RESEARCH ON PYRANES, THEIR ANALOGS, AND RELATED COMPOUNDS

XXIV. Reaction of Methanol with Methyl 4,4-Dichlorochromene-2-Carboxylate*

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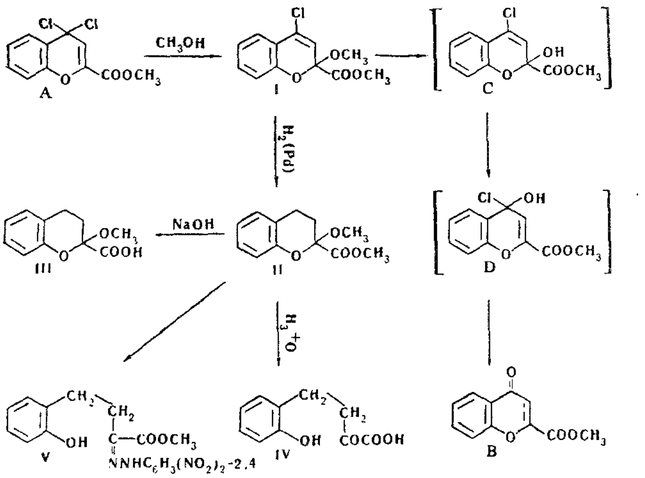
The action of methanol on methyl 4,4-dichlorochromene-2-carboxylate (A) gives a 2-substitution product I, readily hydrolyzed in acid solution to a 2-hydroxy derivative C, which undergoes an allylic rearrangement to an ester of chromane-2-carboxylic acid B. Hydrogenation of compound I gives 2-methoxy-2-carbomethoxychromane (II), which is caused to undergo some chemical reactions.

It was previously shown that the acid chloride derived from 4,4-dichlorochromene-2-carboxylic acid reacts in two ways with water and alcohols: a) to give 4-chlorocoumarin by attack of water or alcohols at position 2 of the chromene system, followed by decarboxylation, and 2) in the direction of regeneration of the starting chromone-2-carboxylic acid [1–3]. There it has been assumed that the second course is followed through replacement of a chlorine atom at position 4, followed by elimination of hydrogen chloride or alkyl halide. It was further noted that treatment of esters of 4,4-dichlorochromene-2-carboxylic acid with water or alcohols, does not result in destruction of the carbon skeleton, but conversion to esters of chromane carboxylic acid. The extents of these conversions were not determined quantitatively.



In the present work it was shown that methanol reacts with methyl 4,4-dichlorochromene-2-carboxylate A to give a 2-substitution product, viz. methyl 2-methoxy-4-chlorochrom-3-ene-2-carboxylate I.

The reaction was carried out both in a methanol solution of sodium methoxide, and in methanol containing triethylamine or a sterically hindered amine, 2,2,6,6-tetramethyl-1,2,5,6-tetrahydropyridine, with which a dichlorochromene is unlikely to give a quaternary salt. The structure of compound I is shown by its hydrogenation to 2-methoxy-2-carbomethoxychromane II.

The PMR spectrum of compound II, (figure, plot 1), measured in CDCl$_3$, shows 2 signals of 2 methylene groups at positions 3 and 4, each with an area of 2 proton units at 2.25 and 2.80 ppm. The 3.30 and 3.90 ppm signals belong respectively, to the two methyl groups of ether and ester groups. In the spectrum of a model compound 2-ethyl chromanate, determined in CHCl$_3$ (figure, plot 2), signals at 2,18 and 2.70 ppm correspond to the two methylene groups at positions 3 and 4, while a methine proton at position 2 gives a triplet at 4.57 ppm. Compound II fails to give a signal in this region.

Alkaline hydrolysis of ester II gives acid III, while acid hydrolysis gives compound IV. In the crystalline state compound IV is present as keto acid, and not as the possible cyclic hemiacetal. This is proved by the IR spectrum (in oil) which shows bands at 1690 and 1740 cm^{-1}, corresponding to vibrations of CO groups of carboxyl and ketone groups. Hydrazone V was obtained by reaction of compound II with 2,4-dinitrophenylhydrazine in methanol containing hydrochloric acid.

