# Synthesis and Application of Imidazole Derivatives. Synthesis of Pyrrolo[1,2-*a*]benzimidazoles and Azepino[1,2-*a*]benzimidazoles

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**4-Methyl-4*H*-pyrrolo[1,2-*a*]benzimidazol-2(1*H*)-one derivatives (11a—d) were synthesized by intramolecular acylation of 1-carboxymethyl-2,3-dimethylbenzimidazolium halides (9a and 8b—d) in good yields. Treatment of the iodide (8a) with an excess of refluxing thionyl chloride gave 1,1,3-trichloro-4-methyl-4*H*-pyrrolo[1,2-*a*]benzimidazol-2(1*H*)-one (14). Introduction of electrophiles into the 1-position of 11d and 6-position of 5-methyl-9,10-dihydro-5*H*-azepino[1,2-*a*]benzimidazol-7(8*H*)-one (2a) was achieved by successive treatment with lithium diisopropylamide and electrophiles such as methyl iodide and ketones. The azepinone 2a was reacted with various electrophiles to give 6-substituted products in good yields.**

**Keywords** benzimidazolium salt; 2-methylbenzimidazole; 1-acyl-1*H*-imidazole; intramolecular cyclization; pyrrolo[1,2-*a*]benzimidazole; azepino[1,2-*a*]benzimidazole; thionyl chloride; enaminone; electrophilic substitution

Imidazole and benzimidazole are interesting heterocycles because they are not only presented in many naturally occurring products and various useful drugs[1] but also show characteristic chemical behavior.[2] In this series of studies, our aims have been to prepare azepino-, pyrido- and pyrrolo[1,2-*a*]benzimidazole derivatives (**2a**, **2b**, **2c**, respectively) and their derivatives such as **3** and **4**, and we also wish to examine their chemical properties and biological activities. In the previous paper, we reported the synthesis and structure determination of tricyclic 5-alkyl-9,10-tetrahydro-5*H*-azepino[1,2-*a*]benzimidazol-7(8*H*)-one (**2a**), which was prepared starting from 2-methylbenzimidazole (**1a**).[3]

This paper deals with several synthetic procedures for a novel tricyclic system, 4-methyl-1,2-dihydro-4*H*-pyrrolo[1,2-*a*]benzimidazol-2(1*H*)-one derivatives (**11**), and electrophilic substitution at the α- and α′-position of the carbonyl group in **11** and **2a**.

The 1-position of 2-methylbenzimidazole (**1a**) was alkylated in 92% yield with ethyl bromoacetate in the presence of sodium hydride, and the resultant ester (**6a**) was treated with methyl iodide to give **7a**, which was hydrolyzed with an equimolar amount of aqueous sodium hydroxide. Neutralization of the hydrolyzate with hydrochloric acid gave the crystalline acid (**8a**) in 85.4% yield from **6a**. Attempts to prepare **11a** by the activation of **8a** by treating with *N*,*N*′-carbonyldiimidazole (CDI) in *N*,*N*′-dimethylformamide (DMF) according to the procedure used for the preparation of **2a**[3] were unsuccessful because of the poor solubility of **8a** in DMF. Therefore, in an attempt to increase the solubility of the benzimidazolium halide, an exchange of the iodide ion to chloride ion was conducted by passing a methanolic solution of **8a** through a column of anion exchanging resin ($Cl^-$ form of Amberlyst A-27 resin). The solubility of the chloride (**9**) in DMF was enhanced, as expected and the reaction of **9** with CDI proceeded smoothly to give the desired cyclized product (**11a**) in 35.3% yield from **9a**.

Spectral and analytical data of **11a** supported the proposed structure (Chart 2). Positive color reaction with methanolic ferric(III) chloride solution was observed with **11a** as well as **2a**, probably because in solution **11a** existed as an enol form (**12a**) to a considerable degree. The proposed structure of **11a** or **12a** in Chart 2 was also supported by the similarity to **2a** in ultraviolet (UV), infrared (IR) and other properties such as appearance, solubility and thin layer chromatography (TLC) behavior.

The analogues **11b—d** were also prepared in fair yields from the corresponding starting materials **1** and **5** in a similar manner.

