Imidazolyl Derivatives of the Chroman Ring. 1.

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The synthesis of 2-(1*H*-imidazol-1-yl)-2,3-dihydro-2*H*-1-benzopyran-4-ones (I) through 3-bromo-2,3-dihydro-4*H*-1-benzopyran-4-ones or more conveniently through chroman ring closure from 2-(1*H*-imidazol-1-yl)-2'-hydroxyacetophenones is described. The ring closure also works well for the pyrazolyl derivatives. Compounds I and the corresponding imidazolylchromanols, -chromenes, and -chromans derived from the former, were pharmacologically investigated.

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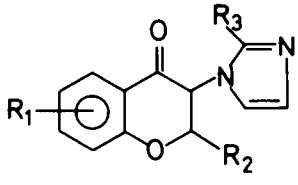
Imidazole and chroman rings are often found in molecules playing an important role in biochemistry *e.g.*, histamine, tocopherols and natural coumarines as well as in many drug molecules, such as coumarin anticoagulants [2], chromone antagonists of SRS-A [3] imidazole antifungal agents [4] or more recently imidazole TXA_2 synthetase inhibitors [5] or anticonvulsants [6].

In the search for new compounds of pharmacological interest we prepared a number of derivatives containing the imidazole and the chroman ring in the same molecule [7].

This paper describes the synthesis of 3-(1*H*-imidazol-1-yl)-2,3-dihydro-4*H*-1-benzopyran-4-ones (I) and of some derived and related compounds.



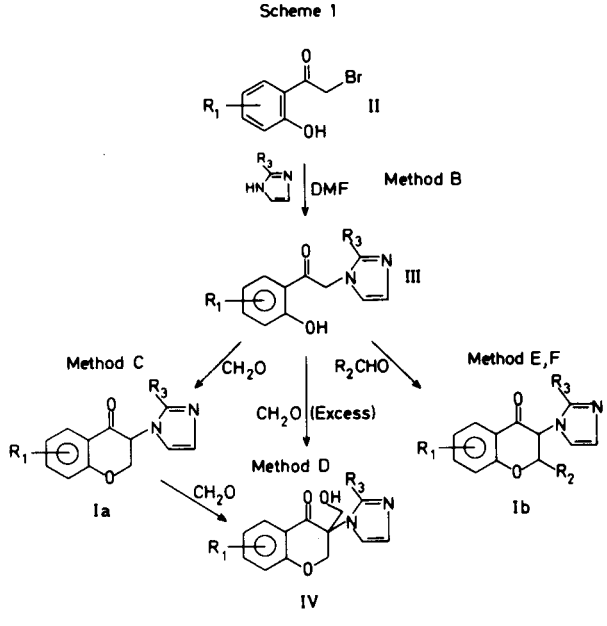
Formula I

R_1 = H, alkyl, OH, alkoxy, halogen, COOH
R_2 = H, alkyl, Ph, Py
R_3 = H, CH_3

The synthesis of I where R_2 is hydrogen was first attempted by reaction of the corresponding 3-bromo-2,3-dihydro-4*H*-1-benzopyran-4-ones with excess imidazole in DMF (Method A). Varying degrees of dehydrohalogenation of 3-bromo-2,3-dihydro-4*H*-1-benzopyran-4-ones took place, giving the corresponding chromones in addition to the desired compounds of formula I.

The side reaction giving chromones could not be eliminated by changing the solvent and temperature or by using imidazole derivatives such as its sodium or silver salt or trimethylsilylimidazole. This is not surprising since it is known that 3-bromo-2,3-dihydro-4*H*-1-benzopyran-4-ones reacting with amines give aminovinyl *o*-hydroxyphenyl ketones through initial dehydrohalogenation [8]. Formation of the chroman ring as the final step of the synthesis, as reported in Scheme 1, was found to be generally a more convenient method of preparation.

Scheme 1

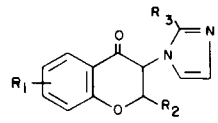


Similar ring closures to chromanones were reported in the literature from *o*-hydroxyphenyl alkyl ketones and an aldehyde in the presence of a base [9]. Recently synthesis of 3-nitroflavanones from 2-nitro-2'-hydroxyacetophenones was reported [10] under conditions very similar to those used by us, namely in acidic medium.

