Imidazolyl Derivatives of the Chroman Ring. 2 [1].

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Received June 28, 1984

The synthesis of 3-(1*H*-imidazol-1-yl)-4*H*-1-benzopyran-4-ones **2** and of 2-(1*H*-imidazol-1-yl)-4*H*-1-benzopyran-4-ones **11** are described. The former proceeds through chroman ring closure from 2-(1*H*-imidazol-1-yl)-2'-hydroxyacetophenones, the latter occurs reacting 3-bromo-4*H*-1-benzopyran-4-ones with imidazole and represents an example of a new synthesis of 2-heteroarylchromones. Compounds **2** can be easily reduced to the corresponding chromanones and chromanols previously described in Part 1.

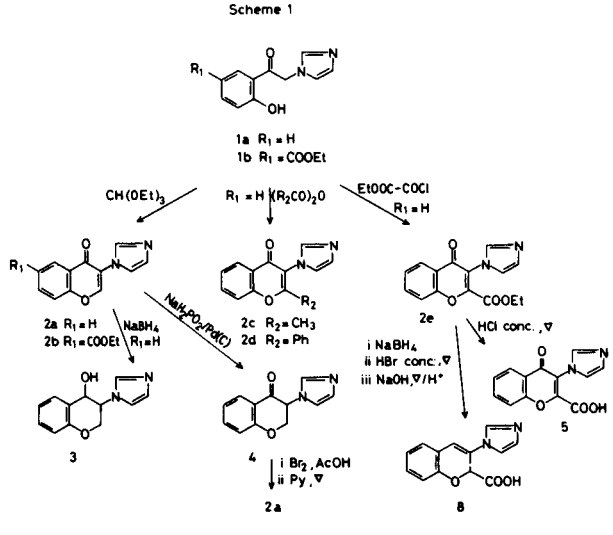
J. Heterocyclic Chem., **22**, 441 (1985).

In the search for new compounds of pharmacological interest containing imidazole and the chroman ring in the same molecule we described in a previous paper [1] the synthesis of 3-(1*H*-imidazol-1-yl)-2,3-dihydro-4*H*-1-benzopyran-4-ones and of some related ocmpounds. Some of them showed interesting pharmacological activities, mainly affecting blood lipids, which will be discussed in a forthcoming paper.

We describe here the synthesis of some imidazolyl chromones, analogues of the former compounds, namely 3-(1*H*-imidazol-1-yl)-4*H*-1-benzopyran-4-ones (**2**), the isomeric 2-(1*H*-imidazol-1-yl)-4*H*-1-benzopyran-4-ones (**11**) and some derived compounds. Compounds **2** were synthesized in excellent yields through a variant of the Kostanecki-Robinson reaction [2] starting from previously described [1] 2-(1*H*-imidazol-1-yl)-2'-hydroxyacetophenones (**1**) as shown in Scheme 1.

Compounds **1a** and **1b** were refluxed in an excess of triethyl orthoformate to give the imidazolyl chromones **2a** and **2b**. Compound **1a** was reacted with an excess of acetic anhydride at 110° or an excess of benzoic anhydride by fusion at 120° to give respectively chromones **2c** and **2d**. Finally **1a** was reacted with ethyl oxalyl chloride in pyridine at room temperature to give **2e**.

Scheme 1

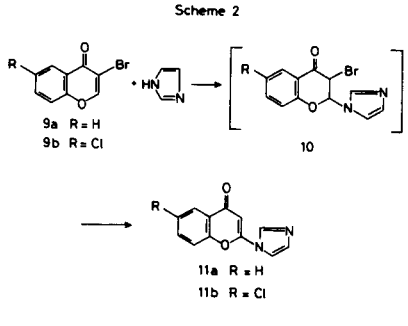


Similar ring closure to chromones bearing various heterocyclic residues, but not 1-imidazolyl residue, in position 3, were described by Khilya and coworkers [3].

