Synthesis of 1-Halophenyl 4-(2-Imidazolyl)-1-butanones and 5-(2-Imidazolyl)-1-pentanones and Their Ketalization with Glycerol

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An alternate synthesis of 1-(2,4-dichlorophenyl)-4-(2-imidazolyl)-1-butanones **5d** is presented after 1-[(dimethylamino)methyl- and 1-methyl]-2-lithioimidazole failed to be substituted satisfactorily by 2-(2,4-dichlorophenyl)-2-(3-iodopropyl)-1,3-dioxolane (**3b**). The Pinner addition of ethanol to 2-(2,4-dichlorophenyl)-2-(3-cyanopropyl)-1,3-dioxolane yielded the corresponding imidate which was reacted with 1-amino-2,2-dimethoxyethane to form an amidine. Hot dilute hydrochloric acid converted this amidine to the 2-imidazolyl ketone **5b**. Syntheses of homologous 1-(4-chloro- and 2,4-dichlorophenyl)-4-(2-imidazolyl)-1-pentanones **20** are described. Ketalizations of **5** and **20** with glycerol formed imidazolyl 1,3-dioxolanyl alcohols. Selective *N*- and *O*-alkylations of some of these imidazolyl alcohols are described.

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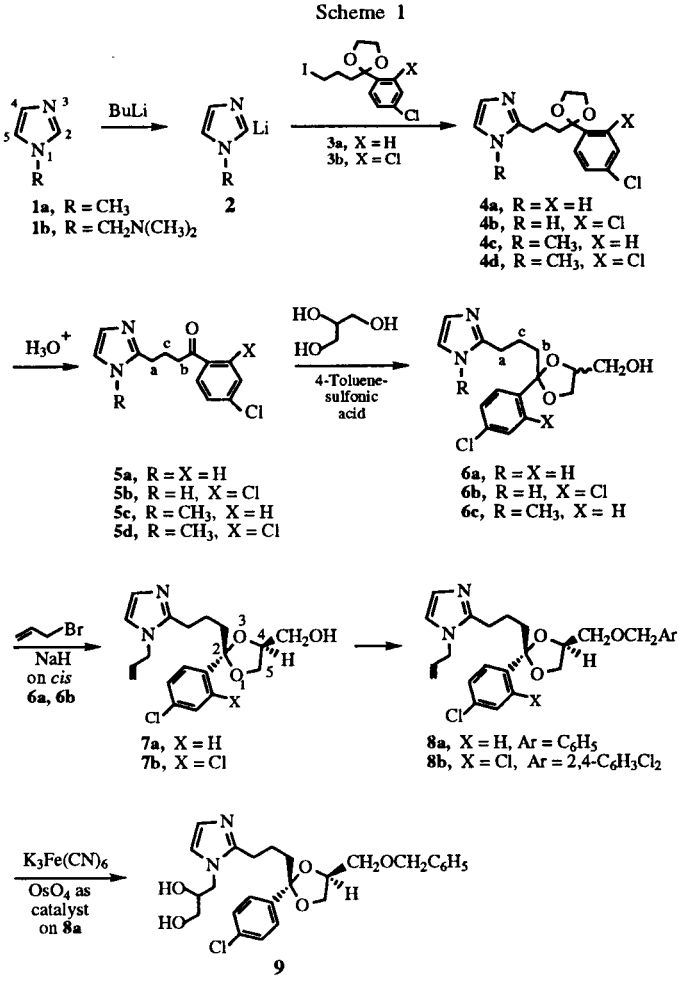
This investigation focuses on the synthesis of certain ω-(2-imidazolyl)alkyl 1-aryl-1-butanones and 1-pentanones and their subsequent ketalizations with glycerol. Substituents can be introduced readily at *C*-2 of *N*-substituted imidazoles to produce 1,2-disubstituted imidazoles. The *N*-substituent could be a "permanent" (*e.g.*, alkyl) or readily removable groups. For example with protective groups like (dimethylamino)methyl, trityl or (*N*,*N*-dimethyl)sulfonamido groups, it was possible to convert imidazole to 2-substituted-1*H*-imidazoles. There are considerable advantages to prepare first the *N*-unsubstituted imidazole since one can introduce different *N*-alkyl groups at later stages, thereby greatly expanding the scope of synthetic schemes.

Synthesis of 1-(Halophenyl)-4-(2-imidazolyl)-1-butanones **5**.

Syntheses of 3-(2-imidazolyl)propyl haloaryl ketones **5** have been described by lithiating C-2 of a requisite *N*-substituted imidazole, followed by substitution by an iodo ketal and subsequent acid-catalyzed hydrolysis (Scheme 1) [1]. While substitution of **1a** by 2-(4-chlorophenyl)-2-(3-iodopropyl)-1,3-dioxolane (**3a**) was very successful in the eventual production of **5c** [1], an analogous sequence of reactions using the 2,4-dichlorophenyl analog **3b** to make **5d**, failed dismally [2]. This raised the question if one could effect substitutions using **3b** by changing the nature of the *N*-substituent of the starting imidazole.

In this vein, we explored several other approaches to synthesize **5d**. By way of background, it has been reported that lithiation of 1-tritylimidazole [**1**, R = $C(C_6H_5)_3$] followed by substitution by **3a** produced ketal **4** [R = $C(C_6H_5)_3$, X = H], which was hydrolyzed to the *N*-unsubstituted ketone **5a** (57%) [1]. An easier and more attractive route to **5a** was developed when 1-(dimethylaminomethyl)imidazole (**1b**), which is readily made from imidazole, formaldehyde and dimethylamine [3], was lithiated and substituted by **3a** to give **4a**. The protective

Scheme 1



group was lost during the simple aqueous workup. More drastic hydrolysis with warm hydrochloric acid furnished **5a** (51%). In a cognate sequence of reactions, the lithio derivative of **1b** refused to be substituted by **3b** to form **4b**. Thin layer chromatography (tlc) and proton nuclear