Next, we tried alkylation of the 1-position of **11d**. Thus, treatment of **11d** with lithium diisopropylamide (LDA) followed by addition of methyl iodide gave the tetramethylpyrrolo[1,2-*a*]benzimidazol-2(1*H*)-one (**11e**) in 73.2% yield. The structure of **11e** was confirmed by spectral and analytical data (IR, mass spectrum (MS), $^1$H-nuclear magnetic resonance ($^1$H-NMR)), and a positive color reaction in the ferric(III) chloride test.

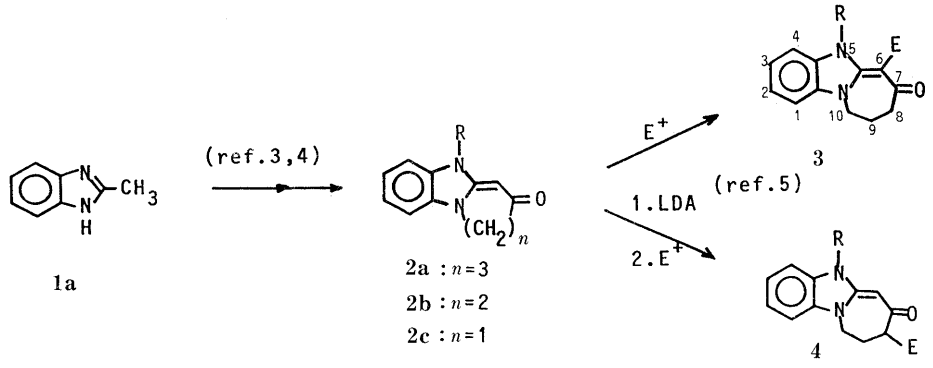


Chart 1

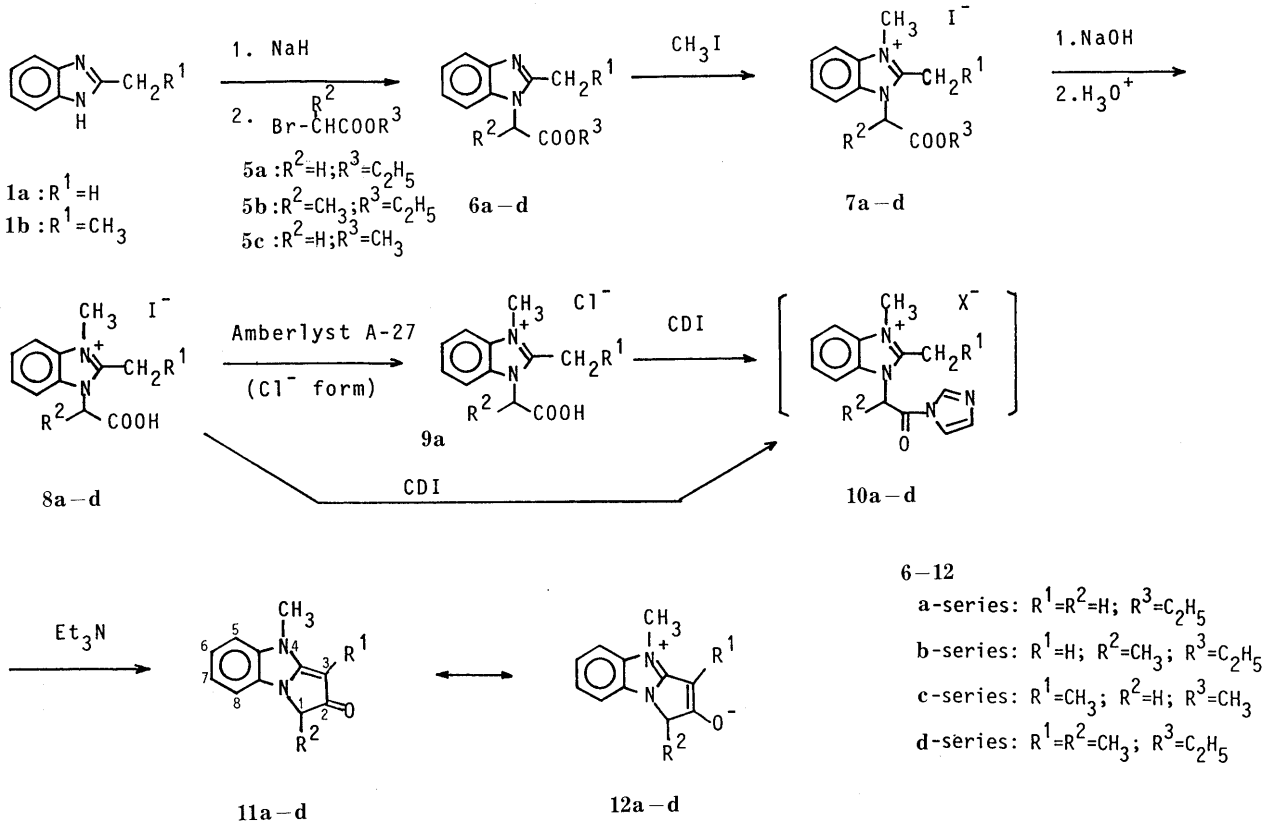


Chart 2

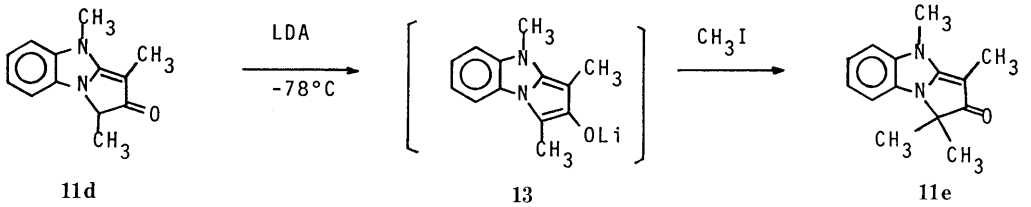


Chart 3

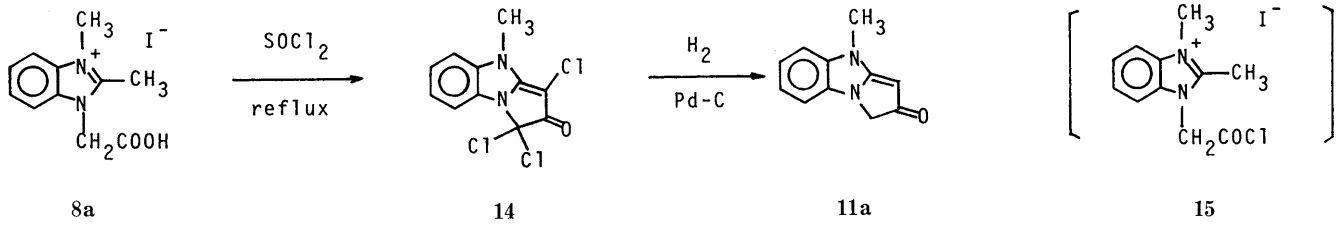


Chart 4

In the initial stage of the present work, we had planned an intramolecular cyclization of the acid chloride **15**. Thus, we heated the carboxylic acid **8a** in an excess of thionyl chloride at 80 °C for 2 h, but the corresponding acid chloride **15** was not obtained. From the reaction mixture, yellow prisms were isolated in 54.8% yield and the structure was, interestingly, estimated as 1,1,3-trichloro-4-methyl-4*H*-pyrrolo[1,2-*a*]benzimidazol-2(1*H*)-one (**14**) based on the positive reaction in the ferric(III) chloride test, MS ($M^+ = 288$ *m/z*), analytical data, and absence of any aliphatic proton signal other than that of $NC\underline{H}_3$ (3.88 ppm, s, 3H). The structure of the trichloride (**14**) was finally confirmed by catalytic hydrogenation in the presence of Pd–charcoal, resulting in the formation of **11a** in quantitative yield.

It is presumed that the trichloride (**14**) is probably produced through a radical reaction process, and in the literature, some abnormal reactions involving thionyl chloride have been described.[4,5] For example, Castle *et al.* reported that 3-(2-naphthyl)-2-propenoic acid was converted in 75% yield to 1-chloronaphtho[2,1-*b*]thiophene-2-carbonyl chloride by treatment with a refluxing mixture of thionyl chloride, chlorobenzene and a catalytic amount of pyridine.[5] The reaction of **8a** to **14** is also presumed to proceed *via* a similar abnormal process.