In our case the azole residue as in the last case the nitro group, clearly plays an important role in inducing nucleophilic reactivity on the methylene group of the starting acetophenones. We prepared 2-bromo-2'-hydroxyacetophenones (II) from the corresponding 2-'-hydroxyacetophenones with cupric bromide following the procedure described by King [11].

2-(1*H*-Imidazol-1-yl)-2'-hydroxyacetophenone (III) was easily prepared from II (Method B) under reaction conditions similar to those described in Method A. The ring closure of III to Ia was performed with paraformaldehyde in glacial acetic acid (Method C). The yields ranged from 40 to 70%. Small amounts of compounds IV were formed

Table I



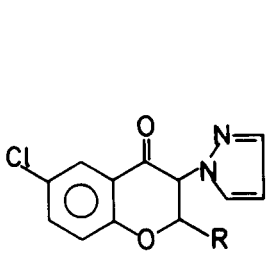
Compound No.	R_1	R_2	R_3	Mp °C [a]	Method	Yield % [b]	Formula	Analysis % C	H	N	Cl/Br
1	H	H	H	156-158	A, C	30, 55	$C_{12}H_{10}N_2O_2$	67.27	4.71	13.08	
								67.21	4.73	12.94	
2	6-CH_3	H	H	105-107	C	50	$C_{13}H_{12}N_2O_2$	68.40	5.29	12.27	
								68.15	5.23	12.22	
3	6-Cl	H	H	123-125	C	45	$C_{12}H_9ClN_2O_2$	57.96	3.64	11.26	14.25
								58.00	3.62	11.28	14.28
4	6-CH_3O	H	H	150-152	A	40	$C_{13}H_{12}N_2O_3$	63.93	4.95	11.47	
								63.85	4.92	11.42	
5	7-CH_3O	H	H	153-155	A	40	$C_{13}H_{12}N_2O_3$	63.93	4.95	11.47	
								63.83	4.93	11.43	
6	H	H	CH_3	180-182	A, C	5, 70	$C_{13}H_{12}N_2O_2$	68.40	5.29	12.27	
								68.20	5.24	12.30	
7	6-Cl	H	CH_3	196-198	C	55	$C_{13}H_{11}ClN_2O_2$	59.44	4.22	10.66	13.49
								59.37	4.20	10.63	13.43
8	H	CH_3	H	144-146	E	82	$C_{13}H_{12}N_2O_2$	68.40	5.29	12.27	
								68.37	5.25	12.30	
9	7-CH_3O	CH_3	H	130-132	E	80	$C_{14}H_{14}N_2O_3$	65.10	5.46	10.85	
								64.95	5.43	10.81	
10	5-CH_3O	CH_3	H	147-149	E	80	$C_{14}H_{14}N_2O_3$	65.10	5.46	10.85	
								64.98	5.42	10.82	
11	6-COOH	CH_3	H	250	E	95	$C_{14}H_{12}N_2O_4$	61.76	4.44	10.28	
								61.68	4.47	10.30	
12 [c]	6,8-Br_2 7-OH	CH_3	H	245 dec	E	85	$C_{13}H_{10}Br_2N_2O_3$	38.84	2.50	6.97	39.75
								38.79	2.53	6.94	39.72
13	H	$CH_2CH_2CH_3$	H	—	E	80	$C_{15}H_{16}N_2O_2$	70.29	6.28	10.29	
								70.35	6.25	10.88	
14	H	C_6H_5	H	201-203	F	75	$C_{18}H_{14}N_2O_2$	74.47	4.86	9.64	
								74.40	4.88	9.68	
15 [d]	H	3-Py [e]	H	70 dec	F	55	$C_{17}H_{13}N_3O_2$	70.09	4.49	14.42	
	70.20	4.45	14.39								

[a] From chromatography column separation except for compound No. **3** crystallized from methanol-water (3:1) and compound **4** crystallized from ethanol-water (3:1). [b] The yields are not optimized. [c] Obtained as mixture of (*cis*) and (*trans*): J (OCHCH) = 4.2 Hz (*cis*) and 12 Hz (*trans*). [d] Obtained as mixture of (*cis*) and (*trans*): J (OCHCH) = 2.2 Hz (*cis*) and 12.2 Hz (*trans*). [e] 3-Py is a 3-Pyridyl radical.