Imidazolylchromones **2** can be reduced to the corresponding chromanols and chromanones so that Scheme 1 shows a convenient alternative synthesis of 3-(1*H*-imidazolyl)chromanones and chromanols previously described in Part 1 [1]. For instance compound **2a** was reduced with sodium borohydride in excellent yields to the corresponding chromanol **3** or to chromanone **4** by transfer hydrogenation with the sodium hypophosphite-Palladium catalyst reducing system first described by Entwistle *et al.* [4] and recently applied to reduction of various organic substrates [5]. Compound **4** was reconverted to **2a** by bromination with bromine in acetic acid and subsequent dehydrobromination in pyridine. Compound **2e** was used as starting material to obtain chromone carboxylic acid **5**, by hydrolysis in concentrated hydrochloric acid or chromene carboxylic acid **8** by intermediate reduction, with sodium borohydride to the corresponding 2-ethoxycarbonylchromanol (**6**), subsequent dehydration with concentrated hydrobromic acid, to the corresponding 2-ethoxycarbonylchromene (**7**), in which conditions the ester group was surprisingly unaffected and final alkaline hydrolysis of the latter.

Compounds **11** were synthesized in good yields when 3-bromo-4*H*-1-benzopyran-4-ones (**9**) were reacted with imidazole, possibly through intitial Michael addition followed by dehydrobromination of intermediate compound **10** as shown in Scheme 2.

Scheme 2



The reaction was carried out by fusion of bromochromones **9** with excess imidazole at 120° or preferably with a mixture of imidazole and its silver salt at 80°. A similar initial Michael addition was postulated for the reaction of primary and secondary amines with 3-bromochromones. In the first case a ring contraction followed, through an imine intermediate, giving a benzofuranone derivative [6]. In the second case, with secondary cyclic amines such as pyrrolidine and piperidine the end-products were the corresponding 3-aminochromones, formed by rearrangement through an intermediate aziridium cation [6,7]. In our case, with imidazole acting as nucleophile, a similar imine or aziridium intermediate could hardly be imagined and dehydrobromination of the intermediate products of the Michael attack **10** can take place giving compounds **11**.

Structures of compounds **11** were confirmed by ^1H and ^{13}C nmr spectra and by comparison with those of the isomeric 3-(1*H*-imidazolyl)chromone (**2a**).

Scheme 2 represents an example of a new synthesis of 2-(*N*-heteroaryl)chromones while the 2-heteroarylchromones which have a carbon-carbon link between the chroman and the heteroaryl residue are usually prepared by ring closure from the corresponding 2-heteroaryl-2'-hydroxyacetophenones [8].

The compounds described in this paper were tested mainly as lipid lowering and antiallergic agents; their pharmacological evaluation is still in progress.

EXPERIMENTAL

Melting points were determined on a Büchi melting point apparatus and are uncorrected. The ^1H nmr spectra were obtained on a Bruker HFX 90 MHz spectrometer in the solvents indicated. The ^{13}C nmr were obtained on a Varian XL-200 spectrometer. Chemical shifts are reported in ppm from TMS as internal standard and are given in δ units. Column chromatographic separations were performed on 0.05-0.20 nm silica gel (Carlo Erba).

3-(1*H*-Imidazol-1-yl)-4*H*-1-benzopyran-4-one (**2a**).

A mixture of 0.3 g (1.48 mmoles) of 2-(1*H*-imidazol-1-yl)-2'-hydroxyacetophenone (**1a**) and 40 ml of triethyl orthoformate was refluxed for 3 hours. Excess triethyl orthoformate was evaporated under reduced pressure and the resulting solid, washed with ethyl ether (2 ml) gave 0.27 g (87%) of **2a** as a white solid, mp 212-214°; ^1H nmr (deuteriochloroform): 7.23 (2H, broad s, NCHCHN), 7.50-7.78 (3H, m, H-6, H-7, H-8), 7.83 (1H, broad s, NCHN), 8.19 (1H, s, H-2), 8.33 (1H, dd, H-5); ^{13}C nmr (deuteriochloroform): 118.3, 119.7, 123.9, 125.9, 126.1, 129.6, 134.5, 137.2, 150.1, 155.7, 172.3.

Anal. Calcd. for $C_{12}H_8N_2O_2$: C, 67.91; H, 3.77; N, 13.19. Found: C, 67.86; H, 3.76; N, 13.21.