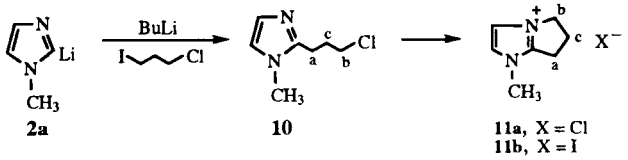
magnetic resonance (^{1}H nmr) spectra clearly indicated a hopeless mixture of many products. The disappearance of **3b** was noted due to the absence of a ^{1}H nmr signal for the methylene protons on the carbon attached to iodine (δ 3.2). It was also concluded that **4d** had not been formed since the ^{1}H nmr spectrum lacked a signal around δ 2.6 expected for the methylene protons on the carbon attached to C-2 of imidazole. The progress of the reaction had been followed closely. Lithiation of **1b** was quantitative (disappearance of ^{1}H nmr signal for H-2 at δ 7.42 in deuteriochloroform after deuteration). Yet, unlike the reaction with **3a**, the course of the reaction with **3b** seemed so different. Also, while lithiation of 1-(*N,N*-dimethylsulfonamido)imidazole [**1**, R = $SO_2N(CH_3)_2$] is successful [4], subsequent substitution by **3b** also did not take place, with starting materials being recovered.

Another attempt to make **5d** was based on the initial synthesis of 4-(1-methyl-2-imidazolyl)butanenitrile, followed by addition of the Grignard reagent from 1-iodo-2,4-dichlorobenzene. To prepare the intermediate nitrile, a halo precursor like **10** needed to be synthesized. Such an alkyl halide should become available based on the preferential lithiation-substitution of 1-methylimidazole (**1a**) by alkyl iodides rather than alkyl chlorides [5]. The reaction of **2a** with 3-chloro-1-iodopropane furnished **10** (Scheme 2). Upon standing, **10** cyclized to a gummy chloride **11a**, which could be characterized as a crystalline iodide **11b** by double decomposition with sodium iodide in methanol. Iodide **11b** can be made directly from **10** after boiling with sodium iodide in methanol. Attempted displacement of the chloro group (of the relatively unstable **10**) by cyanide ion to form 2-(3-cyanopropyl)-1-methylimidazole was unsuccessful. Attempts to make the same nitrile by lithiation-substitution of **1a** with 4-iodobutanenitrile (made from 4-chlorobutanenitrile and sodium iodide) led to a hopeless mixture of unidentifiable products.

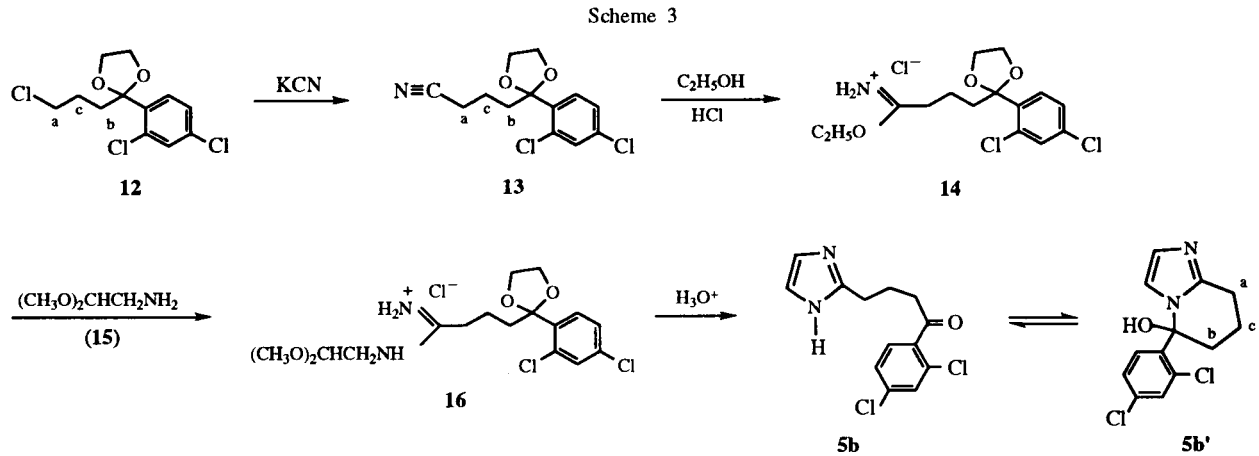
Hence, we turned to a synthesis of **5d** from aliphatic starting materials, modeled after an established imidazole synthesis [6]. The chloro ketone [2] was transformed to the corresponding ethylene glycol ketal **12** which in turn was converted smoothly to the nitrile **13**. After the Pinner addition of ethanol, the imidate hydrochloride **14** was formed and was reacted immediately with 1-amino-2,2-dimethoxyethane (**15**) to produce the corresponding amidine hydrochloride **16**. Hot dilute acids hydrolyzed the acetal and ketal groups of **16** to generate a carboxamidino aldehyde, *in situ*, which spontaneously cyclized to the 2-imidazolyl ketone **5b** (Scheme 3).

The ^{1}H and ^{13}C nmr spectra of **5b** were very confusing but were consistent with a mixture of the expected keto imidazole **5b** and hemiaminal **5b'**. In deuteriochloroform the ratio of **5b**:**5b'** was 1.7:1 and in deuteriodimethyl sulfoxide 5:1, increasing to 11:1 if some deuterium oxide and potassium carbonate was added to the latter solution. The behavior of this ω-[2-(1*H*-imidazolyl)]alkyl haloaryl ketone was quite different to that of many other analogs handled in this Laboratory [1,2,8]. For example, nmr spectra of closely related *p*-halophenyl analog **5a** showed only the ketonic form. The lower homologs of **5a** and **5b**, that is only two methylene links between the halophenyl ketone and C-2 of imidazole [7], or those analogs with one additional methylene group, **20a** and **20b**, as ketones only (nmr). The ^{13}C chemical shift of the hemiaminal carbon in **5b'** was at 84.5 ppm, which is close to the reported shifts in related hemiaminals, around 86 ppm. [9]. Attempts to methylate the mixture of **5b** and **5b'** with

Scheme 2



Scheme 3



one equivalent of methyl iodide and sodium hydride in tetrahydrofuran was not clean-cut. A mixture of products was obtained, with **5d** as the major product (nmr). However, the equilibrium mixture of **5b** and **5b'** ketalized very well with glycerol [8] to form expected *cis* and *trans*-**6b**. This overall method produced 2-substituted 1*H*-imidazolyl ketals, type **6b**, which then lent themselves to independent *N*-alkylations of the imidazole ring [8].