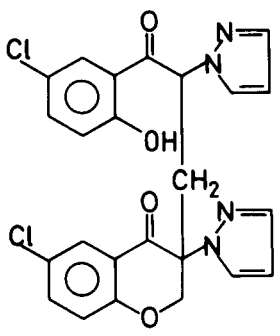
from a second electrophilic attack by formaldehyde. Compounds IV may be obtained from III in high yields using an excess of paraformaldehyde in acetic acid or preferably using a 40% aqueous formaldehyde solution in the presence of sodium metabisulphite (Method D). Compounds IV may be obtained from Ia itself with an excess of paraformaldehyde. Reaction of compounds III with other aldehydes gave compounds Ib predominantly in the *trans* configuration as results from nmr spectral data. In most cases the work-up of the crude product led to the practically pure *trans* derivative. Glacial acetic acid (Method E) or an excess of the reacting aldehyde (Method F) was used as solvent. The yields ranged from 70 to 95%.

Physico-chemical data of some compounds of formula I, methods and yields are reported in Table I.

The ring closure reported in Scheme 1 also works well for 1-pyrazolyl derivatives. For instance *trans*-6-chloro-3-(1*H*-pyrazol-1-yl)-2-methyl-2,3-dihydro-4*H*-1-benzopyran-4-one (**16**) was obtained in high yields from 2-(1*H*-pyrazol-1-yl)-2'-hydroxy-5'-chloroacetophenone (**17**) and acetaldehyde in acetic acid following Method E. The cognate compound 6-chloro-3-(1*H*-pyrazol-1-yl)-2,3-dihydro-4*H*-1-benzopyran-4-one (**18**) was obtained from **17** and paraformaldehyde in a very dilute solution of acetic acid (Method G) because, under the usual conditions reported in Method C for the imidazole analogues, condensation of two molecules of **17** with formaldehyde took place giving a compound to which we assigned the structure of 3-(1*H*-pyrazol-1-yl)-3-[2-(2-hydroxy-5-chlorobenzoyl)-2-(1*H*-pyrazol-1-yl)]ethyl-6-chloro-2,3-dihydrobenzopyran-4-one (**19**).



16 R = CH_3
18 R = H

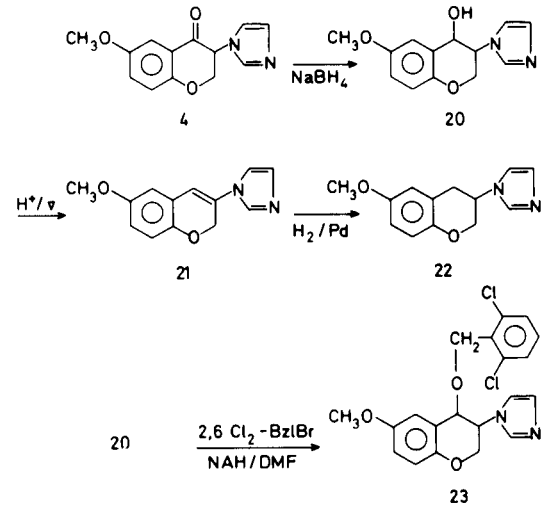


19

By reacting pyrazole with 3-bromo-2,3-dihydro-4*H*-1-benzopyran-4-ones under the conditions described in Method A we recovered the unreacted reagents, whereas when pyrazole was reacted with 2'-hydroxy-5'-chloro-2-bromoacetophenone under reaction conditions similar to those in Method B, compound **17** was obtained.