It is noteworthy that $\nu_{C=O}$ of the trichloride (**14**) is

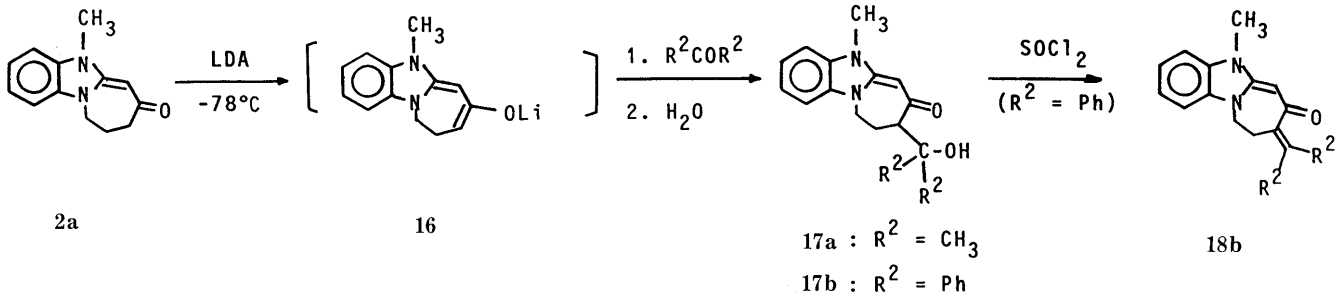


Chart 5

TABLE I. 6-Substituted 5-Methyl-7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]benzimidazol-7-ones Prepared

| Electrophile | Product (E) | Yield (%) | mp (°C) (Solvent) | Molecular formula | IR (KBr) $\nu_{C=O}$ or $\nu_{C=C}$ ($cm^{-1}$) | $^1$H-NMR (TMS) $\delta$, $J$ (Hz) |
|---|---|---|---|---|---|---|
| $(CH_3CO)_2O$ | **19** ($CH_3CO$) | 68 | 230—232 (AcOEt) | $C_{15}H_{16}N_2O_2$ (256.3) | 1615, 1580 | 2.23—2.53 (m, 4H, $-CH_2CH_2CO$), 2.63 (s, 3H, $COCH_3$), 3.66 (s, 3H, $NCH_3$), 4.27 (t, 2H, $NCH_2$, $J$=7 Hz), 7.43 (m, $4H_{arom}$) |
| $(C_6H_5CO)_2O$ | **20** ($C_6H_5CO$) | 57 | 267—269 ($C_6H_6$–*n*-hexane) | $C_{20}H_{18}N_2O_2$ (318.4) | 1615, 1550 | 2.25—2.65 (m, 4H, $CH_2CH_2CO$), 3.64 (s, 3H, $NCH_3$), 4.21—4.38 (m, 2H, $NCH_2$), 7.26—7.72 (m, $9H_{arom}$) |
| $CH_3COCH_2=CH$ | **21** ($CH_3COCH_2CH_2$) | 46 | 152—154 ($C_6H_6$–*n*-hexane) | $C_{17}H_{20}N_2O_2$ (284.4) | 1695, 1520 | 2.16 (s, 3H, $COCH_3$), 2.50 (m, 4H, $CH_2CH_2$-$CH_2CO$), 2.80 (m, 4H, $CH_2CH_2COCH_3$), 3.60 (s, 3H, $NCH_3$), 3.90 (t, 2H, $NCH_2$, $J$=7 Hz), 7.20 (m, $4H_{arom}$) |
| PhNCO | **22** (PhNHCO) | 82 | 202—204 (AcOEt–*n*-hexane) | $C_{20}H_{19}N_3O_2$ (333.4) | 1640 | 2.30—2.55 (m, 4H, $CH_2CH_2CO$), 3.84 (s, 3H, $NCH_3$), 4.18—4.39 (m, 2H, $NCH_2$), 7.04—7.74 (m, $9H_{arom}$), 12.17 (s, 1H, NH) |
| *n*-BuNCO | **23** (*n*-BuNHCO) | 35 | 132—135 (AcOEt–*n*-hexane) | $C_{18}H_{23}N_3O_2$ (313.4) | 1580 | 0.95 (t, 3H, $CH_2CH_3$, $J$=6 Hz), 1.20—1.80 (m, 4H, $CH_2CH_2CH_3$), 2.15—2.70 (m, 4H, $CH_2$-$CH_2CO$), 3.35 (q, 2H, $NHCH_3$), 4.23 (br, 2H, $NCH_2$, $J$=6 Hz), 7.45 (m, $4H_{arom}$), 9.86 (br, 1H, NH) |
| PhNCS | **24** (PhNHC=S) | 31 | 211—213 (AcOEt–*n*-hexane) | $C_{20}H_{19}N_3OS$ (349.5) | 1650 | 2.03—2.46 (m, 4H, $CH_2CH_2CO$), 3.98 (s, 3H, $NCH_3$), 4.35—4.55 (m, 2H, $NCH_2$), 7.12—7.92 (m, $9H_{arom}$), 13.96 (br, 1H, NH) |
| $PhN_2Cl$ | **25**·HCl[a] (PhN=N–) | 72 | 222—224 (EtOH–$Et_2O$) | $C_{19}H_{19}ClN_4O$ (354.8) | 1660 | 2.32—2.54 (m, 2H, $CH_2CH_2CH_2$), 2.72—2.80 (t, 2H, $CH_2CO$, $J$=6 Hz), 4.18 (s, 3H, $NCH_3$), 4.74 (t, 2H, $NCH_2$, $J$=7 Hz), 7.27—8.22 (m, $9H_{arom}$), 14.40 (br, 1H, $N^+H$) |
| $4\text{-}MeOC_6H_4N_2Cl$ | **26**·HCl[a] | 36 | 247—249 (MeOH–$Et_2O$) | $C_{20}H_{21}ClN_4O_2$ (384.9) | 1500 | 2.47—2.52 (m, 2H, $CH_2CH_2CH_2$), 2.70—2.79 (m, 2H, $CH_2CO$), 3.80 (s, 3H, $OCH_3$), 4.16 (s, 3H, $NCH_3$), 4.67 (m, 2H, $NCH_2$), 7.00—8.18 (m, $8H_{arom}$), 14.69 ($N^+H$) |
| PhSeCl | **27** | 75 | 174—176 (AcOEt–*n*-hexane) | $C_{19}H_{18}N_2OSe$ (369.0) | 1495 | 2.65 (m, 4H, $CH_2CH_2CO$), 3.63 (s, 3H, $NCH_3$), 4.13 (t, 2H, $NCH_2$, $J$=6 Hz), 7.00—7.50 (m, $9H_{arom}$) |

