PYRAN, ITS ANALOGS, AND RELATED COMPOUNDS

XXXIX.* REACTION OF PRIMARY AMINES WITH THE tert-BUTYL ESTER AND tert-BUTYL AMIDE OF CHROMONE-2-CARBOXYLIC ACID

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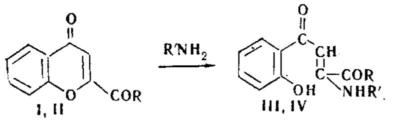
The effect of amines (benzylamine, N,N-dimethylethylenediamine, and ethylenediamine) on the tert-butyl ester (I) and tert-butyl amide (II) of chromone-2-carboxylic acid was studied. In contrast to the sterically unhindered derivatives of chromone-2-carboxylic acid, I and II do not undergo amidation or transamidation by reaction with the amines but are converted directly to pyran-ring-opening products. In the case of ethylenediamine, further intramolecular cyclization also occurs to form 5-(o-hydroxyphenyl)-7-carboxy-1,4-diaza-4,6-cycloheptadiene derivatives (VII and IX).

The reaction of aliphatic amines with 4-benzopyrones (chromones) leads to pyrone-ring-opening products as a result of attack of the amine at the electrophilic center in the 2 position. Chromone-2-carboxylic acid esters also react via this scheme, during which amidation of the ester grouping occurs initially. Products of the amidation and intramolecular cleavage of the pyrone ring, viz., 3-(2-hydroxybenzoylmethylene)-2-piperazinones, are therefore formed by the reaction of the indicated esters with ethylenediamine [1, 2].

Assuming that we could change the direction of the effect of aliphatic amines in their reactions with chromone-2-carboxylic acid esters, we used the tert-butyl ester or tert-butyl amide (I and II) of this acid; one might expect the manifestation of steric hindrance in these molecules not only at the ester or amide carbonyl groups but also at the $C_{(2)}$ atom of the pyrone system. As expected, amidation or transamidation did not occur when benzylamine was used, but imines with preservation of the heterocycle could not be obtained: only the cleavage products, viz., aminovinyl ketones III and IV, were isolated.



I, II

III, IV

I III $R = OC(CH_3)_3$; II, IV, V $R = HNC(CH_3)_3$;
III, IV $R' = CH_2C_6H_5$; V $R = CH_2CH_2N(CH_3)_2$

The reaction of I with ethylenediamine leads to a crystalline substance, the elementary composition of which corresponds to the empirical formula $C_{16}H_{20}N_2O_3$, which attests to the evolution of a water molecule during the reaction of these components. This compound was yellowish-orange, did not dissolve in alkalies, and, under the usual conditions, did not give a color reaction with $FeCl_3$; it is converted to the starting unsubstituted chromone by the action of aqueous acids, and its NMR spectrum in chloroform or deuterochloroform at 18-35°C does not contain signals from the protons of the NH and OH groups. We therefore preliminarily assigned the iminochromene structure (VI) to it [3]. More detailed investigations established that the compound is capable of giving a reaction for the phenolic hydroxyl group with $FeCl_3$ if the test is carried out with concentrated solutions. The phenolic hydroxyl group is also determined by reaction with NaH in dimethylformamide (one mole of H_2 is evolved; the amino group of the usual aliphatic amines, for example, butylamine, benzylamine, and ethylenediamine, does not react with NaH under these conditions). This compound also gives a monohydrochloride and does not form a dihydrochloride under different conditions. One

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*See [6] for communication XXXVIII.