3-(1*H*-Imidazol-1-yl)-2,3-dihydro-4*H*-1-benzopyran-4-ones (I) were used as starting materials to obtain the corresponding 3-(1*H*-imidazol-1-yl)-2,3-dihydro-4*H*-1-benzopyran-4-ols, 3-(1*H*-imidazol-1-yl)-2*H*-1-benzopyrans, and 3-(1*H*-imidazol-1-yl)-3,4-dihydro-2*H*-1-benzopyrans. These compounds are undergoing pharmacological evaluation as hypolipaemic and antiatherosclerotic agents. Some of them show interesting activities both *in vitro* and *in vivo* and will be discussed in future papers. Moreover some alkyl and benzyl ethers of the above 3-(1*H*-imidazol-1-yl)-2,3-dihydro-4*H*-1-benzopyran-4-ols were prepared, which can be considered cyclic analogues of antifungal agents such as miconazole [12] and isosters of the 2-(1*H*-imidazol-1-yl)-1-benzyloxytetralines described by Schröder and coworkers [13]. Some of them were active *in vitro* against Gram-positive bacteria, *Candida albicans* and dermatophytes.

Scheme 2



All the above compounds derived from compound I were prepared following classical procedures.

As an example we report in Scheme 2 the synthetic pathway starting from 3-(1*H*-imidazol-1-yl)-6-methoxy-2,3-dihydro-4*H*-benzopyran-4-one (**4**) leading to the corresponding 3-(1*H*-imidazol-1-yl)-6-methoxy-2,3-dihydro-4*H*-1-benzopyran-4-ol (**20**) (*cis-trans* mixture), 3-(1*H*-imidazol-1-yl)-6-methoxy-2*H*-1-benzopyran (**21**), 3-(1*H*-imidazol-1-yl)-6-methoxy-3,4-dihydro-2*H*-1-benzopyran (**22**) and to 3-(1*H*-imidazol-1-yl)-4-(2,6-dichlorobenzyloxy)-6-methoxy-2,3-dihydro-4*H*-1-benzopyran (**23**) (*cis-trans* mixture). Their synthesis is described in detail in the experimental.

EXPERIMENTAL

Melting points were determined on a Büchi melting point apparatus and are uncorrected. The ir spectra were obtained on a Perkin-Elmer 125 spectrophotometer and the ir spectral data are recorded in reciprocal cm (cm^{-1}). The ^1H nmr spectra were obtained on a Bruker HFX 90 MHz spectrometer in the solvents indicated. Mass spectra were obtained with a Varian CH 7 spectrometer. Chemical shfits 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).

Method A.

3-(1*H*-Imidazol-1-yl)-6-methoxy-2,3-dihydro-4*H*-1-benzopyran-4-one (**4**).

A solution of 7 g (27.2 mmoles) of 3-bromo-6-methoxy-2,3-dihydro-4*H*-1-benzopyran-4-one and 7.3 g (108.8 mmoles) of imidazole in 200 ml of *N,N*-dimethylformamide was heated with stirring at 60° for 5 hours. The solvent was evaporated *in vacuo* and the residue taken up with 100 ml of methylene chloride. The organic phase, washed with water, was extracted with a solution of 7% hydrochloric acid. The aqueous acid solution, separated from the organic layer (solution A), neutralized with sodium bicarbonate, was extracted with methylene chloride and the solvent was evaporated *in vacuo*. The resulting solid was crystallized from ethanol-water (2:1) yielding 2.6 g (40%) of **4** as a white solid, mp 150-152°; nmr (deuteriochloroform): δ 3.85 (3H, s, OCH_3), 4.70 (2H, m, OCH_2), 5.04 (1H, m, OCH_2CH), 6.90-7.60 (6H, m, benzene and imidazole).

Anal. Calcd. for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.85; H, 4.92; N, 11.42.

The above solution A was evaporated to dryness yielding 2.4 g of 6-methoxy-4*H*-1-benzopyran-4-one, mp 91-93° (lit [14] mp 92-94°).

Method B.

2-(1*H*-Imidazol-1-yl)-2'-hydroxy-5'-chloroacetophenone (**24**).

A solution of 7 g (28.1 mmoles) of 2-bromo-2'-hydroxy-5'-chloroacetophenone, 5.73 g (84.3 mmoles) of imidazole in 50 ml of *N,N*-dimethylformamide was heated to 40° for 2 hours. The solution was poured into water, the precipitate was filtered off and taken up with aqueous 10% sodium hydroxide solution. The basic solution, washed with methylene chloride and neutralized with hydrochloric acid was extracted with methylene chloride. The solvent was evaporated *in vacuo* and the resulting solid was crystallized from methanol to give 4.6 g (70%) of **24** as a pale yellow solid, mp 206-208°; ir (Nujol): 3140-3120 cm^{-1} (CH imidazole), 1675 cm^{-1} (C=O).

