DMSO-d_6 for compounds 21, 31 and 32 (Table V), ^1H and ^{13}C chemical shifts of compound 26 in DMSO-d_6 (Figure 4), comparison of ^1H and ^{13}C chemical shifts (in DMSO-d_6) of two 2-(1-pyridinio)benzimidazolate mesomeric betaines 10 and their analogues 1-alkyl-4-benzimidazolylidene-1,4-dihydropyridines 8 (Figure 5), 80-MHz ^1H NMR spectrum of compound 21 at 243 K (Figure 6), total charges at τ_{min} for compounds 16B–18B and 20B–21B (Table VII), comparison of experimental and calculated geometry of compound 16 (Table VIII), elemental analyses of new compounds (Table IX), heats of formation, total enegy, energy barriers, dipolar moments, and bond orders of azolium azolate inner salts 34–44 (Table XI); ^1H NMR spectroscopic data of compounds 34–36 and 45–57 (Table XIV), ^{13}C NMR spectroscopic data of compounds 34–36 and 45–57 (Table XV), total charges at τ_{min} for compounds 34–44 (Table XVII), comparison of experimental and calculated geometry of 2-(3-methyl-1-imidazolium)benzimidazolate inner salt (35) (Table XVIII), list of final positional parameters for non-hydrogen atoms and equivalent temperature coefficients (Table XIX), thermal coefficients for non-H atoms (Table XX), bond lengths and bond angles (Table XXI), and found positional parameters for H atoms (Table XXII) for compound 35 (18 pages). Ordering information is given on any current masthead page. Structure factors tables are available from the authors.

Heterocyclic Betaines. Aza Analogues of Sesquifulvalene. 2. Azolium Azolate Inner Salts: Synthesis, Reactivity, and Structure of a 1:1 Adduct with Dimethyl Acetylenedicarboxylate

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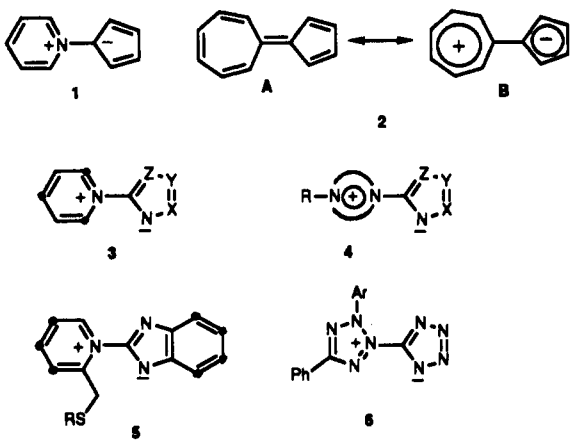
Reaction of an activated 2-chloroazole with several *N*-alkylazoles afforded the *N*-azolylazolium salts, deprotonation of which results in a series of the title mesomeric betaines 7 and 8. Their reactivity toward electrophiles and dipolarophiles under mild conditions reflects the highly dipolar structures of 7 and 8. The thermal stability and dequaternization reactions of some of their corresponding *N*-azolylimidazolium and -pyrazolium salts have also been studied.

Of the vast variety of structures that conjugated heterocyclic mesomeric betaines adopt,[1] few reports have appeared of aza analogues of the *N*-ylide 1 and the dipolar resonance form of sesquifulvalene (2B). Several representative mesomeric betaines of azinium azolate 3 and azolium azolate 4 have been previously reported as part of our research work on aza analogues of 1.[2-5] Other pyridinium benzimidazolate 5 and tetrazolium tetrazolate 6 inner salts have been prepared.[6,7]



The highly dipolar character of mesomeric betaines 3 and 4 has a dominant influence upon their chemistry, which merits study. These systems are suited to a study of their behavior as *dipoles*, where the dipolar moiety contains more than four π electrons, and their reactions with dipolarophiles should be a potentially attractive route for the synthesis of a variety of heterocyclic structures, as well as novel polycyclic ring systems.

As to quaternary salts of nitrogen heteroaromatic compounds, these are usually stable and their dealkylation reactions are of interest. In this context, pyridinium salts, and to a lesser extent, condensed systems derived from six-membered nitrogen heterocycles, are by far the most commonly investigated. This is presumably due to the fact that such studies were directed toward seeking insight into fundamental topics of heteroaromatic chemistry[8a] such as aliphatic nucleophilic substitution reactions, forward and reverse Menschutkin reactions,[9] and the use of pyridine as a leaving group.[8b,10] Furthermore, synthetic methods have been developed during the last two decades using polar aprotic solvents and soft nucleophiles.[8a,11]

Dequaternization of azolium quaternary salts initially involved pyrazolium compounds,[12] which could be pyro-