Synthesis of 1-(Halophenyl)-5-(2-imidazolyl)-1-pentanones **20**.

Lithiation of the 2-methyl group of 1,2-dimethylimidazole (**17a**) [10] and of 1-(dimethylamino)methyl]-2-methylimidazole (**17b**) [11] by butyllithium generated active methylene anions, **18a** and **18b**, which are highly active nucleophiles. Substitution by iodo ketals **3** took place to produce **19**. During aqueous workups, the protective aminal is hydrolyzed to release 1*H*-imidazoles **19a** and **19b**, while the *N*-methyl group remained to form **19c** and **19d**. Hydrolysis of the ethylene glycol ketal with hot dilute aqueous acids produced imidazolyl ketones **20** (Scheme 4). The great disparity exhibited during these nucleophilic substitutions using **3a** and **3b** remains unexplained. Are such differences between the 4-chloro and 2,4-dichlorophenyl derivatives due to some form of steric hindrance created by the presence of the relatively bulky extra "*ortho*" chloro group? Or, can this

Scheme 4

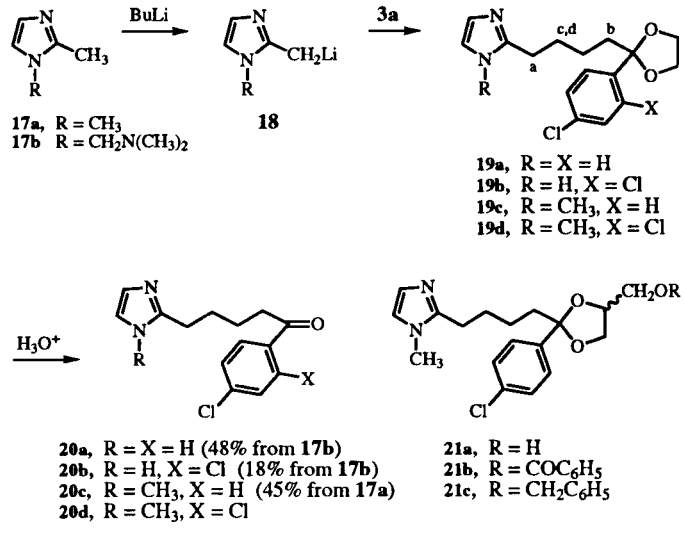


Table 1

Selected Carbon-13 Chemical Shifts [a]

Compound	2-Imidazoyl				Alkyl Spacers			1,3-Dioxolane				
	C-2	C-4	C-5	*N*-Me	$(CH_2)_a$	$(CH_2)_b$	$(CH_2)_c$ and $(CH_2)_d$	C-2	C-4	C-5	CH_2-OR at C-4	C=O
5a	147.7	121.6	121.6	--	27.5	37.4	22.9	--	--	--	--	199.1
5b	147.7	121.6	121.6	--	27.4	41.8	22.9	--	--	--	--	201.7
5b'	145.7	126.7	116.3	--	24.2	35.9	17.7	--	--	--	--	[b]
5c	147.5	126.9	120.6	32.5	25.8	37.4	21.8	--	--	--	--	198.6
cis-**6b**	148.5	121.2	121.2	--	27.7	35.8	22.4	110.6	76.4	65.5	62.3	--
trans-**6b**	148.2	121.1	121.1	--	27.6	37.2	22.4	110.3	78.1	66.7	62.7	--
7a	148.0	126.9	119.2	--	26.1	38.9	21.9	110.7	76.8	65.4	62.7	--
7b	148.0	126.8	119.2	--	26.0	36.0	21.9	110.5	76.7	65.5	62.4	--
8a	147.8	127.2	119.2	--	26.6	40.0	21.9	110.6	74.4	71.0	66.9	--
8b	147.8	127.1	119.2	--	26.6	37.2	21.9	110.5	74.3	71.4	66.8	--
9	148.2	126.5	119.5	--	26.4	39.8	21.9	110.7	74.3	71.0	66.7	--
10	146.8	127.1	120.6	32.5	30.1	44.5	23.4	--	--	--	--	--
11a,b[c]	156.0	129.1, 120.1		37.3	28.3	50.7	24.9	--	--	--	--	--
12	--	--	--	--	45.0	34.9	26.9	109.5	64.7	64.7	--	--
13	--	--	--	--	19.8	36.1	17.1	109.2	64.7	64.7	--	--
19c	148.3	126.9	120.2	32.5	27.8	40.0	23.5, 26.7	109.2	64.5	64.5	--	--
20a	148.2	121.4	121.4	--	27.7	38.0	23.3, 28.2	--	--	--	--	199.2
20b	148.2	121.4	121.4	--	27.8	47.4	23.4, 28.2	--	--	--	--	202.2
20c[d]	147.9	126.9	120.4	32.5	26.5	38.1	23.7, 27.2	--	--	--	--	198.8
cis-**21a**	148.3	126.6	120.3	32.6	26.2	39.7	23.1, 27.5	110.5	76.4	66.0	62.7	--
trans-**21a**	148.3	126.7	120.3	32.6	26.6	40.6	23.4, 27.8	110.6	78.1	67.1	62.7	--
cis-**21b**	148.3	126.9	120.2	32.5	26.6	40.2	23.3, 27.5	110.0	73.4	66.4	64.8	166.3
cis-**21c**	148.2	127.0	120.2	32.5	26.7	40.3	23.4, 27.8	110.7	74.4	71.0	66.9	--

[a] Spectra determined in deuteriochloroform and shifts are reported in ppm (δ) downfield from tetramethylsilane. Assignments are primarily by analogy with chemical shifts reported for very similar compounds in refs 1,2,8. Relatively close chemical shifts may be interchangeable. [b] The chemical shift of the hemiaminal carbon is δ 84.5. [c] Values recorded in deuterium oxide. [d] The nmr correlation experiments of the HETCOR type linked the following ^1H and ^{13}C chemical shifts: δ 3.00 with 38.1; 2.72 with 26.5; 1.85 with 27.2 and 23.7.