Anal. Calcd. for $C_{11}H_9ClN_2O_2$: C, 55.82; H, 3.83; N, 11.84; Cl, 14.98. Found: C, 55.77; H, 3.80; N, 11.87; Cl, 14.94.

By the above procedure the following compound was prepared:

2-(1*H*-Pyrazol-1-yl)-2'-hydroxy-5'-chloroacetophenone (**17**).

This compound had mp 195-196°; ir (Nujol): 3150-3120 cm^{-1} (CH pyrrole), 1680 cm^{-1} (C=O).

Anal. Calcd. for $C_{11}H_9ClN_2O_2$: C, 55.82; H, 3.83; N, 11.84; Cl, 14.98.

Found: C, 55.92; H, 3.81; N, 11.90; Cl, 14.92.

Method C.

3-(1*H*-Imidazol-1-yl)-6-chloro-2,3-dihydro-4*H*-1-benzopyran-4-one (**3**).

A solution of 2.36 g (10.0 mmoles) of **24**, 0.3 g (10.0 mmoles) of paraformaldehyde and 45 ml of glacial acetic acid was refluxed for 30 minutes. The solvent was evaporated *in vacuo* and the residue, taken up with 100 ml of methylene chloride, was washed with water. The organic layer was dried over magnesium sulfate, and concentrated to solid residue which was crystallized from methanol-water (3:1) yielding 1.13 g (45%) of **3** as a white solid, mp 123-125°; nmr (deuteriochloroform): δ 4.60-5.10 (2H, m, OCH_2), 5.84 (1H, m, OCH_2CH), 6.92-7.84 (6H, m, benzene and imidazole).

Anal. Calcd. for $C_{12}H_9ClN_2O_2$: C, 57.96; H, 3.64; N, 11.26; Cl, 14.25. Found: C, 58.00; H, 3.62; N, 11.28; Cl, 14.28.

By the above procedure, starting from **17**, the following compound was obtained:

3-(1*H*-Pyrazol-1-yl)-3-[(2-(2-hydroxy-5-chlorobenzoyl)-2-(1*H*-pyrazol-1-yl)]-ethyl-6-chloro-2,3-dihydro-4*H*-1-benzopyran-4-one (**19**).

This compound had mp 172-175°; yield 80%; nmr (deuteriochloroform): δ 2.81 (1H, dd, CC*H*HCH), 3.57 (1H, dd, CCH*H*CH), 4.31 (1H, d, O-C*H*H-), 4.60 (1H, d, O-CH*H*), 5.89 (1H, dd, $-CH_2-CH-$), 6.44-7.91 (12H, m, benzene and imidazole), 11.56 (1H, bs, OH); ms: m/e (relative intensity) 496 (M^+, 27), 428 (3), 360 (9), 341 (12), 249 (56), 248 (100).

Anal. Calcd. for $C_{24}H_{18}Cl_2N_4O_4$: C, 57.96; H, 3.64; N, 11.26; Cl, 14.25. Found: C, 57.83; H, 3.62; N, 11.24; Cl, 14.22.

Method D.

3-(1*H*-Imidazol-1-yl)-3-hydroxymethyl-6-chloro-4*H*-1-benzopyran-4-one (**25**).

To a solution of 1.32 g (5.2 mmoles) of sodium sulfite heptahydrate in 6 ml of 40% aqueous formaldehyde, 1.23 g (5.2 mmoles) of **24** was added. The mixture was stirred at room temperature for 2 hours. The precipitate, collected by filtration and washed with water, gave 1.3 g (90%) of **25**, mp 175-177°; nmr (DMSO-d_6): δ 4.14 (2H, m, CH_2OH); 4.80-5.30 (2H, m, OCH_2), 7.00-8.00 (6H, m, benzene and imidazole).

Anal. Calcd. for $C_{13}H_{11}ClN_2O_3$: C, 56.02; H, 3.98; N, 10.05; Cl, 12.72. Found: C, 56.00; H, 4.01; N, 10.02; Cl, 12.75.