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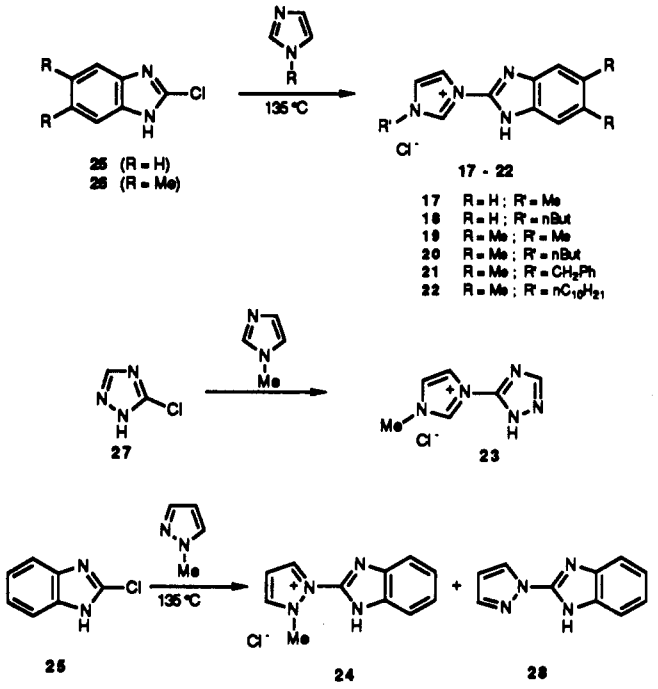
Table I. Physical Data of *N*-Azolylazolium Salts 17–24, and 29, and Azolium Azolate Inner Salts 9–16

compd[a,b]	azolyl or azolate	R′	method[c] (yield, %)	mp (°C) (solvent)	reactn time (h)	TLC[d]
17	1*H*-benzimidazol-2-yl	Me	A (70)	254–5	0.75	A
18	1*H*-benzimidazol-2-yl	nC_4H_9	A (80)	197–8[e]	1.5	A
19	5,6-dimethyl-1*H*-benzimidazol-2-yl	Me	A (90)	252–3	1	A
20	5,6-dimethyl-1*H*-benzimidazol-2-yl	nC_4H_9	A (74)	227–9	1.5	A
21	5,6-dimethyl-1*H*-benzimidazol-2-yl	CH_2Ph	A (78)	217–9	1.5	E
22	5,6-dimethyl-1*H*-benzimidazol-2-yl	$nC_{10}H_{21}$	A (75)	188–90[e]	1	A
23	1*H*-1,2,4-triazol-3(5)-yl	Me	B (22)	203–5[g]	208	D
24	1*H*-benzimidazol-2-yl	Me	C (70)	178–9	122	A
29	1*H*-benzimidazol-2-yl	Me	A (62)	244–5[g]	1	D
31	1-methylbenzimidazol-2-yl	nC_4H_9	F (76)	156–8[h]	7	C
32	1,5,6-trimethylbenzimidazol-2-yl	nC_4H_9	F (85)	154–6	5.5	C
33	1,5,6-trimethylbenzimidazol-2-yl	$nC_{10}H_{21}$	F (73)	95–8[i]	19	C
9	2-benzimidazolate	Me	D (99)	219–20[j]		B
10	2-benzimidazolate	nC_4H_9	D (98)	215–6[k]		B
11	5,6-dimethyl-2-benzimidazolate	Me	D (95), E (80)	248–50		B
12	5,6-dimethyl-2-benzimidazolate	nC_4H_9	D (95)	188–9[j]		B
13	5,6-dimethyl-2-benzimidazolate	CH_2Ph	D (97), E (88)	227–9[g]		B
14	5,6-dimethyl-2-benzimidazolate	$nC_{10}H_{21}$	D (90)	197–70		B
15	3(5)-1,2,4-triazolate	Me	D (98)	*l*		D
16	2-benzimidazolate	Me	D (99)	140–1[j]		B

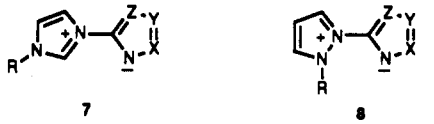
[a] Satisfactory analytical data (±0.4% for C, H, N) were obtained for all compounds. [b] The azolium ring is an imidazolium quaternary salt except for compounds 16 and 24, where it is a pyrazolium, and for 29, where it is a benzimidazolium. [c] Yields were not optimized. [d] See Experimental Section, General Methods. [e] Chloroform. [f] Ethyl acetate. [g] Acetonitrile. [h] Absolute ethanol. [i] Ethyl acetate–hexane. [j] 70% Ethanol. [k] 50% Ethanol. [l] Oily product.

Scheme I



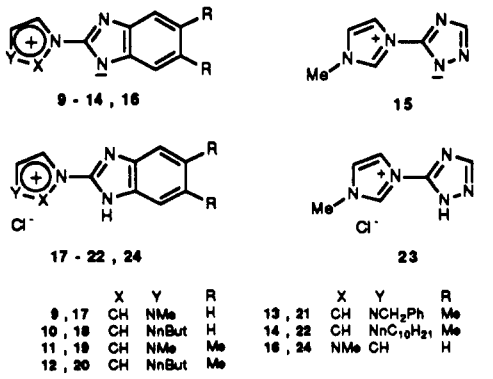
lyzed[12a] in vacuum at ca. 200 °C. The thermal decomposition of imidazolium quaternary salts has been reported by Grimmet et al.[13] as have some other examples.[14,15] On the other hand, the use of the thiophenolate anion under phase-transfer catalysis[12b] proved to be an excellent method of obtaining pyrazoles and indazoles in high yields from their corresponding quaternary salts.