*a*) $^1$H-NMR of the compound was measured in DMSO-$d_6$.

observed at 1710 $cm^{-1}$ while **11a—d** as well as **2a** do not show any $\nu_{C=O}$ absorption near 1700 $cm^{-1}$ in their IR spectra because of the contribution of the dipole structure (**12a**).[3] It can be considered that in **14** the three electronegative chlorine atoms at the 1- and 3-positions electrostatically supress the enolization of the carbonyl group at the 2-position.

Next, we applied the above-described enolate formation procedure to the azepinone (**2a**). The azepinone (**2a**) was treated with an equimolar amount of LDA at −78 °C followed by addition of acetone to give the aldol-type product (**17a**) in 58% yield. The structure of **17a** was supported by its $^1$H-NMR spectrum. When the diphenyl analogue (**17b**) was treated with thionyl chloride at room temperature, the corresponding dehydration product (**18b**) was obtained in 67% yield.

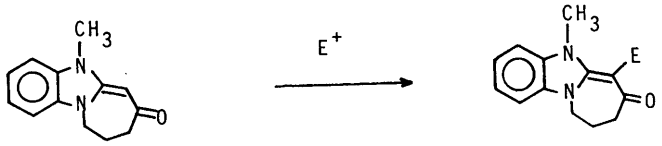


Chart 6

Finally we examined reactivity to electrophiles at the 6-position of the enaminone (**2a**), because the position probably holds key to the reactivity of enamines and ketone enolates, like the 4-position of antipyrine.[6] It was found that treatment of **2a** with acetic anhydride gave the 6-

acetylated product (**19**) in 68% yield as expected. The structure of **19** was supported by its $^1$H-NMR spectrum. Thus, the azepinone (**2a**) was treated with various electrophilic reagents to give smoothly the corresponding 6-substituted products (**20**—**27**) in various yields.

Biological activities of the newly prepared compounds described in this paper are under examination.

## Experimental

All melting points are uncorrected. IR spectra were taken with a Shimadzu IR-410 spectrometer. $^1$H-NMR were obtained at 80 MHz on a Varian CFT-20 spectrometer and the chemical shifts are expressed in $\delta$ (ppm) values with tetramethylsilane as an internal standard. Abbreviations of $^1$H-NMR signal patterns are as follows: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). UV spectra were obtained on a Shimadzu UV-200S spectrometer. Low-resolution MS (LRMS) and high-resolution MS (HRMS) were obtained on a Hitachi M-80 spectrometer. All solvents were removed under reduced pressure in the usual work-up procedure. Unless otherwise stated, anhydrous sodium sulfate was used as a drying agent. A Kugelrohr apparatus was used for vacuum distillations of oily crude products. Silica gel (Merck Art. 7734) was used in column chromatography.