Method E.

trans-2-Methyl-3-(1*H*-imidazol-1-yl)-2,3-dihydro-4*H*-1-benzopyran-4-one (**8**).

In a flask equipped with an efficient reflux condenser, a solution of 6.5 g (32.1 mmoles) of 2-(1*H*-imidazol-1-yl)-2'-hydroxyacetophenone (**26**), (mp 147-149°, prepared following Method B), 20 ml of acetaldehyde and 400 ml of acetic acid was heated at 90° for 10 hours. The solvent was evaporated *in vacuo* and the residue, taken up with 100 ml of methylene chloride, was washed with water. The organic layer was dried (magnesium sulfate) and concentrated to a solid residue which was purified by silica gel column chromatography, eluting with chloroform-methanol (9:1) to yield 6 g (82%) of **8**, as a white powder, mp 144-146°; nmr (deuteriochloroform): δ 1.37 (3H, d, CH_3), 4.50-4.98 (2H, m, J = 12 Hz, OCHCH), 7.02-7.95 (7H, m, benzene and imidazole).

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.40; H, 5.29; N, 12.27. Found: C, 68.37; H, 5.25; N, 12.30.

By the above procedure, starting from **17**, the following compound was prepared:

trans-2-Methyl-3-(1*H*-pyrazol-1-yl)-6-chloro-2,3-dihydro-4*H*-1-benzopyran-4-one (**16**).

The yield was 85%, mp 140-142° (ethanol-water 2:1); nmr (deuteriochloroform): δ 1.11 (3H, d, CH_3), 4.48 (1H, d, J = 12 Hz, OCHC*H*), 4.83 (1H, m, OC*H*CH), 6.12-7.84 (6H, m, benzene and pyrazole).

Anal. Calcd. for $C_{13}H_{11}ClN_2O_2$: C, 59.44; H, 4.22; N, 10.66; Cl, 13.49. Found: C, 59.39; H, 4.19; N, 10.62; Cl, 13.44.

Method F.

trans-2-Phenyl-3-(1*H*-imidazol-1-yl)-2,3-dihydro-4*H*-1-benzopyran-4-one (**14**).

A mixture of 3.5 g (17.3 mmoles) of **26** and 200 ml of benzaldehyde was heated at 110° for 8 hours. The benzaldehyde was evaporated *in vacuo* and the residue, taken up with 100 ml of methylene chloride, was washed with water. the organic layer was dried (magnesium sulfate) and concentrated to a solid residue which was purified by silica gel column chromatography, eluting with chloroform-methanol (9:1), to yield 3.73 g (75%) of **14**; nmr (deuteriochloroform): δ 5.19 (1H, d, J = 12 Hz, OCHC*H*), 5.48 (1H, d, OC*H*CH), 7.75-8.10 (12H, m, benzene and imidazole).

Anal. Calcd. for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.64. Found: C, 74.40; H, 4.88; N, 9.68.

Method G.

3-(1*H*-Pyrazol-1-yl)-6-chloro-2,3-dihydro-4*H*-1-benzopyran-4-one (**18**).

A solution of 5 g (21.1 mmoles) of **17**, 0.63 g (21.1 mmoles) of paraformaldehyde and 1000 ml of glacial acetic acid was heated at reflux for 10 hours. The solvent was evaporated *in vacuo* and the residue, taken up with 100 ml of methylene chloride, was washed with water. The organic layer was dried (magnesium sulfate) and concentrated to solid residue which was crystallized from methanol to give 3.3 g (63%) of **18**, mp 148-150°; nmr (deuteriochloroform): δ 4.84-5.00 (2H, m, OCH_2), 5.36 (1H, m, OCH_2CH), 6.42-7.96 (6H, benzene and pyrazole).

Anal. Calcd. for $C_{12}H_9ClN_2O_2$: C, 57.96; H, 3.64; N, 11.26; Cl, 14.25. Found: C, 58.08; H, 3.61; N, 11.30; Cl, 14.20.

3-(1*H*-Imidazol-1-yl)-6-methoxy-2,3-dihydro-4*H*-1-benzopyran-4-ol (**20**).