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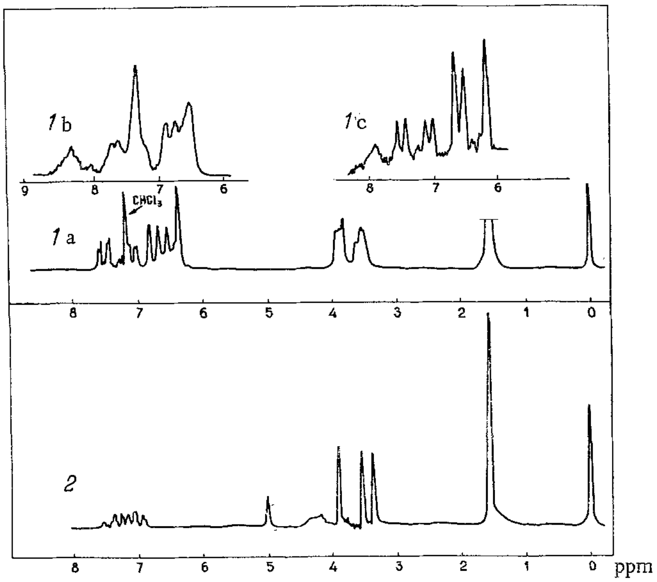
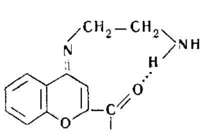
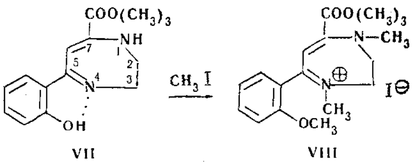


Fig. 1. NMR spectra: 1a) 5-(o-hydroxyphenyl)-7-tert-butoxycarbonyl-1,4-diaza-4,6-cycloheptadiene (VII) at 20° in $CDCl_3$; 1b) VII at −55° in $CDCl_3$; 1c) VII at 18° in dimethyl sulfoxide; 2) N,O-dimethyl-5-(o-hydroxyphenyl)-7-tert-butoxycarbonyl-1,4-diaza-4,6-cycloheptadiene (VIII) at 18° in $CDCl_3$.

might have expected the formation of a dihydrochloride for structure VI, since the imino group, even in the arylimines of chromones, is capable of giving salts in anhydrous and aqueous media [4]. Potentiometric determination of the dissociation constant in methanol (16.5°) indicates that the substance behaves like a monoatomic base with pKa 6.65. The suppression of the basic properties of the second amino group is readily explained if we consider that we are dealing with a system of diimines of β-dicarbonyl compounds in the enamine-imine form, which are vinylogs of amidines. If the NMR spectrum is obtained at −36 to −55° in deuterochloroform (Fig. 1, Curve 1b) or at 18° in dimethyl sulfoxide (Fig. 1, Curve 1c), the signals of the proton of the OH or conjugated NH group can be observed at 8.3 ppm and 7.9 ppm, respectively. We therefore now assign the structure of the ring-chain tautomer (VII), i.e., the product with a cleaved pyrone ring, rather than the structure of the imine of chromone (VI) to the compound obtained. The UV spectrum of VII attests to the presence in the molecule of effective conjugation. The accurate assignment of the bands in the IR spectra of VII and IX in the valence-vibration region of the NH and OH groups is difficult (an approximate assignment is given in the experimental section). VII was converted by exhaustive methylation (with methyl iodide in acetone containing potassium carbonate) to the methiodide of dimethyl derivative (VIII), the NMR spectrum of which (Fig. 1, Curve 2) contains singlets from the three nonequivalent CH_3 groups (δ 3.9, 3.53, and 3.37 ppm). VIII gives 2-methoxybenzoic acid on oxidation with potassium permanganate.



VI



VII

VIII

It should be noted that, in addition to the structure with an unopened pyran ring of the VI type previously proposed by us, others in which the pyran ring is preserved are also conceivable for the product of the reaction of ethylenediamine with I, but all of them should be rejected as not satisfying the set of physicochemical and chemical data. As for the structure with an open pyran ring, one can conceive of a large number of forms which differ with respect to their fine structure (due to tautomerism, conformation, and configuration) which can be determined in particular by the temperature conditions, solvent, etc. The most probable form under the conditions studied by us is the 5-(o-hydroxyphenyl)-7-tert-butoxycarbonyl-1,4-diaza-4,6-cycloheptadiene form expressed by formula VII. In accordance with this, the quaternary nitrogen atom in the methiodide is preferably found in the 4 position of the seven-membered ring.

tert-Butyl amide II reacts with ethylenediamine in the same way as ester I to give 5-(o-hydroxyphenyl)-7-tert-butylaminocarbonyl-1,4-diaza-4,6-cycloheptadiene (IX). The path for the formation of VII and IX apparently consists of opening of the pyrone ring by one amino group of the ethylenediamine molecule and closing of the seven-membered ring by reaction of the other primary amino group of this diamine with the β-carbonyl group with the evolution of water. However, one cannot exclude the possibility that VII and IX are obtained from imines of the VI type as a result of tautomerization.