Table2

Selected Proton Chemical Shifts [a]

Compound	Imidazole [b]			AlkylSpacers			1,3-Dioxolane			
	H-4	H-5	*N*-Me	$(CH_2)_a$	$(CH_2)_b$	$(CH_2)_c$ and $(CH_2)_d$	H-4	H-5	CH_2-OR at C-4	NH, OH [c]
5a	6.96	6.96	--	2.83	3.03	2.16	--	--	--	--
5b	6.88	6.88	--	2.78	2.96	2.10	--	--	--	9.80
5c[d]	6.90	6.79	3.59	2.78	3.10	2.18	--	--	--	--
***cis*-6b**	6.89	6.89	--	2.73, 2.88	2.10	1.80	4.12	3.06-3.90		6.50
7a	6.94	6.77	--	2.62, 2.92	1.95	1.78	4.14	3.71, 3.90	3.64, 3.81	--
7b	6.94	6.78	--	2.62, 2.95	2.16	1.82	4.15	3.74, 3.95	3.64, 3.86	4.85
8a	6.93	6.76	--	2.60	1.95	1.79	4.12	3.49, 3.61	3.76	--
8b	6.94	6.76	--	2.62	2.18	1.80	4.16	3.61, 3.70	3.83	--
9	6.76, 6.78		--	2.59	1.91	1.75	4.12	3.42-3.89		3.02
10	6.83, 6.91		3.60	2.83	3.65	2.27	--	--	--	--
11a,b[e]	7.32, 7.34		3.78	3.17	4.27	2.80	--	--	--	--
12	--	--	--	3.55	2.25	1.85	3.78, 4.05		--	--
13	--	--	--	2.40	2.24	1.76	3.78, 4.05		--	--
19c	6.89	6.75	3.52	2.60	1.91	1.45, 1.72	3.73, 4.00		--	--
20a	6.98	6.98	--	2.81	2.95	1.81	--	--	--	11.40
20b	6.97	6.97	--	2.80	2.92	1.78	--	--	--	10.65
20c	6.90	6.78	3.58	2.72	3.00	1.85	--	--	--	--
***cis*-21a**	6.87	6.75	3.52	2.62	1.92	1.47, 1.72	4.07	3.71	3.71, 3.87	5.42
***cis*-21b**	6.94	6.74	3.49	2.58	1.92	1.48, 1.71	4.28	3.83, 3.93	4.36, 4.46	--
***cis*-21c**	6.89	6.74	3.50	2.57	1.95	1.45, 1.72	4.12	3.49, 3.60	3.76	--

[a] Spectra determined in deuteriochloroform and shifts are reported in ppm (δ) downfield from tetramethylsilane; for the ketones the chemical shifts of $(CH_2)_c$ and $(CH_2)_d$ happen to coincide, but were different for the ketals; no coupling constants are reported. [b] Most of the chemical shifts for H-4 and H-5 are assigned by analogy (*see*, Ref. 1,2,8); when observable, $J_{4,5}$ = 1.2 Hz. [c] In deuteriochloroform, individual ^1H nmr signals for imidazole NH or alcoholic OH protons are rarely observed. [d] The ^1H chemical shift of H-5 of imidazol, δ 6.79, was confirmed by nOe experiments. Irradiation of the*N*-methyl signals at δ 3.59 caused an increase of the δ 6. 79 signal by 5.1%. [e] Chemical shifts recorded in deuteriumoxide.

difference in rates of reaction be attributed to an electronic effect such as repulsion between the non-bonding electrons of the *ortho*-chloro group with those of the pyridine nitrogen of the imidazole ring? In that respect, it is interesting to note reactions involving protonated imidazole species (in acid-catalyzed reactions) take place equally well for 4-chloro and 2,4-dichlorophenyl derivatives.

Ketalizations of **5** and **20** with Glycerol and Subsequent Derivatizations.

The 4-toluenesulfonic acid catalyzed condensation of these 4-(2-imidazolyl)alkyl ketones with glycerol provided the expected mixture of *cis*- and *trans*-1,3-dioxolanes, **6** and **21** [12]. Racemic diastereomeric ketals were separated by column chromatography on silica gel, either as 1,3-dioxolanyl-4-methanols, or, sometimes better as their corresponding benzoate esters. The stereochemistry of these *cis*- and *trans*-1,3-dioxolanes was established by a series of nmr correlation experiments, as described previously [2,8]. Selected ^1H and ^{13}C chemical shifts are listed in Tables 1 and 2. Whenever some of the values are relatively close, these could be interchangeable. Several specific chemical shift differences are germane to stereochemical assignments of these *cis*- and *trans*-1,3-dioxolanes. In general, ^1H chemical shifts of the methine proton of *cis*-isomers (H-4) was 0.1 to 0.2 ppm upfield from that of the corresponding *trans*- isomer. Also, ^{13}C chemical shifts of C-4 of *cis*-1,3-dioxolanes were some 2 ppm upfield from that of C-4 of the corresponding *trans*-isomers.

Selective *N*- and *O*-alkylations of such 1*H*-imidazolyl alcohols as **6a** and **6b** are described. After creation of the imidazolyl anion (using one equivalent of sodium hydride), reaction with an alkylating agent forms the corresponding *N*-alkylimidazole derivative exclusively. Experimentally, we have found that it was advantageous (ease of separation of stereoisomeric *H*-imidazolyl alcohols, better yields of cleaner products) to *N*-alkylate such 1*H*-2-substituted imidazolyl ketals rather than the precursor ketones like **5a**, **5b**, **20a** and **20b**. Further alkylation of these *N*-alkyl imidazole alcohols produce the corresponding ethers. These sequences are demonstrated by the *N*-allylation of **6a** and **6b** with one equivalent of allyl bromide in the presence of sodium hydride. Benzylation of **7a** and **7b** forms *O*-benzyl ethers **8a** and **8b**. It was of interest to hydroxylate the double bond of one of the allyl derivatives **8a** *via* the osmate oxidation [13] and the ensuing diol **9** was isolated (Scheme 1).

EXPERIMENTAL

General Procedures.

