RESEARCHES ON PYRANES, THEIR ANALOGS, AND RELATED COMPOUNDS

XXI. Some Acyl Derivatives of Chromones*

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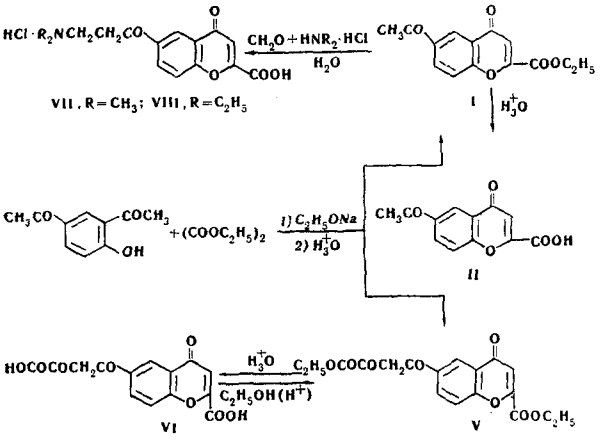
Condensation of 2, 4-diacetylphenol with diethyl oxalate serves as a basis for preparing 2-carbethoxy- and 2-carboxy-6-acetylchromones (I, II), 2-carbethoxy-6-ethoxyoxalylacetylchromone (V), and 2-carboxy-6-hydroxyoxalylacetylchromone (VI). The Mannich reaction is used to synthesize 6-(ω-dialkylaminopropionyl)-2-carboxychromones (VII, VIII) from compound I. Reaction of chromone-2-carbonyl chloride with enamines prepared from cyclohexanone and tetrahydrothiopyrone-4- gives syntheses of 2-(chromonoyl-2)cyclohexanone (III) and 3-(chromonoyl-2)tetrahydrothiopyrone-4 (IV). Hydrazine hydrate and compound III give the pyrazole derivative IX, while hydrazine hydrate and compound IV give pyrazole derivative X along with pyrazolylpyrazole derivative XI, which results from a second molecule of hydrazine hydrate opening the chromone ring.

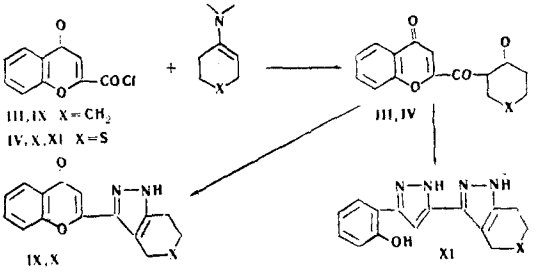
It is generally considered that the γ-pyrone ring is slightly aromatic. Of the electrophilic substitution reactions in the pyrone ring of chromone, only those giving 3-derivatives have been investigated. Thus for example the Mannich reaction was used to prepare 3-aminomethylchromones [1]. The pyrone ring is less reactive in nitration and sulfonation than the benzene one, so that only the benzene ring undergoes substitution [2, 3]. The pyrone system of chromones is quite vulnerable to nucleophilic reagents, because the C atom at position 2 has a considerable fractional positive charge. Thus for example the γ-pyrone ring is easily opened by bases, although (e.g., under the action of primary amines) as a rule the pyrone ring is unattacked. Introducing such electron-accepting substituents as carbalkoxy or acyl into the chromone molecule changes the electron density distribution in the pyrone ring. Nevertheless the specificity of the chemical changes is determined not only by this factor, but rather by the presence of an additional electrophilic center at the carbonyl of the acyl or carbalkoxyl group. Information has previously been given [4–6] regarding the action of nucleophilic reagents on esters of chromono-2-carboxylic acids. Nucleophilic reactions are well known to proceed ambiguously with 3-acylchromones. Depending on the reaction conditions and nature of the reagent, splitting off of acyl, ring opening, or substitution of the oxygen of the acyl carbonyl can occur. There is only brief information about 2-acylchromones, made by selenium dioxide oxidation of dialkylchromones [7]. Chromones with acyl substituents in the benzene ring without hydroxyl groups are quite unknown.

Continuing research previously commenced on the action of electrophilic and nucleophilic reagents on α- and γ-benzpyrones, especially those with various functional substituents, we have synthesized 2-carbethoxy- and 2-carboxy-6-acetylchromones (I, II) and compounds of the type 2-acetoacetylchromone, viz., 2-(chromonoyl-2)cyclohexanone (III) and 3-(chromonoyl-2)tetrahydrothiopyrone-4 (IV), and carried out some reactions with them. Compound I was prepared by condensing 2, 4-diacetylphenol with diethyl oxalate in the presence of 2 moles of sodium ethoxide. Simultaneously 2-carbethoxy-6-ethoxyoxalylacetyl chromone (V) is formed, as a result of Claisen condensation of a second acetyl group with diethyl oxalate. When an equimolecular quantity of ethoxide is used there is no condensation, because the ethoxide is neutralized by the phenolic hydroxyl:



Separation of diketone V from ketone I is effected via the copper derivative of V, diacid VI being initially isolated after acid decomposition of the copper compound, and esterification converting it back to V. Acid hydrolysis of compound I gives II. The Mannich reaction between I, formaldehyde, and dimethylamine and diethylamine hydrochloride with simultaneous hydrolysis of the ester group yields 6-(ω-dimethyl- and diethylaminopropionyl)-2-carboxychromones (VII, VIII). That the aminomethyl group is in the side chain and not in the pyrone ring, is confirmed by the UV spectra. The plot of the spectrum of hydrochloride VIII with absorption maxima at 242, 304, and 314 nm agrees with the plot for the starting ketone II, and differs from the plot for 3-methylchromone-2-carboxylic acid, which has an additional maximum at 274 nm [8] that is characteristic of the system of a 2, 3-disubstituted chromone [9].

Ketones III and IV are synthesized by the Stork reaction from chromone-2-carbonyl chloride and enamines of the appropriate cyclic ketones.



*For Part XX see [11].

There are 5 most characteristic electrophilic centers in each of compounds III and IV. Hence the direction of reaction with such electrophilic reagents as amines must depend on the size of the positive charges at their centers (with the side chain there is a simultaneous tendency to enolize) and on steric factors. In treatment of III or IV with 1 mole hydrazine only the β-diketone group of these reacts. The products are 3-(chromonoyl-2)-5, 6-dihydro-α-thiopyrano[3', 4':4, 5] pyrazole (X). Triketones III and IV behave differently towards excess hydrazine (>2 equivalents). In the case of the sulfur-containing triketone IV there is also scission of the pyrone ring to give 3-[3"-(o-hydroxyphenyl)-pyrazolyl-5"]-5', 6'-dihydro-α-thiopyrano [3', 4':4, 5]pyrazole (XI), while III gives only IX.

EXPERIMENTAL

2-Carbethoxy- and 2-carboxy-6-acetylchromones (I and II), 2-carbethoxy-6-ethoxyoxalylacetylchromone (V), and 2-carboxy-6-hydroxyoxalylacetylchromone (VI). A sodium ethoxide solution was prepared from 2.72 g (0.118 mole) Na and 60 ml dry EtOH, to it were added 10.5 g (0.059 mole) 2, 4-diacetylphenol and 17.2 g (0.118 mole) diethyl oxalate, and the whole was stirred and heated on a water bath for 4 hr, then cooled to ~40°, 10 ml conc. HCl was added, the mixture refluxed for 30 min, and then left overnight. The products were poured into a saturated solution of 12.5 g $Cu(OAc)_2 \cdot H_2O$, made alkaline with Na_2CO_3 (pH 5–6), and after 2 hr extracted with 250 ml benzene. The precipitated copper complex was filtered off and washed with benzene. The combined benzene solutions were dried over $MgSO_4$, and the solvent distilled off, to give 6.5 g (42.4%) I, mp 143°–144° C (ex EtOH). Found: C 64.95, 65.04; H 4.36, 4.71%, calculated for $C_{14}H_{12}O_5$: C 64.61; H 4.65%. The Cu complex was treated with 50 ml glacial AcOH, 15 ml conc. HCl, and 100 ml benzene, the whole filtered, and the benzene solution separated off, dried, and the solvent distilled off. 30 ml AcOH and 10 ml conc. HCl were added to the residue, and the whole was heated for 6 hr on a water bath. The precipitate formed was filtered off, dissolved in 5% $NaHCO_3$, filtered, the filtrate treated with decolorizing charcoal, and then acidified with conc. HCl to give 1 g VI, mp 230°–231° C (decomp). 1 g VI was refluxed for 6 hr with 75 ml absolute EtOH containing 1 ml conc. H_2SO_4, and after cooling the products were filtered to give 0.72 g V, mp 141°–142° C. After evaporating the mother liquor, the residue was treated with dil. $NaHCO_3$ solution, to give an additional 0.23 g V. Total yield 0.95 g (5.3% on the diacetylphenol taken), mp 142°–143° C (ex EtOH). Found: C 60.04, 59.84; H 4.32, 4.38%, calculated for $C_{18}H_{16}O_8$: C 60.00; H 4.48%.

10.4 g (0.04 mole) I was heated for 6 hr on a boiling water bath with 35 ml conc. HCl and 200 ml AcOH, cooled, the solid filtered off, and reprecipitated from bicarbonate solution, yield 7.1 g (83.4%) II, mp 243°–244° C (decomp, ex EtOH). UV spectrum (70% EtOH, $c\ 1 \cdot 10^{-4}$): λ_{max}, nm (lg ε) 244 (4.53), 307 (3.79). Found: C 62.30, 62.03; H 3.60, 3.48%, calculated for $C_{12}H_8O_5$: C 62.06; H 3.47%. Running the condensation in the presence of 3 moles NaOEt as indicated above gave 21% II and 29% VI.