To a solution of 2.7 g (11.0 mmoles) of **4** in 70 ml of methanol 1.25 g (33.0 mmoles) of sodium borohydride at 5-10° was added portionwise. After stirring at room temperature for 2 hours the mixture was poured into 200 ml of water. The methanol was evaporated under reduced pressure. The resulting solid was filtered, washed with water, dried and then crystallized from ethanol yielding 2.6 g (95%) of **20** as colorless crystals, mp 172-173°; nmr (DMSO-d_6): δ 3.72 (3H, s, OCH_3), 4.20-5.00 (4H, m, CH_2CHCH), 6.76-7.64 (6H, m, benzene and imidazole).

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.72; N, 11.37. Found: C, 63.36; H, 5.70; N, 11.34.

3-(1*H*-Imidazol-1-yl)-6-methoxy-2*H*-1-benzopyran (**21**).

A solution of 3.5 g (14.2 mmoles) of **20** in 45 ml of glacial acetic acid and 10 ml of concentrated sulfuric acid was heated at 80° for 2 hours. After cooling, the reaction mixture was poured onto crushed ice, neutralized with ammonium hydroxide and extracted with methylene chloride. The organic layer was dried (magnesium sulfate) and concentrated to a solid residue which was purified by silica gel column chromatography, eluting with chloroform-methanol (9:1), to yield 2.0 g (62%) of **21** as a white solid, mp 104-106°; nmr (deuteriochloroform): δ 3.77 (3H, s, OCH_3), 5.00 (2H, d, OCH_2), 6.46 (1H, br s, OCH_2CCH), 6.61-7.74 (6H, m, benzene and imidazole).

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.40; H, 5.30; N, 12.27. Found: C, 68.33; H, 5.27; N, 12.24.

3-(1*H*-Imidazol-1-yl)-6-methoxy-3,4-dihydro-2*H*-1-benzopyran (**22**).

A mixture of 0.5 g (2.19 mmoles) of **21**, 0.1 g of 10% palladium on activated carbon, 50 ml of ethanol, 20 ml of glacial acetic acid and 3 ml of concentrated hydrochloric acid was hydrogenated for 8 hours at room temperature in a Parr-Burgess low pressure hydrogenator at an initial pressure of 50 psi. At the end of this time the theoretical amount of hydrogen had been absorbed. The catalyst was filtered off and the acid solution, neutralized with ammonium hydroxide, was extracted with methylene chloride. The solvent, dried and evaporated, gave 0.45 g (90%) of **22** as a white solid; nmr (deuteriochloroform): δ 3.10-3.42 (2H, m, OCH_2CHCH_2), 3.80 (3H, s, OCH_3), 4.10-4.25 (2H, m, OCH_2), 4.67 (1H, m, OCH_2CH), 6.60-7.64 (6H, m, benzene and imidazole).

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.12; N, 12.11. Found: C,

67.77; H, 6.15; N, 12.19.

3-(1*H*-Imidazol-1-yl)-4-(2,6-dichlorobenzyloxy)-6-methoxy-2,3-dihydro-4*H*-1-benzopyran (**23**).

A solution of 2.46 g (10.0 mmoles) of 20 in 10 ml of anhydrous *N,N*-dimethylformamide was added under stirring to a suspension of 0.24 g (10.0 mmoles) of sodium hydride in 5 ml of anhydrous *N,N*-dimethylformamide. The reaction mixture was gently heated at 50°, cooled to room temperature, then a solution of 2.4 g (10.0 mmoles) of 2,6-dichlorobenzylbromide in 10 ml of anhydrous *N,N*-dimethylformamide was added portionwise. After stirring at room temperature for 4 hours, the reaction mixture was evaporated to dryness *in vacuo* and the residue was crystallized from ethyl acetate to yield 3 g (74%) of **23** as a white powder; mp 159-161°; nmr (deuteriochloroform): δ 3.73 (3H, s, OCH_3), 4.20-4.90 (6H, m, alifatic), 6.7-7.60 (9H, m, benzene and imidazole).

Anal. Calcd. for $C_{20}H_{18}Cl_2N_2O_3$: C, 59.27; H, 4.47; N, 6.91; Cl, 17.49. Found: C, 59.21; H, 4.49; N, 6.93; Cl, 17.52.

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