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. A Varian XL-300 spectrometer was used to obtain nmr spectra and ^{1}H and ^{13}C nmr chemical shifts are tabulated in Tables 1 and 2. Research chemicals were purchased from Aldrich Chemical Co. Milwaukee, WI, and were used as supplied. Aldrich grade 60Å silica gel (200-400 mesh) was used for column chromatography. Elemental analyses were performed by Midwest Microlab, Indianapolis, IN. Most of the reactions and column chromatographic separations were followed by thin layer chromatograms (tlc) using silica gel (impregnated with a 254 nm fluorescent indicator) on glass plates, layer thickness 250 µm, particle size 5-17 µm, pore size 60Å (Aldrich). Spots were visualized by iodine vapor and/or uv light.

Most of the reactions in organic solvents were worked up by first removing solvents by means of a rotary evaporator at the water pump (20-30 torr) at about 40°. The residue was diluted with water and the organic product extracted into ethyl acetate or dichloromethane. The organic extract was washed with brine, dried (sodium sulfate) and solvents removed, *in vacuo*. The product of the extraction was recrystallized or chromatographed.

1-(4-Chlorophenyl)-4-(2-imidazolyl)-1-butanone (**5a**).

To a stirred cold (~ -60 -70°) solution of **1b** [3] (1.78 g, 14 mmoles) in anhydrous tetrahydrofuran (70 ml) was added butyllithium in hexanes (6 ml, 2.5 *M*, 15 mmoles), dropwise (under nitrogen). After 1 hour at this temperature, **3a** (5.29 g, 15 mmoles) in anhydrous tetrahydrofuran (10 ml) was added, dropwise. This mixture was stirred at -60° (45 minutes) and was then allowed to warm to room temperature (5 hours). After the usual workup (dichloromethane), the crude ketal (**4a**, 6.4 g) was obtained as an oil, which was hydrolyzed immediately. After boiling the ketal with 3*N* hydrochloric acid (30 ml) in methanol (100 ml) for 1.5 hours, solvents were evaporated, *in vacuo*. The residue was diluted with water (80 ml) and concentrated hydrochloric acid (5 ml). Acidic impurities were removed by extraction with dichloromethane (100 ml). Upon adjusting the *p*H of the aqueous layer to 8 by means of sodium bicarbonate, extraction with dichloromethane (2 x 200 ml) a solid was isolated (2.96 g), which was purified by chromatography. Elution with dichloromethane-methanol (47:3) provided **5a** (1.77 g, 51%) as colorless needles, mp 141.5-142°, (lit [1] mp, 142°).

2-(2,4-Dichlorophenyl)-2-(3-chloropropyl)-1,3-dioxolane (**12**).

A stirred mixture of 1-(2,4-dichlorophenyl)-4-chloro-1-butanone [2] (7.54 g, 30 mmoles), ethylene glycol (14.9 g, 240 mmoles) and 4-toluenesulfonic acid monohydrate (1.7 g, 9.0 mmoles) in benzene (150 ml) was refluxed with azeotropic removal of water (10 hours). After cooling, the mixture was poured into saturated sodium bicarbonate solution (100 ml). The usual workup provided an oil which was chromatographed on silica gel. Elution with petroleum ether-ethyl acetate (20:1) furnished **12** (7.61 g, 86%) as an amber oil; tlc, R_f = 0.50 (petroleum ether-ethyl acetate, 20:1).

Anal. Calcd. for $C_{12}H_{13}Cl_3O_2$: C, 48.76; H, 4.43. Found: C, 48.83; H, 4.38.

2-(2,4-Dichlorophenyl)-2-(3-cyanopropyl)-1,3-dioxolane (**13**).

A mixture of **3b** [2] (1.94 g, 5 mmoles) and potassium cyanide (391 mg, 6 mmoles) in dimethylformamide (7 ml) was stirred at room temperature (48 hours). After dilution with water and extraction with ethyl acetate, there was obtained an amber oil (1.46 g). Chromatography (ethyl acetate-petroleum ether, 2:3), provided a colorless oil (1.37 g, 96%).

Anal. Calcd. for $C_{13}H_{13}Cl_2NO_2$: C, 54.57; H, 4.58; N, 4.89. Found: C, 54.50; H, 4.59; N, 4.82.

The same product was obtained when a stirred mixture of **12** (1.48 g, 5 mmoles), was reacted with potassium cyanide (423 mg, 6.5 mmoles) in dimethylformamide (10 ml) in the presence of 18-crown-6 (200 mg) at room temperature (12 hours), and then 50-60° (5 hours). Workup as described above yielded **13** (1.24 g, 87%).

1-(2,4-Dichlorophenyl)-4-(2-imidazolyl)-1-butanone (**5b**).

Through a cold solution (0-5°) of nitrile **13** (28.6 g, 0.1 mole) in anhydrous ethanol (29.7 ml, 0.5 mole) was bubbled hydrogen chloride (18.1 g, 0.5 mole). The mixture was kept at room temperature (2 days). Concentration, *in vacuo*, provided the crude imidate as a brown oil, which was diluted with anhydrous methanol (80 ml) and aminoacetaldehyde dimethyl acetal (21.8 ml, 0.2 mole) was added. The resulting solution was stirred at room temperature (24 hours) and then refluxed (2 hours). After evaporation of the solution, *in vacuo*, there was added concentrated hydrochloric acid (25 ml) and water (50 ml). The mixture was stirred at 80° (3 hours), cooled and extracted with ethyl acetate (2 x 200 ml) to remove impurities. The aqueous solution was neutralized by solid potassium carbonate to *p*H of about 9. After extraction with dichloromethane, there was obtained an amber gum (24.4 g) which was chromatographed on silica gel. Elution (ethyl acetate-methanol, 8:1) furnished the crude ketone which was recrystallized (ethyl acetate) to afford colorless needles (11.2 g, 40%), mp 89-92°, identified as a mixture of **5b** and **5b'**.

Anal. Calcd. for $C_{13}H_{12}Cl_2N_2O$: C, 55.14; H, 4.27; N, 9.89. Found: C, 55.10; H, 4.20; N, 9.80.

1-(4-Chlorophenyl)-5-(2-imidazolyl)-1-pentanone (**20a**).