EXPERIMENTAL

The NMR spectra were obtained with a JEOL spectrometer with an operating frequency of 60 MHz in the δ scale relative to tetramethylsilane (TMS). The IR spectra were obtained with a UR-10 spectrometer, while the UV spectra were obtained with an SF-4 spectrometer.

Chromone-2-carboxylic Acid tert-Butyl Ester (I). tert-Butyl alcohol [8.9 g (0.12 mole)] was added gradually with stirring at 0° to 8.36 g (0.04 mole) of the acid chloride of chromone-2-carboxylic acid in 28 ml of dry pyridine. The mixture was held at 20° for 1 h and poured into dilute HCl containing ice. The precipitate was filtered, washed with sodium bicarbonate solution, and extracted with benzene. The residue after distillation of the solvent was crystallized from petroleum ether–benzene to give 1.6 g of I. Another 3.25 g of I was isolated from the mother liquor. The overall yield of product with mp 103-104° (from alcohol, dried in vacuo over P_2O_5) was 4.85 g (49%), IR spectrum (dioxane, c 0.034 M, d 0.166 mm): 1740 (ester C=O), 1660 cm^{-1} (pyrone C=O). UV spectrum: λ_{max} 236 (log ε 4.30) and 308 nm (log ε 3.85). Found %: C 68.6; H 5.9. $C_{14}H_{14}O_4$. Calc. %: C 68.3; H 5.7.

Compound I readily forms a crystalline hydrate with mp 134-135° (from alcohol). Found %: C 63.4; H 6.1. $C_{14}H_{14}O_4 \cdot H_2O$. Calc. %: C 63.6; H 6.0.

Chromone-2-carboxylic Acid tert-Butyl Amide (II). A solution of 1.04 g (5 mmole) of the acid chloride of chromone-2-carboxylic acid in 10 ml of anhydrous dichloroethane was added with adequate stirring to a mixture of 0.37 g (5 mmole) of tert-butylamine, 0.42 g (4 mmole) of sodium carbonate, 5 g of water, and 5 g of ice. After 30 min the mixture was extracted with dichloroethane, and the solvent was removed by distillation to give 0.92 g (76%) of II with mp 158-158.5° (from 50% methanol). Found %: C 68.7; H 6.2. $C_{14}H_{15}NO_3$. Calc. %: C 68.6; H 6.2.

tert-Butyl 3-(2-Hydroxybenzoyl)-2-benzylaminoacrylate (III). A mixture of 1.23 g (5 mmole) of I and 0.59 g (5.5 mmole) of benzylamine in 25 ml of absolute alcohol was refluxed for 10 h, the solution was cooled, and the precipitate was filtered to give 0.95 g (53.7%) of yellow crystals of III with mp 86-86.5° (from alcohol); a concentrated alcohol solution of the product gives a dark-red color with ferric chloride. Found %: C 71.7; H 6.6; N 4.0. $C_{21}H_{23}NO_4$. Calc. %: C 71.4; H 6.6; N 4.0.

III was heated in alcohol for 1 h (and held at 20° for 16 h), and starting I, formed due to the reversibility of the cleavage of the pyrone ring, was detected by chromatography in a thin layer of Al_2O_3 (activity II, $CHCl_3$).