Alkalies or silver nitrate split off the halogen atom from compound I very slowly. In acid solution the splitting off occurs extremely fast, to give methyl chromate (B). Undoubtedly ester B is formed by hydrolysis of the acetal group of compound I to hydroxy derivative C, which suffers allylic rearrangement to the intermediate compound D, which rapidly loses hydrogen chloride. The facile rearrangement of C to D provides a basis for the hypothesis that regeneration of esters of chromane carboxylic acid when water acts on a type A dichloride, can proceed not only via an intermediate compound of type D, but also through one of type C. It can be postulated that rearrangement of a type C hydroxy compound is accelerated by acids, since such usually obtains in the rearrangement of allylic alcohols. This is confirmed by the fact that methoxy derivative I is also able to undergo rearrangement in the presence of an acid catalyst, p-toluene sulfonic acid. The resultant intermediate methyl ester of 4-chloro-4-methoxychromene carboxylic acid (E) decomposes spontaneously to give the methyl ester of a chromane carboxylic acid, and methyl chloride. The latter was characterized as methyltriethylammonium chloride and methyltriethylammonium triphenylborate.

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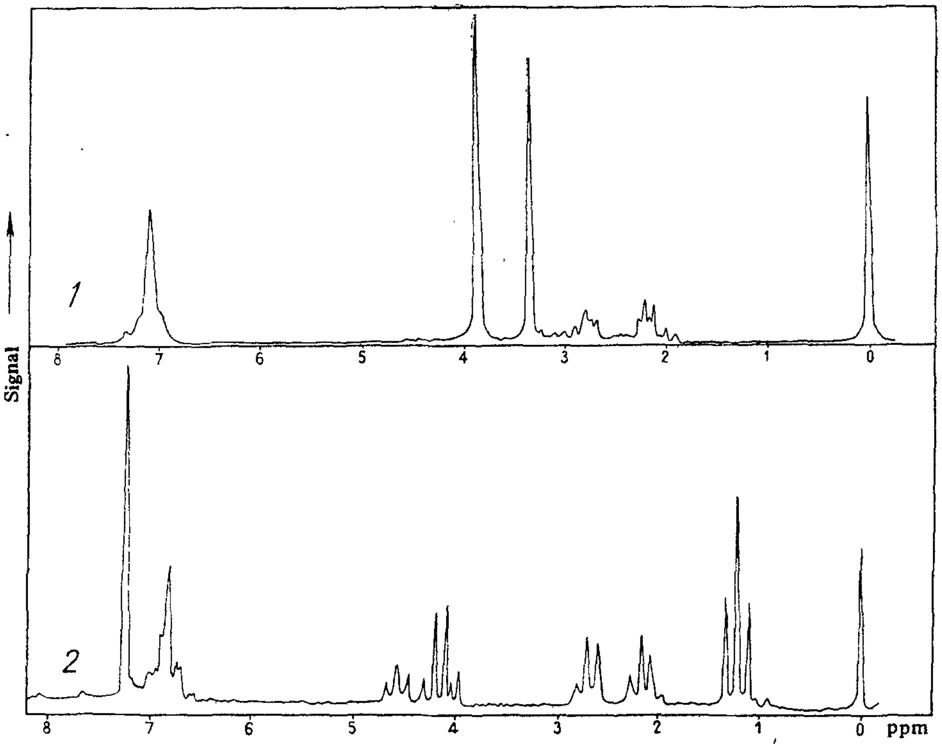
*For Part XXIII see [4]



PMR spectra (instrument working frequency 60 Mc, internal standard tetramethylsilane): 1) 2-Methoxy-2-carbomethoxychromane II in $CDCl_3$; 2) Ethyl chromate in $CHCl_3$.

