene was added 2.98 g (0.01 mole) of $SbCl_5$. The resulting precipitate was filtered, washed with benzene and then with ether to give 5.2 g (93.7%) of the salt VIIa, decomp. 180° C. IR spectrum (in oil): 1760 (ester C=O), 1625 and 1590 cm^{-1} (double bonds of the benzene and pyran rings). Found, %: Cl 43.99, 43.96; Sb 21.62, 21.69. Calculated for $C_{11}H_8Cl_7O_2Sb$, %: Cl 44.48; Sb 21.82.

2-Ethoxycarbonyl-4-chlorobenzopyrylium hexachloroantimonate (VIIb). To a solution of the dichloro compound **VI** (from 1.09 g of 2-ethoxycarbonylchromone) in 20 ml of dry benzene was added 1.49 g (5 mM) of $SbCl_5$ while dry hydrogen chloride was passed in at the same time. The precipitate was filtered off to give 1.6 g (56%) of the salt VIIb, mp 177° C (decomp., from dichloroethane). Found, %: Cl 43.43; Sb 21.62. Calculated for $C_{12}H_{10}Cl_7O_3Sb$, %: Cl 43.38; Sb 21.28. The IR spectrum (in oil) shows bands at 1760, 1625, and 1690 cm^{-1}.

REFERENCES

1. V. A. Zagorevskii, I. D. Tsvetkova, E. K. Orlova, and S. L. Portnova, KhGS [Chemistry of Heterocyclic Compounds], 422, 1969.

24 December 1966

Institute of Pharmacology and
Chemotherapy AMN USSR,
Moscow