By the above procedure, starting from 2-(1*H*-imidazol-1-yl)-2'-hydroxy-5'-ethoxycarbonylacetophenone (**1b**) (mp 168-170°, prepared following the precedure reported in Part 1).

3-(1*H*-Imidazol-1-yl)-6-ethoxycarbonyl-4*H*-1-benzopyran-4-one (**2b**).

This compound was obtained in 89% yield, mp 198-200°; ^1H nmr (deuteriochloroform): 1.43 (3H, t, CH_3), 4.42 (2H, q, CH_2), 7.24 (2H, m, NCHCHN), 7.60 (1H, d, H-8), 7.84 (1H, broad s, NCHN), 8.23 (1H, s, H-2), 8.39 (1H, dd, H-7), 8.93 (1H, d, H-5).

Anal. Calcd. for $C_{15}H_{12}N_2O_4$: C, 63.37; H, 4.25; N, 9.85. Found: C, 63.40; H, 4.24; N, 9.83.

2-Methyl-3-(1*H*-imidazol-1-yl)-4*H*-1-benzopyran-4-one Hydrochloride (**2c**).

A mixture of 1.4 g (6.92 mmoles) of **1a** and 100 ml of acetic anhydride was heated at 110° for 3 hours. After cooling, the reaction mixture was poured into crushed ice and 8% hydrochloric acid (20 ml) was added. The acidic aqueous solution was washed with methylene chloride and evaporated under reduced pressure. The resulting solid was washed with 1-butanol and ethyl ether yielding 1.5 g (83%) of **2c** as a white solid, mp >225°; ^1H nmr (DMSO-d_6 and trifluoroacetic acid): 2.43 (3H, s, CH_3), 7.40-8.0 (5H, m, H-6, H-7, H-8 and NCHCHN), 8.14 (1H, dd, H-5), 9.26 (1H, broad s, NCHN).

Anal. Calcd. for $C_{13}H_{11}ClN_2O_2$: C, 59.46; H, 4.18; N, 10.66; Cl^-, 13.50. Found: C, 59.39; H, 4.20; N, 10.60; Cl^-, 13.54.

2-Phenyl-3-(1*H*-imidazol-1-yl)-4*H*-1-benzopyran-4-one (**2d**).

A mixture of 0.5 g (2.4 mmoles) of **1a** and 5 g of benzoic anhydride was heated at 120° for 3 hours. After cooling the reaction mixture was poured into crushed ice and extracted with methylene chloride. The organic layer was extracted with a solution of 8% hydrochloric acid. The acidic aqueous solution, separated from the organic layer, was neutralized with sodium bicarbonate, extracted with methylene chloride and the solvent was evaporated *in vacuo* yielding 0.55 g (77%) of **2d**, mp 195-197°; ^1H nmr (deuteriochloroform): 6.92 (1H, broad s, NC*H*CHN), 7.15 (1H, broad s, NCHC*H*N), 7.32 (1H, broad s, NCHN), 7.2-7.7 (7H, m, H-6, H-8 and phenyl H), 7.75 (1H, ddd, H-7), 8.27 (1H, dd, H-5).

Anal. Calcd. for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.19; N, 9.71. Found: C, 75.06; H, 4.20; N, 9.69.

2-Ethoxycarbonyl-3-(1*H*-imidazol-1-yl)-4*H*-1-benzopyran-4-one (**2e**).

To a solution of 11 g (54.39 mmoles) of **1a** in 300 ml of pyridine, 7.42 g (54.39 mmoles) of ethyl oxalyl chloride were added. The mixture was stirred for 1 hour at room temperature, then another portion of 7.42 g (54.39 mmoles) of ethyl oxalyl chloride was added and the resultant mixture was stirred again for 2 hours at room temperature. The reaction mixture was poured into water and extracted with methylene chloride. The organic layer was dried over magnesium sulfate and evaporated to dryness giving a solid residue which, after washing with ethyl ether, yielded 14.0 g (90%) of **2e**; ^1H nmr (deuteriochloroform): 1.18 (3H, t, CH_3), 4.25 (2H, q, CH_2), 7.03 (1H, broad s, NC*H*CHN), 7.20 (1H, broad s, NCHC*H*N), 7.35-7.95 (4H, m, H-6, H-7, H-8 and NCHN), 8.32 (1H, dd, H-5).