To ascertain the capacity of 4, 4-dichlorides of chromenes to convert alcohols to alkyl halides, the reaction was run between butan-1-ol and the dichloride A. Butyl chloride was obtained in 70% yield. Probably part of the butyl chloride is formed by direct formation of a type E compound, and part by rearrangement of the 2-hydroxybutyl derivative, similar to compound I.

EXPERIMENTAL

Methyl 2-methoxy-4-chlorochromene-2-carboxylate I. 5 g (0.0235 mole) methyl chromone-2-carboxylate and 15 ml $SOCl_2$ were refluxed together for 10 hr. Excess of the latter was carefully distilled off with benzene, the residue of dichloride A dissolved in 100 ml dry petrol ether, and a solution of sodium methoxide made from 0.60 g (0.026 g-at) Na and 50 ml MeOH added. The mixture was shaken for 1 hr (the solution must remain alkaline), 50 ml water added, the whole extracted with petrol ether, and the extract dried over calcined Na_2SO_4. The petrol ether was distilled off, and the residue vacuum distilled with protection against moisture of the air, to give 4.85 g (81%) oily compound I, bp 173–175°(3 mm), n_d^{20} 1.5601. Found: C 57.11, 57.18; H 4.44, 4.42; Cl 14.29, 14.23%, calculated for $C_{12}H_{11}ClO_4$: C 56.59; H 4.36; Cl 13.92%.

Decomposition of chloroester I. a) 0.5 g chloroester I and 10 ml saturated $NaHCO_3$ solution (about 12 hr/20°) gave 0.4 g compound mp 120–122°, identical, as shown by mixed mp, with B. 0.4 g chloroester I was treated with 2 N HCl (oil rapidly converted to a solid), and gave 0.3 g ester B.

b) To the oil chloroester I prepared from 2.04 g (0.01 mole) B, 0.17 g (0.001 mole) p-toluene sulfonic acid was added in a current of nitrogen. The methyl chloride evolved was carried by the nitrogen through a tube filled with alkali, to an ampul containing Et_3N at –40° to –50°. The ampul was sealed and heated for 6 hr at 100°, to give 0.18 g (35%) methyltriethylammonium chloride. The compound was quite hygroscopic. Found: Cl 22.62, 22.79%, calculated for $C_7H_{18}ClN$: Cl 23.37%. Reaction of an aqueous solution of the methyltriethylammonium chloride with sodium tetraphenylborate dissolved in water gave methyltriethylammonium tetraphenylborate, whose IR spectrum (in KBr discs) was identical in the 500–2000 cm^{-1} region with the spectrum of a known specimen, made from methyltriethylammonium iodide and sodium tetraphenylborate. Found: C 86.15; H 8.88%, calculated for $C_{31}H_{38}BN$: C 85.48; H 8.80%.

Reaction of ethyl 4,4-dichlorochromene-2-carboxylate with butanol. The dichloride was prepared from 10.9 g (0.05 mole) 2-ethyl chromate, and to it was added 3.7 g (0.05 mole) absolute butanol (spontaneous heating). The whole was then heated for 1 hr at about 100°C, and after 16 hr 1.02 g BuCl, bp 65–70°, distilled off on a water bath. Distillation was continued with an oil bath at 120–200°, when 2.9 g bp 76–78° came over. Redistillation gave 3.26 g (70.2%) BuCl bp 73–78.8° n_d^{20} 1.4017.