This paper describes the synthesis of several imidazolium and pyrazolium azolate mesomeric betaines 7 and 8, their reactivity toward electrophiles (MeI) and dipolarophiles, and the structure elucidation of a 1:1 adduct with dimethyl acetylenedicarboxylate (DMAD). The thermal stability and dequaternization reactions of some of their corresponding *N*-azolylimidazolium and -pyrazolium salts have also been studied.



Results and Discussion

Synthesis. The inner salts of imidazolium benzimidazolate 9–14, imidazolium 1,2,4-triazolate 15, and pyrazolium benzimidazolate 16 were obtained by deprotonation of the corresponding *N*-azolylazolium salts 17–24, using an anionic ion-exchange resin (hydroxide form), in nearly quantitative yields (see Table I).



N-Benzimidazolylimidazolium salts 17–22 were obtained by reaction of 2-chlorobenzimidazoles 25 and 26 with several *N*-alkylimidazoles in fairly high yields for this type of reaction (Scheme I, Table I). In contrast, the known lower reactivity of 3-chloro-1,2,4-triazoles, in comparison with 2-chlorobenzimidazoles, toward S_NAr reactions, has been a limitation of the method. Thus, reaction of 3-

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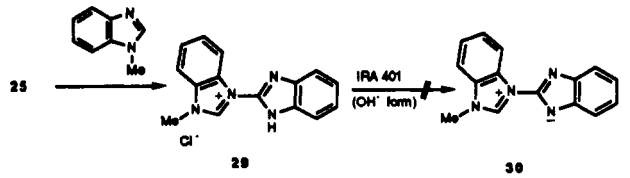
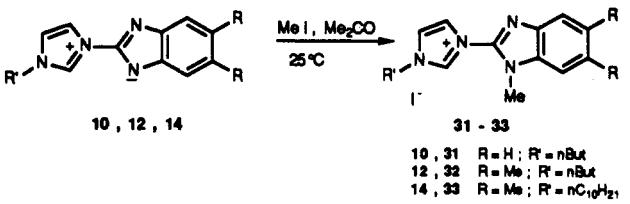
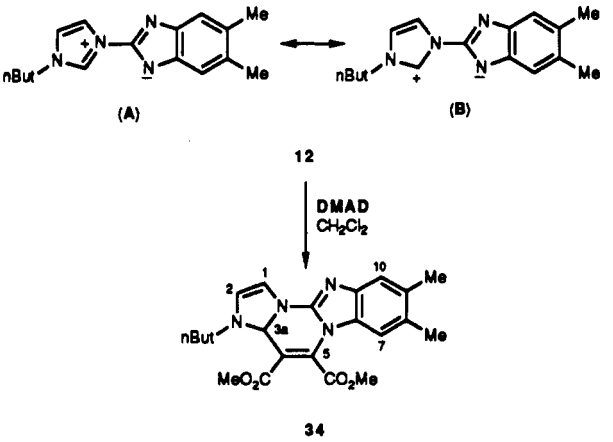
Scheme II



Scheme III



Scheme IV



chloro-1,2,4-triazole (27) and 1-methylimidazole was investigated by trying a variety of conditions (Scheme I). Higher yields of the salt 23 were obtained by maintaining the temperature at 135 °C in a sealed tube for a long period of time (see Table I and Experimental Section).

With regard to 1-(1*H*-benzimidazol-2-yl)-2-methylpyrazolium chloride (24), reaction of 2-chlorobenzimidazole (25) and *N*-methylpyrazole in the same experimental conditions, at 135 °C, as for compound 17 (see Table I and Experimental Section) proceeded with formation of the salt 24 (15%) together with the demethylated compound 28 (11% yield). Different conditions were experimented, and when the reaction was carried out in a sealed tube at 80 °C the salt 24 was obtained in good yield (70%; see Experimental Section, Method C) (Scheme I).

Finally, displacement of the chlorine atom in 25 by *N*-methylbenzimidazole produced the desired *N*-benzimidazol-2-ylbenzimidazolium salt 29, which is rather unstable, particularly in solution. Thus, several attempts have been made to obtain the corresponding betaine 30, using different procedures previously described[3,5] (see Experimental Section, Methods D and E) but all failed to produce this inner salt, and only decomposition products were detected, probably due to the instability of 29 and/or 30, which hindered its isolation (Scheme II).

Physical data of azolium azolate inner salts 9–16 and *N*-azolylazolium salts 17–24 and 29 are listed in Table I. The structures of all the new compounds have been unambiguously characterized, mainly on the basis of their spectroscopic data.[16] All of them gave satisfactory elemental analysis.

Reactivity toward Electrophiles (MeI). It is known that the N-alkylation of the benzimidazole nucleus by alkyl halides under neutral conditions (usually not mild ones) produces yields that are restricted to around 50%.[17] Nevertheless, due to the highly dipolar structure of the mesomeric betaines of azolium azolate class 4, it could be expected that electrophilic attack at a nitrogen atom of the benzimidazolate ring would take place under neutral and mild conditions. The betaines of imidazolium benzimidazolate 10, 12, and 14 did indeed react with methyl iodide/acetone at room temperature to afford the 1-(1-methylbenzimidazol-2-yl)-3-alkylimidazolium iodides 31–33 (yield >81%) (Scheme III).