Anal. Calcd. for $C_{15}H_{12}N_2O_4$: C, 63.37; H, 4.25; N, 9.85. Found: C, 63.42; H, 4.23; N, 9.82.

3-(1*H*-Imidazol-1-yl)-2,3-dihydro-4*H*-1-benzopyran-4-ol (**3**).

To a solution of 0.5 g (2.3 mmoles) of **2a** in 50 ml of methanol 0.4 g (10.5 mmoles) of sodium borohydride was added portionwise at 5-10°. After stirring at room temperature for 2 hours the mixture was poured into 70 ml of water. Methanol was evaporated under reduced pressure and the aqueous solution was extracted with methylene chloride. The solvent was dried and evaporated under reduced pressure giving 0.49 g (96%) of **3**, mp 126-128° [9].

3-(1*H*-Imidazol-1-yl)-2,3-dihydro-4*H*-1-benzopyran-4-one (**4**).

A mixture of 0.25 g (1.17 mmoles) of **2a**, 0.25 g (2.35 mmoles) of sodium hypophosphite monohydrate, 35 ml of ethanol, 5 ml of water and 0.25 g of 10% palladium-charcoal was heated at reflux for 16 hours. The catalyst was filtered off and the solution was evaporated under reduced pressure. The solid residue was purified by silica gel column chromatography, eluting with methylene chloride-methanol-acetic acid (90:10:1) to yield 0.136 (53%) of **4**, mp 156-158° [1].

3-(1*H*-Imidazol-1-yl)-4*H*-1-benzopyran-4-one (**2a**).

To a solution of 2.5 g (11.6 mmoles) of 3-(1*H*-imidazol-1-yl)-2,3-dihydro-4*H*-1-benzopyran-4-one (**4**) in 100 ml of glacial acetic acid, 1.86 g (11.6 mmoles) of bromine was added. The reaction mixture was stirred at room temperature for 2 hours. The precipitate, collected by filtration was dissolved in 40 ml of pyridine, and the solution was heated at 100° for 1

hour. The solvent was evaporated under reduced pressure and the residue was washed with water and ethyl ether to yield 1.7 g (68%) of **2a**, mp 212-214°.

2-Carboxy-3-(1*H*-imidazol-1-yl)-4*H*-1-benzopyran-4-one (**5**).

Compound **2e** (1.2 g, 4.22 mmoles) was refluxed for 4 hours in concentrated hydrochloric acid (100 ml). The aqueous solution was evaporated to dryness under reduced pressure and the resulting solid, after washing with isopropanol, gave 0.95 (87%) of **5**, mp 202-205° dec; ^{1}H nmr (trifluoroacetic acid): 7.50-8.50 (6H, m, benzene H and NCHCHN), 8.90 (1H, broad s, NCHN).

Anal. Calcd. for $C_{13}H_8N_2O_4$: C, 60.93; H, 3.14; N, 10.93. Found: C, 60.87; H, 3.11; N, 10.96.

2-Ethoxycarbonyl-3-(1*H*-imidazol-1-yl)-2,3-dihydro-4*H*-1-benzopyran-4-ol (**6**).

To a solution of 9.4 g (33.0 mmoles) of **2e** in 500 ml of ethanol, 3.75 (99.0 mmoles) of sodium borohydride was added portionwise at 5-10°. After stirring at room temperature for 1 hour the mixture was poured into 400 ml of water. The ethanol was evaporated under reduced pressure and the resulting aqueous solution was extracted with methylene chloride. The organic layer was dried over magnesium sulfate with ethyl ether and filtered yielding 8.3 g (87%) of **6** as a white solid, mp 152-154°; ^{1}H nmr (deuteriochloroform): 1.10 (3H, t, CH_3), 4.14 (2H, q, CH_2), 4.94 (1H, dd, H-3), 5.08 (1H, d, H-2), 5.30 (1H, d, H-4), 6.70-7.70 (7H, m, benzene H and imidazole H).

Anal. Calcd. for $C_{15}H_{16}N_2O_4$: C, 62.48; H, 5.59; N, 9.72. Found: C, 62.40; H , 5.61; N, 9.77.