**1-(3-Ethoxycarbonylmethyl)-2-methylbenzimidazole (6a)** 2-Methylbenzimidazole (**1a**, 2.64 g, 20 mmol) was added under an $N_2$ atmosphere to an ice-cooled suspension of 97% NaH (0.55 g, 22 mmol) in dry tetrahydrofuran (THF, 20 ml) and the mixture was stirred for 30 min. Ethyl bromoacetate (**5a**, 3.67 g, 22 mmol) was added to the cooled mixture and the whole was stirred for 2 h at room temperature. Water (20 ml) was added to the reaction mixture, and the product was extracted with AcOEt (50 ml × 3). The organic phase was washed with brine (10 ml) and dried. A pale yellow crystalline residue was obtained after evaporation. The product was purified by recrystallization from $CCl_4$ to give colorless needles, mp 105—106 °C. Yield, 3.99 g (91.5%). IR $\nu_{max}$ cm$^{-1}$: 1750 (C=O). $^1$H-NMR (in $CDCl_3$) ppm: 1.25 (t, 3H, $CH_2C\underline{H}_3$, $J$=7 Hz), 2.57 (s, 3H, $C\underline{H}_3C$=), 4.17 (q, 2H, $OC\underline{H}_2CH_3$, $J$=7 Hz), 4.78 (s, 2H, $NC\underline{H}_2$), 7.18—7.31 (m, 3H, Ar-H), 7.64—7.73 (m, 1H, Ar-H). *Anal.* Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.63; H, 6.76; N, 12.75.

**1-(1-Ethoxycarbonylethyl)-2-methylbenzimidazole (6b)** **6b** was prepared in a similar manner starting from **1a** (5.0 g, 38 mmol), ethyl 2-bromopropionate (7.20 g, 40 mmol) and NaH (1.03 g, 42 mmol). The crude product was purified by vacuum distillation, bp 150—152 °C (3 mmHg). Yield, quantitative. IR $\nu_{max}$ cm$^{-1}$: 1740 (C=O). $^1$H-NMR (in $CDCl_3$) ppm: 1.15 (t, 3H, $OCH_2C\underline{H}_3$, $J$=7 Hz), 1.80 (d, 3H, $>CHC\underline{H}_3$, $J$=7 Hz), 2.62 (s, 3H, $=CC\underline{H}_3$), 4.19 (q, 2H, $OC\underline{H}_2CH_3$, $J$=7 Hz), 5.10 (q, 1H, $>C\underline{H}CH_3$, $J$=7 Hz), 7.12—7.38 (m, 3H, Ar-H), 7.60—7.75 (m, 1H, Ar-H). *Anal.* Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.03; H, 7.03; N, 11.91.

**2-Ethyl-1-methoxycarbonylmethylbenzimidazole (6c)** **6c** was prepared in a similar manner starting from **1b** (0.60 g, 4.1 mmol), methyl bromoacetate (0.69 g, 4.5 mmol) and NaH (0.11 g, 4.5 mmol). The crystalline crude product was recrystallized from $C_6H_6$–*n*-hexane to give colorless needles, mp 124—125 °C. Yield, 0.77 g (85.7%). IR $\nu_{max}$ cm$^{-1}$: 1740 (C=O). $^1$H-NMR (in $CDCl_3$) ppm: 1.46 (t, 3H, $CH_2C\underline{H}_3$, $J$=7 Hz), 2.85 (q, 2H, $=CC\underline{H}_2CH_3$, $J$=7 Hz), 3.75 (s, 3H, $COOC\underline{H}_3$), 4.81 (s, 2H, $C\underline{H}_2COO$), 7.13—7.33 (m, 3H, Ar-H), 7.66—7.81 (m, 1H, Ar-H). *Anal.* Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.38; H, 6.36; N, 13.04.