Reactivity toward Dipolarophiles. A preliminary investigation of the behavior of azolate azolium inner salts 4 toward dipolarophiles has been carried out (Scheme IV). Study of the ability of 5,6-dimethyl-2-(3-butyl-1-imidazolium)benzimidazolate (12) to add to dimethyl acetylenedicarboxylate (DMAD) was then undertaken. When equimolar amounts of 12 and DMAD were mixed in dichloromethane at 25 °C for 3 h, the major product obtained was a *1:1 adduct*, the new tetracyclic structure 34 (51% yield).

Among the wide range of acetylene equivalents[18] acting as dipolarophiles, phenyl vinyl sulfoxide has been selected. The attractiveness of this reagent is that it acts in one step, as does acetylene itself.[18,19] Unfortunately, reaction of 12 and the less reactive phenyl vinyl sulfoxide gave *no adduct* under different conditions. Only unreacted and/or alteration or decomposition products could be detected by ^{1}H NMR spectroscopy and TLC, and these were therefore not further studied. Of special note is the finding that betaine 12 itself is stable under the same reaction conditions (solvent and temperature; see Experimental Section).

The novel tetracyclic structures of the *1:1 adduct* may be inferred from their mass and ^{1}H and ^{13}C NMR spectra data.

3a*H*-Imidazo[1′,2′:3,4]pyrimido[1,2-*a*]benzimidazole (34): ^{1}H NMR ($CDCl_3$, δ) 7.48 (d, 1 H, H-1), 7.41 (s, 1 H, H-10), 7.17 (s, 1 H, H-7), 6.61 (d, 1 H, H-2), 6.20 (s, 1 H, H-3a), 3.66 (s, 3 H, 5-CO_2Me), 3.61 (s, 3 H, 4-CO_2Me), 4.56 and 3.87 (m, 1 H + 1 H, NCH_2-), 1.67 (m, 2 H, -CH_2-), 1.24 (m, 2 H, -CH_2-), 0.89 (t, 3 H, Me-C_3H_6) and 2.34 (s, 6 H, Me-8,9); ^{13}C NMR ($CDCl_3$, δ) 146.3 (C-5), 140.7 (C-11a), 136.6 (C-10a), 131.6 (C-8, C-9), 130.6 (C-6a), 120.1 (C-2), 118.9 (C-10), 110.7 (C-1), 61.8 (C-4), 54.5 (C-3a), 170.4 and 52.3 (4-CO_2Me), 164.1 and 50.1 (5-CO_2Me), 20.2 and 20.1 (Me-8,9), 49.7, 30.1, 19.3, and 13.4 (nBu).

The assignment of protons was quite straightforward, except for H-1, H-2, CO_2Me-4, and CO_2Me-5, which were assigned by homonuclear NOE enhancement. Thus, irradiation of CH_2-2′ (δ 1.67) resulted in NOE enhancement (4.8%) at H-2 (δ 6.61), while the doublet at δ 7.48 (H-1) was unaffected. Irradiation of H-3a (δ 6.20) resulted in NOE enhancement (~2%) at CO_2Me-4 (δ 3.51).

The ^{13}C NMR chemical shifts of 34 have been unambiguously assigned, using SFORD,[20a] SEFT,[20a] and HETNOE[20b] techniques, as shown in Figure 1 (supplementary material). For assignment of the protonated carbons, intermediate power selective decoupling (SFORD) of the corresponding H-1, H-2, H-3a, H-7, H-10, and CO_2Me-5 has been used, as has also the spin–echo Fourier transform

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Scheme V

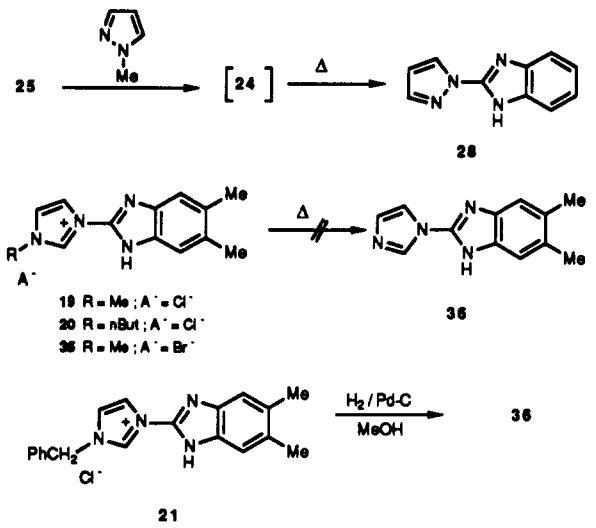

Table III. Dequaternization Experiments with Pyrazolium Salt 24 and Imidazolium Salts 19, 20, 21, and 35

compd	method	temp (°C)	time (h)	products[a]
19	A	230	4[b]	19
20	A	230	4[b]	20
35	A	230	8	35, 36
24	A	200	3	28
19	B	135	*c*	*c*
20	B	135	*c*	*c*
24	B	135	2	24, 28
19	C	180	24[b]	19
20	C	180	23	20
35	C	180	5	*d*
21	D	25	*e*	36

[a] The progress of the reaction was monitored by TLC and ^{1}H NMR of aliquots. [b] After this period of time, the imidazolium salt decomposed. [c] See Table I (method A). [d] Only decomposition products were detected. [e] See text.

sequence (SEFT). For the quaternary carbon atoms that remain uncertain, a series of HETNOE experiments (Table II, supplementary material) have been carried out, and they provided conclusive evidence for C-4, C-5, C-6a, C-8, C-9, C-10a, and the carbonylic carbons of CO_2Me-4 and CO_2Me-5.