tert-Butyl Amide of 3-(2-Hydroxybenzoyl)-2-benzylaminoacrylic Acid (IV). A mixture of 1.23 g (5 mmole) of II and 0.8 g (7.5 mmole) of benzylamine in 25 ml of benzene was refluxed for 10 h with simultaneous removal of water in a Dean-Stark trap. The solution was evaporated, and the residue was recrystallized from absolute alcohol to give 0.85 g (48.3%) of a yellow substance (IV) with mp 133-133.5°. The product gave a dark-red color with alcoholic ferric chloride. Found %: C 71.6; H 7.0. $C_{21}H_{24}N_2O_3$. Calc. %: C 71.6; H 6.9. Starting II [0.4 g (33%)] was isolated from the mother liquor. The yield of IV was 45% when the reaction was carried out for 1.5 h in refluxing alcohol. When IV (2 mmole) was refluxed in benzene in the presence of benzylamine (1 mmole) for 3 h, starting II was detected by chromatography in a thin layer of Al_2O_3.

tert-Butyl Amide of 3-(2-Hydroxybenzoyl)-2-(N,N-dimethylaminoethylamino)acrylic Acid (V). A mixture of 1.23 g (5 mmole) of II and 0.66 g (8.8 mmole) of N,N-dimethylethylenediamine in 25 ml of benzene was refluxed for 10 h. The solution was evaporated in vacuo, and the residue was treated with toluene–petroleum ether (1:3) to give 1.24 g (74.7%) of yellow crystals of V with mp 149-149.5° (from toluene). The product gave a color with ferric chloride and dissolved in aqueous alkalis. IR spectrum from 1600-3600 cm^{-1} ($CHCl_3$, c 0.5 M, d 0.25 mm): narrow band at 3420 cm^{-1} (amide NH), broad band at 3300 cm^{-1} (associated NH), 2500-2800 cm^{-1} (chelated OH group), and 1680 cm^{-1} (amide C=O). Found %: C 65.2; H 8.1; N 12.7. $C_{18}H_{27}N_3O_3$. Calc. %: C 64.9; H 8.2; N 12.6.

5-(o-Hydroxyphenyl)-7-tert-butoxycarbonyl-1,4-diaza-4,6-cycloheptadiene (VII). A mixture of 2.46 g (0.01 mole) of I and 0.9 g (0.015 mole) of ethylenediamine in 50 ml of benzene was refluxed for 10 h using a Dean-Stark adapter containing solid KOH. The benzene was then removed by vacuum distillation, and the residue was treated with 2 N HCl, and 0.32 g (13%) of starting I was removed by filtration. The acidic solution was made alkaline with solid sodium bicarbonate, and the mixture was allowed to stand for 2 h in a refrigerator. The resulting precipitate was filtered, washed with water, and dried to give 1.7 g (59%) of VII. The yield of VII was 69% when the reaction was carried out in absolute alcohol (refluxing for 1.5 h). The product melted at 163° (dec., from absolute alcohol). UV spectrum in alcohol for c 10^{-4} M, λ_{max}, nm (log ε): 240 (4.00), 284 (3.75), 368 (3.99), 430 (4.03) with a "tail" at 500 nm (log ε 3.0). IR spectrum in mineral oil: 3000-3200 cm^{-1} (weak, probably associated NH group), 2500-2800 cm^{-1} (weak, broad band, OH group), 1720 cm^{-1} (intense, ester C=O), 1618 cm^{-1} (very intense); in $CHCl_3$ (c 0.1 M, d 0.1 mm): 3455, 3416, and 3150 cm^{-1} (probably free and associated NH groups), 2600-2800 cm^{-1} (very weak), 1718 cm^{-1} (C=O), 1623 cm^{-1}. The bands at 3455 and 3416 cm^{-1} do not change on dilution to 0.01 M, while the band at 3150 cm^{-1} vanishes. One broad band at 3370 cm^{-1} was observed in dioxane solution (c 0.01 M, d 1 mm) from 3100 to 3600 cm^{-1}. NMR spectrum (Fig. 1, Curve 1a) ($CDCl_3$, 18°): 1.57 ppm [singlet, 9H, $C(CH_3)_3$]; 3.4-4.0 ppm (group of signals, 4H, CH_2CH_2); 6.35-7.65 ppm (group of signals, 5H, C_6H_4, and vinyl proton attached to $C_{(6)}$ of the seven-membered ring). pKa 6.65 (16.5°, determined by potentiometric titration of a methanol solution of the compound with 0.1 N HCl with an LPU-0.1 potentiometer). Found %: C 66.7; H 7.9; H_{act} 0.4;* N 9.3; mol. wt. 288.† $C_{16}H_{20}N_2O_3$. Calc. %: C 66.6; H 7.0; H_{act} 0.35; N 9.7; mol. wt. 288.3.