2-Ethoxycarbonyl-3-(1*H*-imidazol-1-yl)-2*H*-1-benzopyran (**7**).

Compound **6** (3.3 g, 511.44 mmoles) was refluxed for 1 hour in 48% hydrobromic acid (250 ml). The aqueous solution was evaporated to dryness under reduced pressure. The solid residue was purified by silica gel column chromatography, eluting with methylene chloride-methanol (9:1), to yield 2.3 g (74%) of **7**; ^{1}H nmr (deuteriochloroform): 1.10 (3H, t, CH_3), 4.15 (2H, q, CH_2), 5.55 (1H, s, H-2), 6.65 (1H, s, H-4), 7.00-7.40 (6H, m, benzene H and NCHCHN), 7.93 (1H, broad s, NCHN).

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.72; H, 5.20; N, 10.35.

2-Carboxy-3-(1*H*-imidazol-1-yl)-2*H*-1-benzopyran (**8**).

Compound **7** (2.1 g, 7.76 mmoles) was dissolved in 1% solution of potassium hydroxide in 95% ethanol (56 ml) and refluxed for 30 minutes. After cooling the reaction mixture was diluted with water and neutralized with 8% hydrochloric acid. The ethanol was evaporated under reduced pressure and the resulting aqueous solution was washed with ethyl acetate and evaporated to dryness. the solid residue consisted of 1.3 g (69%) of **8**, mp 228-230° dec; ^{1}H nmr (DMSO-d_6): 6.09 (1H, s, H-2), 6.8-7.3 (6H, m, H-4, NCHC*H*N) and benzene H), 7.73 (1H, broad s, NC*H*CHN), 8.21 (1H, broad s, NCHN).

Anal. Calcd. for $C_{13}H_{10}N_2O_3$: C, 64.45; H, 4.16; N, 11.56. Found: C, 64.50; H, 4.18; N, 11.51.

2-(1*H*-Imidazol-1-yl)-4*H*-1-benzopyran-4-one (**11a**).

A mixture of 1.6 g (7.1 mmoles) of 3-bromo-4*H*-1-benzopyran-4-one (**9a**), 2.49 g (14.2 mmoles) of imidazole silver salt and 2.43 g (35.7 mmoles) of imidazole was heated at 80° for 30 minutes. After cooling, the reaction mixture was poured into water and extracted with chloroform. The resulting solution was washed with 1*N* sodium hydroxide and water, dried over magnesium sulfate and evaporated to dryness. The residue crystallized from absolute ethanol gave 1.3 g (74%) of **11a**, mp 184-185°; ^{1}H nmr (deuteriochloroform): 6.40 (1H, s, H-3), 7.26 (1H, broad s, NC*H*CHN), 7.44 (1H, broad s, NCHC*H*N), 7.3-7.9 (3H, m, H-6, H-7 and H-8), 8.19 (1H, dd, H-5), 8.22 (1H, broad s, NCHN); ^{13}C nmr (deuteriochloroform): 97.1, 115.9, 117.6, 123.4, 126.0, 126.2, 131.8, 134.3, 134.8, 153.3, 154.2, 177.7.

Anal. Calcd. for $C_{12}H_8N_2O_2$: C, 67.91; H, 3.77; N, 13.19. Found: C, 67.95; H, 3.78; N, 13.18.

By the above procedure, starting from 3-bromo-6-chloro-4*H*-1-benzopyran-4-one (**9b**) the 2-(1*H*-imidazol-1-yl)-6-chloro-4*H*-1-benzopyran-4-one (**11b**) was obtained, mp 201-203° (ethanol).

Anal. Calcd. for $C_{12}H_7ClN_2O_2$: C, 58.4; H, 2.96; N, 11.30; Cl, 14.4. Found: C, 58.30; H, 2.98; N, 11.28; Cl, 14.42.

Acknowledgement.

The authors wish to thank Dr. S. De Munari and Mr. G. Marazzi for the execution of ^{1}H nmr and ^{13}C nmr spectra and helpful discussion, and Mr. L. Bertone for his valuable technical collaboration.

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