Dequaternization of *N*-Azolylazolium Salts. As mentioned before, in the preparation of 1-(1*H*-benzimidazol-2-yl)-2-methylpyrazolium chloride (**24**), the formation of 2-(pyrazol-1-yl)-1*H*-benzimidazole (**28**) was detected when the reaction was carried out at 135 °C (see Scheme I).

The more stable imidazolium salts were used for evidence, and thermolysis of the imidazolium salts **19**(Cl^-), **35**(Br^-), and **20**(Cl^-) was carried out under standard conditions[13] (Scheme V). Except for **35**(Br^-), the other imidazolium salts **19**(Cl^-) and **20**(Cl^-) resulted in complete decomposition of the substrates, so that no identificable products were observed by ^{1}H NMR and TLC. When the thermolysis was carried out at low temperatures the, starting imidazolium salts **19**(Cl^-) and **20**(Cl^-) were recovered either unaltered or together with products of decomposition (see Experimental Section and Table III).

Finally, dequaternization of 1-(1*H*-benzimidazol-2-yl)-3-benzylimidazolium chloride (**21**) has been achieved by hydrogenolysis, and 2-(imidazol-1-yl)-1*H*-benzimidazole (**36**) was obtained in quite good yield (73%). To the best of our knowledge, this is the first example of imidazolium salt dequaternization by hydrogenolysis, since only a few dequaternizations of imidazolium quaternary salts have been reported thus far.[13-15] Furthermore, the use of *N*-benzyl derivatives (nonquaternary salts) as N-1 classical protecting groups of azoles[21a] and imidazole,[21,22] which are then debenzylated by hydrogenolysis, is well known.

Experimental Section

General Methods. Melting point (uncorrected): CTP-MP 300 hot-plate apparatus, (given in Table I). IR (KBr disks): Perkin-Elmer 1430 spectrophotometer. ^{1}H NMR: Varian XL-200, Bruker AM-100, or Perkin-Elmer R-24B spectrometers (200, 100, and 60 MHz, respectively). ^{13}C NMR: Bruker AM-100 Fourier transform spectrometer (25.1 MHz). NMR spectra were determined in dimethylsulfoxide-d_6, and chemical shifts are expressed in parts per million (δ) relative to TMS as internal standard or the central peak of dimethyl sulfoxide-d_6. EIMS: Finnigan TSQ-70 and Hewlett-Packard 5988A spectrometers. Distillation: Büchi GKR-50 Kugelrohr apparatus. TLC: Merck silica gel 60 F_{254} plates. Solvent systems: A, methanol–diethyl ether (8:2); B, diethyl ether–methanol (9.5:0.5); C, chloroform–methanol (9:1); D, methanol–diethyl ether (9:1); E, chloroform–diethyl ether (8:2); F, chloroform–methanol (9.5:0.5); detection by UV light. Flash chromatography (FC): Macherey Nagel silica gel kiesegel 60. Ion-exchange chromatography: Amberlite IRA-401 (OH^- form).[3] If necessary, the compounds were dried by overnight heating at 110 °C in a vacuum oven. Where microanalyses are indicated by symbools of the elements, the analytical results were within ±0.4% of the theoretical values (see Table IV); they were performed on a Carlo Erba 1106 analyzer by the Centro de Investigación y Desarrollo, CSIC, Barcelona, Spain.

Materials. The 1-methylimidazole, 1-*n*-butylimidazole, and the dipolarophiles used in this study are commercially available. 2-Chlorobenzimidazole,[23] 2-chloro-5,6-dimethylbenzimidazole,[24] 3(5)-chloro-1,2,4-triazole,[25] 1-benzylimidazole,[26] 1-*n*-decylimidazole,[2] 1-methylpyrazole,[27] and 1-methylbenzimidazole[28] were prepared as in the literature.

Preparation of *N*-Azolylazolium Salts 17–24 and 29 (Table I). Method A. A stirred mixture of the 2-chlorobenzimidazole **25** or **26** (10 mmol) and *N*-alkylimidazole (30 mmol), under an atmosphere of nitrogen, was heated on a bath at 135 °C for the time specified in Table I. After cooling, chloroform or diethyl ether (ca. 30 mL) was added to give a solid, which was then filtered, washed with chloroform or diethyl ether, and recrystallized (Table I).

1-(1*H*-Benzimidazol-2-yl)-3-methylbenzimidazolium chloride (29): ^{1}H NMR (DMSO-d_6, δ) 10.89 (s, 1 H, H-2), 8.67–8.78 (m, 1 H, H-7), 8.13–8.23 (m, 1 H, H-3), 7.78–7.88 (m, 2 H, H-5,6), 7.68–7.78 (m, 2 H, H-3′,7′), 7.30–7.40 (m, 2 H, H-5′,6′), 4.25 (s, 3 H, N-CH_3); ^{13}C NMR (DMSO-d_6, δ) 142.5 (C-2), 141.1 (C-2′), 137.0 (C-3′a,7′a), 131.8 and 129.1 (C-3a,7a), 128.2 and 127.5 (C-5,6), 123.4 (C-5′,6′), 116.0 and 114.1 (C-4,7), 115.6 (C-4′,7′), 34.1 (CH_3).