Hydrochloride of VII. A solution of HCl in ether was added to an alcohol solution of the base to give a hydrochloride with mp 220° (dec.). IR spectrum (in mineral oil): 2400-3300 cm^{-1} (a number of broad bands of the HO, NH, and $\overset{+}{N}H$ groups); 1735 cm^{-1} (C=O); 1626 cm^{-1}. Found %: C 59.2; H 6.45; Cl 11.1. $C_{16}H_{20}N_2O_3 \cdot HCl$. Calc. %: C 59.2; H 6.5; Cl 10.9.

N,O-Dimethyl-5-(o-hydroxyphenyl)-7-tert-butoxycarbonyl-1,4-diaza-4,6-cycloheptadiene Methiodide (VIII). A mixture of 5.76 g (0.02 mole) of VII, 17.04 g (0.12 mole) of methyl iodide, and 16.56 g (0.12 mole) of potassium carbonate in 100 ml of acetone was refluxed for 20 h. The acetone was removed by vacuum distillation, and the residue was treated with a small amount of water and extracted with benzene. The extract was partially evaporated in vacuo, and the residue was filtered and washed with ether to give 3.4 g (37%) of VIII, which was purified by precipitation from alcohol with ether to give a product with mp 127° (dec.). NMR spectrum (in $CDCl_3$): 1.57 ppm [singlet, 9H, $C(CH_3)_3$]; 3.37 and 3.53 ppm (two singlets each for the 3H, $\overset{+}{N}CH_3$, and NCH_3 groups); 3.90 ppm (singlet, 3H, CH_3O); 4.10-4.40 ppm (multiplet, 4H, CH_2CH_2); 5.05 ppm (singlet, 1H, $C_{(6)}-H$); 6.9-7.6 ppm (multiplet, 4H, C_6H_4). Found %: C 49.7; H 5.9; I 28.1; N 5.9. $C_{19}H_{27}N_2O_3I$. Calc. %: C 49.8; H 5.9; I 27.7; N 6.1.

2-Methoxybenzoic acid was obtained by oxidation of VIII with potassium permanganate in aqueous solution at ~ 20° until no more oxidant was required (~ 16 h); the acid was purified by successive vacuum sublimation, recrystallization from petroleum ether–benzene, and sublimation at atmospheric pressure to give a product with mp 97.5-98.5°; a mixture of this product with an authentic sample [5] did not give a melting-point depression, and its IR spectrum was identical to that of the authentic sample.

5-(o-Hydroxyphenyl)-7-tert-butylaminocarbonyl-1,4-diaza-4,6-cycloheptadiene (IX). This product [0.7 g (48.6%); 0.22 g of II was recovered)] was obtained like VII from 1.23 g (5 mmole) of II and 0.45 g (7.5 mmole) of ethylenediamine in 25 ml of anhydrous benzene in the form of yellowish-orange crystals with mp 248-249° (dec., from absolute alcohol). IR spectrum ($CHCl_3$, c 0.0166 M, d 0.25 mm): unsymmetrical band at 3400 cm^{-1} (probably NH group); 1675 cm^{-1} (C=O); 1620 cm^{-1}. Found %: C 67.0; H 7.3; N 14.9. $C_{16}H_{21}N_3O_2$. Calc. %: C 66.9; H 7.4; N 14.6.

The hydrochloride of IX decomposed at 240°. Found %: Cl 11.3. $C_{16}H_{21}N_3O_2 \cdot HCl$. Calc. %: Cl 11.0.

The yield of IX was 31% in an experiment without removal of water by distillation; the yield was 58% when the reaction was carried out in refluxing alcohol for 1.5 h.

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*Determined in the apparatus of A. P. Terent'ev; the solvent was a dimethylformamide–ether mixture, the reagent was sodium hydride.

†According to mass spectral data.

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