6-(ω-Dimethylaminopropionyl)-2-carboxychromone hydrochloride (VII). 1.3 g I, 4 ml 32% formaldehyde, 0.9 g dimethylamine hydrochloride, and 0.2 ml conc. HCl were refluxed together for 3 hr, the precipitate filtered off, washed with absolute EtOH, then with ether, yield 0.64 g (39%) VII, mp 239°–240° C (ex 50% EtOH). Found: C 54.92, 54.92; H 4.92, 4.76; Cl 10.77, 10.78%, calculated for $C_{15}H_{15}NO_5 \cdot HCl$: C 55.30; H 4.95; Cl 10.88%.

6-(ω-Diethylaminopropionyl)-2-carboxychromone hydrochloride (VIII). Prepared similarly with 37% yield, mp 204°–205° C (decomp, ex 50% EtOH). UV spectrum (70% EtOH, $c\ 1 \cdot 10^{-4}$): λ_{max}, nm (lg ε) 242 (4.61), 304 (3.84), 314 (3.81). Found: Cl 9.93, 8.83%, calculated for $C_{17}H_{19}NO_5 \cdot HCl$: Cl 10.02%.

3-(Chromonoyl-2)tetrahydrothiopyr-4-one (IV). A solution of 4.17 g (0.02 mole) chromone-2-carbonyl chloride [8] in 25 ml dry dioxane was added dropwise to a solution of 3.42 g (0.02 mole) 4-pyrrolidino-2, 3-dihydro-α-thiopyrane [10] and 3.3 g (0.02 mole) Et_3N in 15 ml dry dioxane. Then 30 ml 10% HCl was added over 2 hr and the whole stirred for 1 hr 30 min at ~20° C, the solid was filtered off, washed with $NaHCO_3$ solution, yield 3 g (52%) IV, mp 162°–163° C (ex EtOH). The compound was soluble in 10% NaOH and gave a red color with $FeCl_3$. Found: S 11.36, 11.39%, calculated for $C_{15}H_{12}O_4S$: S 11.12%.

2-(Chromonoyl-2)cyclohexanone (III). A solution of 4.17 g (0.02 mole) chromone-2-carbonyl chloride in 25 ml dry dioxane was added dropwise to a solution of 3.3 g (0.02 mole) 1-piperidinocyclohexene and 2.02 g (0.02 mole) Et_3N in 15 ml dry dioxane. The mixture was kept for 1 hr at ~20° C, then refluxed for 2 hr, the precipitate filtered off, washed with ether, filtrate and ether solution combined, the ether distilled off, 30 ml 10% HCl added, and the whole refluxed for 1 hr. After cooling 2.48 g III was filtered off. Ether extraction of the filtrate gave 0.15 g III. Total yield 2.63 g (48.7%), mp 149°–150° C (ex EtOH). Bright yellow compound, soluble in 10% NaOH, dark red color with ethanolic $FeCl_3$. Found: C 71.07; 71.06; H 5.18; 5.14%, calculated for $C_{16}H_{14}O_4$: C 71.11; H 5.22%.

3-(Chromonoyl-2)-4, 5, 6, 7-tetrahydrobenzpyrazole (IX). A mixture of 1 g (0.0037 mole) III and 0.18 g (0.0037 mole) hydrazine hydrate was refluxed for 3 hr in 40 ml absolute EtOH, the EtOH distilled off under vacuum, to give 0.98 g (100%) IX, mp 226°–226.5° C (ex EtOH). The compound was alkali-insoluble and did not give a color with $FeCl_3$. Found: C 72.33; 72.08; H 5.33; 5.31; N 10.90; 10.99%, calculated for $C_{16}H_{14}N_2O_2$: C 72.16; H 5.30; N 10.52%.

3-(Chromonoyl-2)-5', 6'-dihydro-α-thiopyrano[3', 4';4, 5] pyrazole (X). A solution of 0.32 g (0.0011 mole) IV and 0.056 g (0.0011 mole) hydrazine hydrate in 20 ml EtOH was held at ~20° C for 48 hr, the EtOH vacuum distilled off, and the residue treated with 5 ml 10% HCl to give 0.3 g (97%) X, mp 245°–246° C. The compound was insoluble in alkali and did not give a color reaction with $FeCl_3$. Found: S 11.56; 11.41; N 9.74; 9.72%, calculated for $C_{15}H_{12}N_2O_2S$: S 11.28; N 9.86%.

3-[3"-(o-Hydroxyphenyl)pyrazolyl-5"]-5', 6'-dihydro-α-thiopyrano[3', 4':4, 5]-pyrazole (XI). 0.75 g (0.015 mole) hydrazine hydrate was added to a suspension of 1.44 g (0.005 mole) IV in 25 ml absolute ethanol, the whole refluxed for 3 hr, the products cooled, and compound XI filtered off, yield 0.99 g (69.7%), mp 270° C (decomp). XI was insoluble in alkali and gave a dark green color with $FeCl_3$. Found: S 10.55; 10.48; N 18.49; 18.6%, calculated for $C_{15}H_{14}N_4OS$: S 10.76; N 18.78%.

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