Method B. A mixture of 3(5)-chloro-1,2,4-triazole (**27**) (3.0 g, 29.26 mmol) and *N*-methylimidazole (3.56 mL, 44.81 mmol), in a sealed tube, was heated on a bath at 135 °C (Table I). To the cooled reaction mixture were added acetonitrile (50 mL) and acetone (75 mL), and the resulting solid was filtered to afford compound **23** (Tble I).

Method C. A mixture of 2-chlorobenzimidazole (**25**) (1.52 g, 10 mmol) and *N*-methylpyrazole (2 mL, 30 mmol), in a sealed tube, was heated on a bath at 80 °C (Table I). The mixture was cooled, and insoluble materials were removed by filtration. To the filtrate

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were added chloroform (50 mL) and acetone (50 mL), and the resulting precipitate was filtered to give compound **24** (Table I).

It is noteworthy that reaction of compound **25** (10 mmol) and *N*-methylpyrazole (30 mmol) used as nucleophile and solvent in a bath at 135 °C as in method A for 1 h afforded compound **24** (0.34 g, 15%) and the demethylated product **28** (0.20 g, 11%) (see Scheme I). Thus, the mixture was cooled, and insoluble materials were removed by filtration. To the filtrate were added chloroform (ca. 30 mL) and slowly precipitated 2-chlorobenzimidazole (**25**), which was then filtered (0.1 g). The chloroform solution was evaporated, and the residue was treated with chloroform (ca. 50 mL) and a white solid slowly precipitated, which was then filtered to give 340 mg (15%) of the salt **24**. The filtrate was evaporated, and the residue was treated twice with acetone to afford the demethylated product **28** (0.20 g, 11%) (see scheme I).

Preparation of Azolium Azolate Inner Salts 9–16 (Table I). Method D. A column packed with anion-exchange Amberlite resin IRA-401 was used, and the chloride form was converted to the hydroxide form.[3] A solution of *N*-azolylazolium salt (1 mmol) in 70% ethanol (50 mL) was passed through the column. The neutral eluates were concentrated on a rotary evaporate at 45 °C to give the corresponding mesomeric betaine (Table I).

Method E. A solution of *N*-benzimidazolylimidazolium salt **19** or **21** (2 mmol) in water (40 mL) with a few drops of ethanol was neutralized with solid K_2CO_3 to pH 8, and the solids were collected, washed with water, and recrystallized (Table I).

EIMS *m/z* (rel intensity): **9**, 198 (M^+, 100); **10**, 240 (M^+, 100); **11**, 226 (M^+, 100); **12**, 268 (M^+, 100); **13**, 302 (M^+, 15), 91 (100); **14**, 352 (M^+, 66), 211 (45), 41 (100); **15**, 149 (M^+, 100); **16**, 192 (M^+, 62), 170 (100).

Preparation of 1-(1-Methylbenzimidazol-2-yl)-3-alkylimidazolium Iodides 31–33. Method F. A solution of methyl iodide (0.52 mL, 8.88 mmol) in dry acetone (5 mL) was added dropwise at 0–5 °C to a solution of the imidazolium benzimidazolate inner salts **10**, **12**, and **14** (2.22 mmol) in dry acetone (25 mL) under an atmosphere of nitrogen, and stirring was continued at room temperature for the time specified in Table I. The progress of the reaction was monitored by TLC (chloroform–methanol, 9:1) and by ^1H NMR of aliquots.

The resulting solution was evaporated to dryness, and the residue was recrystallized for compounds **31** and **33**, while for compound **32** the residue was washed with diethyl ether (25 mL), filtered, and dried (Table I).

Reaction of 5,6-Dimethyl-2-(3-butyl-1-imidazolium)benzimidazolate (12) with Dimethyl Acetylenedicarboxylate (DMAD). A solution of DMAD (0.3 mL, 2.46 mmol) in dry dichloromethane (10 mL) was added to a solution of **12** (0.64 g, 2.38 mmol) in dry dichloromethane (20 mL), under an atmosphere of nitrogen, and stirring was continued at room temperature for 3 h.

The resulting solution was evaporated to dryness, and the residue was chromatographed. Pure 3a*H*-imidazo[1′,2′:3,4]pyrimido[1,2-*a*]benzimidazole (**34**) (0.53 g, 51%) was obtained by FC (ethyl acetate/hexane, 8:2) and subsequent recrystallization (dichloromethane–diethyl ether): mp 182 °C; EIMS *m/z* (rel intensity) 410 (M^+, 6), 379 (M − 31, 10), 351 (100, M − 59), 263 (43), and 235 (26). Anal. Calcd for $C_{22}H_{26}N_4O_4$: C, 64.4; H, 6.3; N, 13.7. Found: C, 64.0; H, 6.8; N, 13.75.