To a stirred cold (-70°) solution of **17b** (1.25 g, 9.0 mmoles) in anhydrous tetrahydrofuran (60 ml), blanketed under nitrogen, was added butyllithium in hexanes (3.6 ml, 2.5 *M*, 9.0 mmoles), dropwise (5 minutes). After 30 minutes, **3a** (3.52 g, 10.0 mmoles) in anhydrous THF (5 ml) was added, dropwise. The mixture was stirred at -70° (30 minutes) and then allowed to warm to room temperature (10 hours). The usual workup (dichloromethane) provided an oil (3.3 g), which was hydrolyzed (2 hours) in boiling methanol (60 ml, containing 20 ml 3 *N* hydrochloric acid). Solvents were evaporated, *in vacuo*. The residue was diluted with water (20 ml) and concentrated hydrochloric acid (5 ml) and was extracted with dichloromethane (100 ml) removed some impurities (1.3 g). The *p*H was adjusted to 8 by means of sodium bicarbonate and was extracted with dichloromethane (2 x 150 ml). After the usual workup, there was obtained a solid (1.69 g), which was chromatographed, eluting with ethyl acetate-methanol (10:1) to provide **20a** (1.135 g, 48%) as colorless needles, which were recrystallized from ethyl acetate, mp 118-119°; tlc, R_f = 0.47 (ethyl acetate-methanol, 8:1);

Anal. Calcd. for $C_{14}H_{15}ClN_2O$: C, 64.00; H, 5.75; N, 10.66. Found: C, 63.82; H, 5,62; N, 10.66.

1-(2,4-Dichlorophenyl)-5-(2-imidazolyl)-1-pentanone (**20b**).

The preparation was carried out in the same way as described above for **20a**. 1-[*N,N*-(dimethylamino)methyl]-2-methylimidazole **17b** (1.63 g, 11.7 mmoles), butyllithium in hexanes (4.7 ml, 2.5 *M*, 11.7 mmoles) and **3b** (5.0 g, 12.9 mmoles) in THF (70 ml) were used to furnish **20b** (629 mg, 18%) as an amber gum, which solidified to a solid, mp 70-71°; tlc, R_f = 0.53 (ethyl acetate-methanol, 8:1);

Anal. Calcd. for $C_{14}H_{14}Cl_2N_2O$: C, 56.58; H, 4.75; N, 9.43. Found: C, 56.65; H, 4.81; N, 9.23.

2-(4-Chlorophenyl)-2-[4-(1-methyl-2-imidazolyl)butyl]-1,3-dioxolane (**19c**) [14].

In an atmosphere of nitrogen, an ice-cold solution of 1,2-dimethylimidazole **17a** (4.8 g, 0.05 mole) in anhydrous tetrahydrofuran (150 ml) was treated with butyllithium in hexane (20.0 ml of 2.5 *M* solution, 0.05 mole), dropwise. After 2 hours at 5-10°, there was added **3a** (17.6 g, 0.05 mole) in tetrahydrofuran (25 ml). After 5 hours, the mixture was diluted with saturated sodium bicarbonate solution (50 ml) and the majority of the solvents were removed, *in vacuo*. The residue was partitioned between ethyl acetate (200 ml) and water (100 ml). The organic phase was worked up as usual to provide a brown oil (15.9 g). A part of the product (1.0 g) was chromatographed on silica gel (25 g) and pure **19c** (0.574 g) was eluted by ethyl acetate-methanol, 8:1, R_f = 0.54). The yield was calculated to be 60%.

Anal. Calcd. for $C_{17}H_{21}ClN_2O_2$: C, 63.64; H, 6.60; N, 8.73. Found: C, 63.67; H, 6.56; N, 8.69.

1-(4-Chlorophenyl)-5-(1-methyl-2-imidazolyl)-1-pentanone (**20c**).

A solution of **19c** (3.5 g, 11 mmoles) in methanol (100 ml) and 2*N* hydrochloric acid (25 ml) was refluxed for 2 hours. Solvents were removed, *in vacuo*. The residue was partitioned between ethyl acetate (400 ml) and saturated sodium carbonate solution (100 ml) and the ketone isolated by means of the usual workup. There was isolated an amber solid (3.09 g), which was recrystallized from petroleum ether-ethyl acetate to afford **20c** as colorless needles (2.69 g, 89%), mp 90-91°; tlc, R_f = 0.52 (ethyl acetate-methanol, 8:1).

Anal. Calcd. for $C_{15}H_{17}ClN_2O$: C, 65.10; H, 6.19; N, 10.12 Found: C, 64.91; H, 6.09; N, 9.98.

cis-2-(2,4-Dichlorophenyl)-2-[3-(2-imidazolyl)-propyl]-4-(hydroxymethyl)-1,3-dioxolane (**6b**).

A mixture of **5b** (7.0 g, 24.7 mmoles), glycerol (9.14 g, 98.8 mmoles) and 4-toluenesulfonic acid monohydrate (9.43 g, 49.4 mmoles) was refluxed (6 hours) in benzene (250 ml), with continuous azeotropic removal of water (Dean-Stark trap). The reaction was monitored by tlc for the disappearance of the ketone. The reaction mixture was cooled to room temperature and was poured into a saturated sodium bicarbonate solution (300 ml). The products was extracted with dichloromethane (3 x 250 ml). The extract was worked up as usual to provide the crude product (10.5 g) as an amber gum. The ratio of *cis*- and *trans*-**6b** was estimated to be about 2.5:1, based on the integration of ^1H nmr signals of the ketal methine at δ 4.12 and 4.28, and the imidazolyl-H-4(5) at 6.88 and 6.90 of *cis*- and *trans*-**6b**, respectively. Column chromatography on silica gel (180 g) and elution with dichloromethane-ethanol (6:1) provided pure a *cis*-**6b** (gum, 3.5 g, 40%) and a 1:1 mixture of *cis*- and *trans*-isomers (gum, 3.83 g). The total yield of **6b** was 83%.

Anal. Calcd. for *cis*-$C_{16}H_{18}Cl_2N_2O_3$: C, 53.80 ; H, 5.08; N, 7.84. Found: C, 53.69; H, 5.17; N, 7.55.

cis- and *trans*-2-(4-Chlorophenyl)-2-[4-(1-methyl-2-imidazolyl)butyl]-4-(hydroxymethyl)-1,3-dioxolane (**21a**).