Methyl 2-methoxychromane-2-carboxylic acid (II). a) 3.78 g (0.0148 mole) chloroester I was hydrogenated in dry thiophene-free benzene, containing 2.02 g (0.02 mole) Et_3N and 0.5 g 5% Pd/$BaSO_4$, for 18 hr under ordinary conditions (0.023 mole H_2 absorbed). The catalyst and precipitate of $Et_3N \cdot HCl$ were filtered off, and washed with benzene. The benzene solution was washed with water, the benzene vacuum distilled off, and the residue distilled, to give 2.7 g (75%) compound II, bp 142° (2 mm), mp 71–71.5° (ex MeOH). Found: C 65.17, 65.17; H 6.39, 6.40%, calculated for $C_{12}H_{14}O_4$: C 64.85; H 6.35%.

b) 4.08 g (0.02 mole) methyl chromone-2-carboxylate was refluxed with $SOCl_2$ for 10 hr, excess $SOCl_2$ distilled off, and the residue of dichloride A distilled (bp 150–152° (1 mm)), dissolved in 30 ml dry boiling petrol ether (charcoal), filtered, and cooled to 0°, to give a precipitate of dichloride A (2 g). A mixture of 100 ml absolute MeOH and 3.03 g (0.03 mole) Et_3N was added to the precipitate. After keeping for 1 hr (20°), the solution was hydrogenated using 1 g 5% Pd/$BaSO_4$, for 1 1/2 hr under ordinary conditions (0.034 mole H_2 absorbed). The catalyst was filtered off, the MeOH distilled off, the residue washed with water, dried, and crystallized from petrol ether, to give 1.1 g (56.2% on dichloride A) ester II, mp 70–71°. Undepressed mixed mp with the compound prepared as in a).

c) A mixture of 3.6 g (0.0204 mole) 2,2,6,6-tetramethyl-1,2,5,6-tetrahydropyridine hydrochloride and a solution of sodium methoxide (from 100 ml MeOH and 0.02 g-at Na) was added to 1.20 g (0.0045 mole) well-purified dichloride A. After 30 min (alkaline medium) the whole was hydrogenated using 10% Pd/C, the catalyst being replaced by fresh Pd/C at intervals, until 745 ml H_2 had been absorbed. (Part of the hydrogen was used in hydrogenating the unsaturated amine.) The catalyst was filtered off, the solution evaporated, the residue treated with benzene, the 2,2,6,6-tetramethylpyridine hydrochloride filtered off, and the benzene solution evaporated to give 0.45 g (45%) compound II mp 64–69°. Undepressed mixed mp with a specimen prepared by method (a).

2-Methoxychroman-2-carboxylic acid (III). 0.15 g (0.68 mM) ester II in 10 ml dioxane and 2 ml 2 N NaOH were mixed and then left at 20° for 18 hr, evaporated to 1/3 volume under vacuum, acidified, and extracted with ether. The extract was washed with water, a little toluene added, and the solvent distilled off, to give compound III, mp 124.5–125° (ex benzene–petrol ether). Found: 63.36, 63.59; H 5.98, 5.93%, calculated for $C_{11}H_{12}O_4$: C 63.45; H 5.81%.

4-(o-Hydroxyphenyl)-2-ketobutyric acid (IV). 0.5 g (2.25 mole) ester II in 5 ml dioxane and 1 ml 2 N HCl were heated together at about 100° for 3 hr, then the products evaporated under vacuum, the residue treated with $NaHCO_3$ solution, and extracted with ether. The bicarbonate solution was acidified with 2 N HCl, extracted with ether, the extract washed with water, and evaporated, to give 0.25 g (57.5%) compound IV mp 107–108° (ex benzene). Found: C 61.70; H 5.23%, calculated for $C_{10}H_{10}O_4$: C 61.84; H 5.19%.

Methyl 4-(o-hydroxyphenyl)-2-ketobutyrate 2,4-dinitrophenylhydrazone (V). 0.22 g (1 mM) ester II, 0.2 g (1 mM) 2,4-dinitrophenylhydrazine, and 1 ml conc HCl in 10 ml MeOH were refluxed together for 4 hr, and left for 18 hr at 20°, when 0.32 g (82.5%) dark orange crystals of compound V mp 186–187° (ex EtOH–dioxane) precipitated. Found: C 52.67; 52.85; H 4.05; 4.22; N 14.41; 14.36%, calculated for $C_{17}H_{16}N_4O_7$: C 52.58; H 4.15; N 14.42%.

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