Reaction of the Mesomeric Betaine 12 with Phenyl Vinyl Sulfoxide. A solution of phenyl vinyl sulfoxide (0.21 mL, 1.61 mmol) in dry toluene (50 mL) was added to a cooled solution (5–10 °C) of **12** (0.35 g, 1.31 mmol) in dry toluene (150 mL), under an atmosphere of nitrogen, and stirring was continued at 85–90 °C. The reaction was monitored by TLC and ^1H NMR of aliquots, and only the starting betaine **12** was detected. Dry pyridine (0.16 mL, 1.98 mmol) was then added and the reaction allowed to proceed under the same conditions for 16 h.

The resulting solution was evaporated and the residue purified by FC (benzene–methanol, 9:1). The starting betaine was recovered (0.19 g); A fraction (0.18 g) was obtained, but only products of decomposition or alteration, which were not further investigated, were observed.

Dequaternization Experiments with Pyrazolium Hydrochloride 24 and Imidazolium Salts 19–21 and 35 (Table IV). Method A. Pyrolysis of **19**, **20**, **24** or **35** (0.38 mmol) was carried out in a Kugelrohr apparatus at 200 °C or 230 °C (the maximum oven temperature) with pressures below 0.5 mm (0.1–0.4 mm), over a time specified in Table III.

For the imidazolium chlorides **19** and **20**, only starting materials were recovered. The reaction with the imidazolium bromide **35** was monitored by TLC (diethyl ether–methanol, 8:2). The experiment was stopped after 8 h when unidentifiable decomposition products were detected. An aliquot of the reaction mixture was shown by ^1H NMR to contain **35** (43%), **36** (44%), and unidentified products (13%).

In contrast, the pyrazolium chloride **24** was demethylated by sublimation and pure 2-(pyrazol-1-yl)-1*H*-benzimidazole (**28**) was collected in quantitative yield: mp 220–221 °C; ^1H NMR (DMSO-d_6, δ) 13.1 (1 H, NH), 8.62 (1 H, H-3′), 7.93 (1 H, H-5′), 7.55 (2 H, H-4,7), 7.22 (2 H, H-5,6), 6.62 (1 H, H-4′); ^{13}C NMR (DMSO-d_6, δ) 146.1 (C-2), 142.7 (C-3′), 129.0 (C-5′), 122.2 (C-5,6), 108.4 (C-4′). The other benzimidazole carbon signals were not observed due to prototropic annular tautomerism. ^{13}C NMR [DMSO-d_6/TFAA (8:2), δ]: 146.1 (C-3′), 144.5 (C-2), 132.2 and 131.5 (C-5′ and C-3a,7a), 125.5 (C-5,6), 115.1 (C-4,7) and 111.7 (C-4′). Anal. Calcd for $C_{11}H_{10}N_4 \cdot H_2O$: C, 61.1; H, 5.55; N, 25.9. Found: C, 60.8; H, 5.7; N, 25.7.

Method B. A stirred solution of 2-chlorobenzimidazole (1.52 g, 10 mmol) in *N*-methylpyrazole (2 mL, 30 mmol), under an atmosphere of nitrogen, was heated in a bath at 135 °C for 2 h. The reaction mixture was filtered, and to the resulting solution was added acetone (25 mL). The precipitate was filtered and washed with acetone to give 0.38 g of a white solid, which was then identified by ^1H NMR as a mixture of 2-(pyrazol-1-yl)-1*H*-benzimidazole (**28**) and 1-(1*H*-benzimidazol-2-yl)-2-methylpyrazolium chloride (**24**), the relative proportions of which were 5:1, respectively, ≈0.31 g (16% yield) of the demethylated product **28**.

Method C. A stirred solution of the imidazolium salts **19**, **20**, or **35** (0.46 mmol) in *o*-dichlorobenzene (60 mL) was refluxed for the time specified in Table IV. The reaction solution was concentrated to 5 mL, to give a solid, which was then filtered and washed with hexane (3 × 5 mL). By means of ^1H NMR, this solid was found to be the starting imidazolium salt (**19**, **20**, or **35**) or unidentified compounds (see Table III).

Method D. A solution of 1-(1*H*-benzimidazol-2-yl)-3-benzylimidazolium chloride (**21**) (0.50 g, 1.47 mmol) in methanol (75 mL) was hydrogenated at atmospheric pressure in the presence of 0.08 g of 10% palladium on carbon. After debenzylation was complete, the solution was filtered from the catalyst and concentrated to dryness. The residue was chromatographed. Pure 2-(imidazol-1-yl)-1*H*-benzimidazole **36** (0.23 g, 73%) was obtained by FC (chloroform–methanol, 9.5:0.5): mp 158–160 °C; ^1H NMR (DMSO-d_6, δ) 8.42 (1 H, H-2′), 7.86 (1 H, H-5′), 7.30 (2 H, H-4,7), 7.14 (1 H, H-4′), 2.32 (6 H, Me); ^{13}C NMR (DMSO-d_6, δ) 142.8 (C-2), 136.0 (C-3a,7a), 130.5 and 117.2 (C-4′ and 5′), 135.3 (C-2′), 129.8 (C-5,6), 114.9 (C-4,7) and 19.8 (Me); EMIS *m/z* (rel intensity) 212 (M^+, 100). Anal. Calcd for $C_{11}H_{10}N_4$: C, 67.9; H, 5.7; N, 26.4; Found: C, 67.95; H, 5.3; N, 26.7.

In the dequaternization experiments described above, the progress of the reaction was monitored by TLC (chloroform–methanol, 9:1) and ^1H NMR aliquots.