Ketone **20c** (1.6 g, 5.6 mmoles) was condensed with glycerol (5.65 g, 62 mmoles) in the presence of 4-toluenesulfonic acid monohydrate (1.4 g, 7.3 mmoles) in boiling benzene (70 ml), with azeotropic removal of water (7 hours). After solvents were removed, *in vacuo*, the residue was poured into cold saturated sodium bicarbonate solution (100 ml) and extracted with dichloromethane. The usual workup provided an oil (2.45 g), which consisted of a mixture of *cis*- and *trans*-**21a** (2:1, based on the integration of the signals at δ 4.07 and 4.33, arising from H-4 of 1,3-dioxolane of *cis*- and *trans*-**21a**, respectively). In addition, the crude mixture contained a trace of starting ketone, with a characteristic ^1H nmr signal at δ 7.88.

After chromatography (silica gel, 80 g), eluting with ethyl acetate-methanol (8:1) an inseparable mixture of *cis*- and *trans*-**21a** (1.82 g, 90%) was obtained as a colorless gum.

Anal. Calcd. for *cis*- and *trans*-$C_{18}H_{23}ClN_2O_3$: C, 61.62; H, 6.61; N, 7.98 Found: C, 61.25; H, 6.54; N, 7.90.

cis- and *trans*-{2-(4-Chlorophenyl)-2-[4-(1-methyl-2-imidazolyl)butyl]-4-(benzoyloxy)methyl}-1,3-dioxolane (**21b**).

To a stirred solution of *cis* and *trans*-**21a** (*ca.* 2:1, 1.2 g, 3.4 mmoles) in dry dichloromethane (70 ml) and pyridine (2.7 ml, 34 mmoles) at 0-5° was added, dropwise, benzoyl chloride (0.8 ml, 6.8 mmoles). After stirring 1.5 hours at 0-5°, the reaction appeared complete (tlc). Solvents were removed, *in vacuo,* and the residue was diluted with water, and worked as usual (ethyl acetate) to provide an oil, which was purified by chromatography (silica gel, 80 g). Elution with 300 ml of ethyl acetate-methanol (10:1) furnished *cis*-**21b** (640 mg, 41%) as a colorless gum; tlc, R_f = 0.61 (ethyl acetate -methanol, 10:1); followed by an additional 350 ml of eluting solvent to provide a mixture of *cis* and *trans*-**21b** (642 mg, 41%).

Anal. Calcd. for *cis*-$C_{25}H_{27}ClN_2O_4$: C, 66.00; H, 5.98; N, 6.16. Found: C, 65.78; H, 6.13; N, 6.02.

Hydrolysis of *cis*-**21b** (456 mg, 1.0 mmole) with sodium carbonate (212 mg, 2.0 mmoles), water (1 ml) and methanol (20 ml) was complete after 1 hour of reflux (tlc). Solvents were removed, *in vacuo,* and the *alcohol* isolated after usual workup (ethyl acetate). The gum was chromatographed (silica, 40 g, ethyl acetate-methanol, 8:1) to provide *cis*-**21a** as a colorless gum (316 mg, 90%).

Anal. Calcd. for $C_{18}H_{23}ClN_2O_3$: C, 61.62; H, 6.61; N, 7.98. Found: C, 61.31; H, 6.81; N, 7.73.

cis-{2-(4-Chlorophenyl)-2-[3-(1-allyl-2-imidazolyl)propyl]-4-(hydroxymethyl)}-1,3-dioxolane (**7a**).

To a stirred cold solution (5-10°) of *cis*-**6a** [8] (323 mg, 1.0 mmole) in anhydrous tetrahydrofuran (10 ml) at room temperature was added sodium hydride (60% suspension in mineral oil, 42 mg, 1.05 mmoles). After stirring for 5 minutes, there was added allyl bromide (0.095 ml, 1.1 mmoles) and the mixture was stirred at room temperature for 10 hours, after which the reaction appeared

complete (tlc). Solvents were removed, *in vacuo*, at about 40° and the residue was diluted with water (20 ml) and extracted with ethyl acetate (80 ml). After the usual workup, the gum was chromatographed on silica gel (20 g) to afford *cis*-**7a** (305 mg, 84%, eluted by ethyl acetate-methanol, 8:1; R_f = 0.51) as a colorless gum.

Anal. Calcd. for $C_{19}H_{23}ClN_2O_3$: C, 62.89; H, 6.39; N, 7.72. Found: C, 62.50; H, 6.32; N, 7.64.

cis-2-(2,4-Dichlorophenyl)-2-[3-(1-allyl-2-imidazolyl)propyl]-4-(hydroxymethyl)-1,3-dioxolane (**7b**).

The alkylation was carried out in the same manner as for **7a** with alcohol *cis*-**6b** (2.3 g., 6.44 mmoles), sodium hydride (60% suspension in mineral oil, 270 mg, 6.76 mmoles), allyl bromide (0.585 ml, 6.76 mmoles) in anhydrous tetrahydrofuran (100 ml). After 10 hours, and the usual workup, the crude product (2.43 g) was chromatographed on silica gel to afford *cis*-**7b** (2.15 g, 84%, eluted by ethyl acetate-methanol, 8:1; R_f = 0.50) as a colorless gum.

Anal. Calcd. for $C_{19}H_{22}Cl_2N_2O_3$: C, 57.44; H, 5.58; N, 7.05. Found: C, 57.04; H, 5.64; N, 6.89.

cis-{2-(4-Chlorophenyl)-2-[3-(1-allyl-2-imidazolyl)propyl]-4-(benzyloxy)methyl}-1,3-dioxolane (**8a**).

To a stirred solution of **7a** (363 mg, 1.0 mmole) in anhydrous tetrahydrofuran (15 ml) was added sodium hydride (60% suspension in mineral oil, 80 mg, 2.0 mmoles) at room temperature. After stirring for 10 minutes, benzyl bromide (0.238 ml, 2.0 mmoles) was added. The mixture was stirred at room temperature for 10 hours when the reaction appeared complete (tlc). Solvents were removed, *in vacuo*, and the mixture worked up, as usual, and **8a** was isolated as a colorless oil by chromatography on silica gel (eluted by ethyl acetate-methanol, 9:1, R_f = 0.77, 389 mg, 86%).

Anal. Calcd. for $C_{26}H_{29}ClN_2O_3$: C, 68.94; H, 6.45; N, 6.18. Found: C, 69.15; H, 6.58; N, 6.19.

cis-{2-(2,4-Dichlorophenyl)-2-[3-(1-allyl-2-imidazolyl)propyl]-4-(2,4-dichlorobenzyloxy)methyl}-1,3-dioxolane (**8b**).

To a stirred solution of *cis*-**7b** (397 mg, 1.0 mmole) in anhydrous tetrahydrofuran (10 ml) was added sodium hydride (60% suspension in mineral oil, 56 mg, 1.4 mmoles). After 10 minutes, 2,4-dichlorobenzyl chloride (0.195 ml, 1.4 mmoles) was added. The resulting mixture was refluxed (20 hours). Solvents was removed, *in vacuo*, and the residue was chromatographed and elution with ethyl acetate-methanol (10:1) led to pure *cis*-**8b** (284 mg) as an amber gum. Continued elution with ethyl acetate-methanol (6:1) provided unreacted alcohol *cis*-**7b** (164 mg). The yield of *cis*-**8b** was 87% based on recovered alcohol *cis*-**7b**.

Anal. Calcd. for $C_{26}H_{26}Cl_4N_2O_3 \cdot 0.2H_2O$: C, 55.77; H, 4.75 N, 5.00. Found: C, 55.80; H, 4.88; N, 4.78.

cis-2-(4-Chlorophenyl)-2-[4-(1-methyl-2-imidazolyl)butyl]-4-[(benzyloxy)methyl]-1,3-dioxolane (**21c**).

After stirring a solution of *cis*-**21a** (95 mg, 0.27 mmole) in anhydrous tetrahydrofuran (8 ml) and sodium hydride (21 mg, 60% suspension in mineral oil, 0.54 mmole) at room temperature under nitrogen for 10 minutes, benzyl bromide (0.064 ml, 0.54 mmole) was added. The alkylation appeared complete (tlc) after 10 hours at room temperature. Solvents were removed, *in vacuo*, and the usual workup yielded a colorless oil (124 mg), which was purified by chromatography (silica gel, 20 g, ethyl acetate-methanol, 10:1) to provide *cis*-**21c** (98 mg, 82%); tlc, R_f = 0.54 (ethyl acetate-methanol, 10:1).

Anal. Calcd. for $C_{25}H_{29}ClN_2O_3$: C, 68.09; H, 6.63; N, 6.35. Found: C, 67.98; H, 6.72; N, 6.33.

cis-{2-(4-Chlorophenyl)-2-[3-(1-(2,3-dihydroxypropyl)-2-imidazolyl)-propyl]-4-(benzyloxy)methyl}-1,3-dioxolane (**9**).

To a stirred solution of *N*-allyl compound **8a** (136 mg, 0.3 mmole) in *tert*-butyl alcohol-water (1:1, 6 ml) was added potassium ferricyanide (988 mg, 3.0 mmoles), potassium carbonate (415 mg, 3.0 mmoles) and the toluene solution of osmium tetroxide (0.15 *M*, 0.2 ml, 0.03 mmole). The reaction mixture was stirred for 3 days at room temperature after which solid sodium sulfide (500 mg) was added, and the mixture was stirred for 3 hours. It was then concentrated to dryness, *in vacuo*, and the residue was extracted with chloroform. Workup followed by column chromatography (ethyl acetate-methanol, 3:1), provided pure **9** (114 mg, 78%) as a colorless gum; tlc, R_f = 0.63 (ethyl acetate-methanol, 3:1)

Anal. Calcd. for $C_{26}H_{31}ClN_2O_5$: C, 64.13; H, 6.42; N, 5.75. Found: C, 64.15; H, 6.67; N, 5.59.

1-Methyl-2-(3-chloropropyl)imidazole (**10**) and 1(3)-Methyl-2,3-trimethylenimidazolium Chloride (**11a**) and Iodide (**11b**).

Under a blanket of nitrogen, a solution of butyllithium in hexanes (2.5 *M*, 10 ml, 25 mmoles) was added dropwise to a cold (~ -50-60°) solution of **1a** (2.0 ml, 25 mmoles) in anhydrous tetrahydrofuran (50 ml). After 1 hour, 1-chloro-3-iodopropane (2.8 ml, 25 mmoles) was added dropwise, and the mixture was allowed to (slowly) warm to room temperature (7 hours). Ethyl acetate (100 ml) and brine (60 ml) were added and the organic phase was separated and dried (sodium sulfate). After evaporation (< 40°), *in vacuo*, the nmr spectrum of crude **10** indicated the presence of about 35% starting **1a**. Elution from a column of silica gel by ethyl acetate-methanol, 8:1, yielded pure (nmr) **10** (1.74 g, 44%) as an amber oil; R_f = 0.59 (ethyl acetate-methanol, 8:1).

This product was not analyzed because of its inherent instability. After standing at room temperature for 5-7 days, **10** (1.0 g) changed (nmr). The product was washed with dichloromethane and the amber oil proved to be **11a** (0.96 g, 96%).

Anal. Calcd. for $C_7H_{11}ClN_2 \cdot H_2O$: C, 47.60; H, 7.42; N, 15.86. Found: C, 47.66; H, 7.04; N, 15.76.

To a solution of **10** (500 mg, 3.2 mmoles) in methanol (4 ml) was added sodium iodide (528 mg, 3.5 mmoles). The mixture was refluxed for 3 hours, cooled to room temperature and was filtered to remove sodium chloride. The filtrate was concentrated, *in vacuo*, to give a slight yellow solid, which was dissolved with dichloromethane (4 ml) and filtered again. After removal of the solvent, the solid was recrystallized twice from methanol-ethyl acetate to afford **11b** (568 mg, 72%) as colorless needles, mp 194-195°.

Anal. Calcd. for $C_7H_{11}IN_2 \cdot 0.5H_2O$: C, 32.45; H, 4.67; N, 10.81. Found: C, 32.36; H, 4.23; N, 10.63.

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