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Registry No. **9**, 116830-67-2; **10**, 116830-68-3; **11**, 133797-74-7; **12**, 116830-69-4; **13**, 133797-75-8; **14**, 133797-76-9; **15**, 116830-72-9; **16**, 116830-70-7; **17**, 133797-77-0; **18**, 133797-78-1; **19**, 133797-79-2; **20**, 133815-68-6; **21**, 133797-80-5; **22**, 133815-69-7; **23**, 133797-81-6; **24**, 133797-82-7; **25**, 4857-06-1; **26**, 39791-96-3; **27**, 6818-99-1; **28**,

6488-88-6; 29, 26559-04-6; 31, 116830-73-0; 32, 116830-74-1; 33, 133797-83-8; 34, 116882-69-0; 35, 133797-84-9; 36, 133797-85-0; *N*-methylimidazole, 616-47-7; *N*-methylpyrazole, 930-36-9; phenyl vinyl sulfoxide, 20451-53-0.

Supplementary Material Available: ^{13}C NMR of compound 34, individual assignments using SFORD, SEFT, and HETNOE techniques (Figure 1), percentage heteronuclear NOE enhancements on irradiation of some protons of compound 34 in $CDCl_3$ (Table II), and elemental analyses of new compounds (Table IV) (3 pages). Ordering information is given on any current masthead page.

Synthesis of (*S*)-(+)-Mevalonolactone and Mevalonate Analogues[1]

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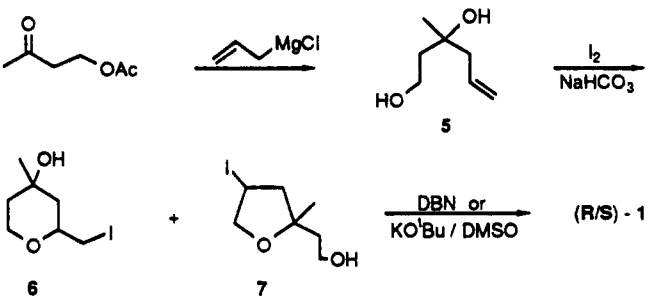
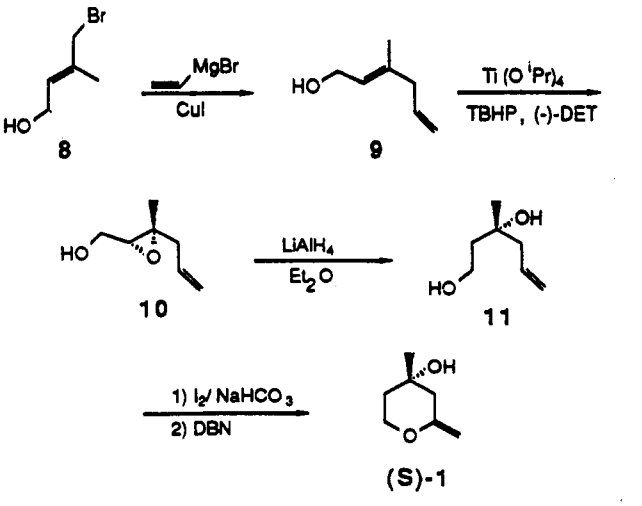
Tetrahydropyran (*R*/*S*)-1, a vinylidene analogue of mevalonolactone, was prepared by addition of excess allyl Grignard to 4-acetoxy-2-butanone, iodoetherification of the resultant diol 5, and DBN-mediated dehydrohalogenation. Sharpless asymmetric epoxidation of 3-methylhexa-2,5-dien-1-ol (9) gave epoxide 10 that was reduced to diol 11 (>95% ee) by $LiAlH_4$. Annulation and elimination of HI as described for 5 furnished (*S*)-1. Ozonolysis of (*S*)-1 yielded (*S*)-mevalonolactone (2), whereas bromomethoxylation and controlled hydrolysis led to 3, a reactive analogue of (*S*)-mevalonic acid. Analogue 4, a nonionizable lipophilic version of (*S*)-mevalonic acid, was generated upon exposure of (*S*)-1 or 2 to excess Tebbe–Grubbs reagent.

Living systems precisely regulate the biosynthesis of mevalonate (present as mevalonolactone or mevalonic acid), the essential precursor to a vast array of terpenoids, sterols, cytokines, and other isoprenoids.[2] Issues concerning the mechanism of regulation[3] and the disposition of mevalonate between competing pathways[4] have come under greater scrutiny recently with the ultimate aim of intervening in vital cellular functions ranging from cholesterol homeostasis[5] to cell proliferation promoted by prenylated enzymes such as *ras*-protein.[6] While several syntheses of mevalonolactone have been reported,[7] little is known about the pharmacologic profile[8] of the unnatural *S* enantiomer 2 and its interactions with regulatory components of the mevalonate and isoprenoid pathways. To expedite current biological evaluations of structural variance, we describe herein an efficient total synthesis of the vinylidene analogue 1 of (*S*)-mevalonolactone and its

Scheme I



Scheme II



further transformation to 2 as well as the seco analogues 3 and 4.

Convenient access to (*R*/*S*)-1 on a multigram scale was achieved by addition of allylmagnesium chloride to 4-

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