**1-(1-Ethoxycarbonylethyl)-2-ethylbenzimidazole (6d)** **6d** was prepared in a similar manner starting from **1b** (1.00 g, 6.9 mmol), ethyl 2-bromopropionate (1.30 g, 7.2 mmol) and NaH (0.19 g, 7.5 mmol). The crude oily product was purified by vacuum distillation, bp 153—155 °C (3 mmHg). Yield, quantitative. IR $\nu_{max}$ cm$^{-1}$: 1740 (C=O). $^1$H-NMR (in $CDCl_3$) ppm: 1.14 (t, 3H, $OCH_2C\underline{H}_3$, $J$=7 Hz), 1.47 (t, 3H, $=CCH_2C\underline{H}_3$, $J$=7 Hz), 1.80 (d, 3H, $CHC\underline{H}_3$, $J$=7 Hz), 2.91 (q, 2H, $=CC\underline{H}_2CH_3$, $J$=7 Hz), 4.18 (q, 2H, $OC\underline{H}_2CH_3$, $J$=7 Hz), 5.12 (q, 1H, $C\underline{H}CH_3$, $J$=7 Hz), 7.13—7.38 (m, 3H, Ar-H), 7.64—7.80 (m, 1H, Ar-H). HRMS *m/z*: Calcd for $C_{14}H_{18}N_2O_2$: 246.1368. Found: 246.1356 ($M^+$).

**1-Ethoxycarbonylmethyl-2,3-dimethylbenzimidazolium Iodide (7a)** A mixture of **6a** (1.15 g, 5.3 mmol), $CH_3I$ (3.3 ml, 53 mmol) and AcOEt (20 ml) was refluxed at 80 °C for 2 h. The reaction mixture was cooled in an ice-water bath, then the precipitated crystals were filtered off under suction. Recrystallization of the crude product from 2-propanol gave pale yellow prisms, mp 197—199 °C. Yield, 1.77 g (92.9%). IR $\nu_{max}$ cm$^{-1}$: 1740 (C=O). $^1$H-NMR (in DMSO-$d_6$) ppm: 1.26 (t, 3H, $OCH_2C\underline{H}_3$, $J$=7 Hz), 2.89 (s, 3H, $=CC\underline{H}_3$), 4.06 (s, 3H, $NC\underline{H}_3$), 4.24 (q, 2H, $OC\underline{H}_2CH_3$, $J$=7 Hz), 5.62 (s, 2H, $NC\underline{H}_2$), 7.59—7.71 (m, 2H, Ar-H), 7.93—8.05 (m, 2H, Ar-H). *Anal.* Calcd for $C_{13}H_{17}IN_2O_2$: C, 43.35; H, 4.76; N, 7.78. Found: C, 43.25; H, 4.84; N, 8.10.

**1-(1-Ethoxycarbonylethyl)-2,3-dimethylbenzimidazolium Iodide (7b)** **7b** (yield, 12.97 g, 91.6%) was obtained in a similar manner starting from **6b** (8.70 g, 37.5 mmol), MeI (12.3 ml, 190 mmol) and AcOEt (40 ml). The crude product was recrystallized from 2-propanol to give pale yellow needles, mp 150—151 °C. IR $\nu_{max}$ cm$^{-1}$: 1750 (C=O). $^1$H-NMR (in DMSO-$d_6$) ppm: 1.19 (t, 3H, $OCH_2C\underline{H}_3$, $J$=7 Hz), 1.83 (d, 3H, $>CHC\underline{H}_3$, $J$=7 Hz), 2.93 (s, 3H, $=CC\underline{H}_3$), 4.03 (s, 3H, $NC\underline{H}_3$), 4.23 (q, 2H, $OC\underline{H}_2CH_3$, $J$=7 Hz), 6.04 (q, 1H, $>C\underline{H}CH_3$, $J$=7 Hz), 7.50—7.84 (m, 2H, Ar-H), 7.87—8.11 (m, 2H, Ar-H). *Anal.* Calcd for $C_{14}H_{19}IN_2O_2$: C, 44.93; H, 5.12; N, 7.49. Found: C, 45.08; H, 5.07; N, 7.53.

**2-Ethyl-1-methoxycarbonylmethyl-3-methylbenzimidazolium Iodide (7c)** **7c** (yield, 0.517 g, 95.2%) was obtained in a similar manner starting from **6c** (329 mg, 1.5 mmol), $CH_3I$ (0.5 ml, 7.6 mmol) and AcOEt (3 ml). The crude product was recrystallized from MeOH–AcOEt to give pale yellow prisms, mp 190—192 °C. IR $\nu_{max}$ cm$^{-1}$: 1745 (C=O). $^1$H-NMR (in DMSO-$d_6$) ppm: 1.25 (t, 3H, $CH_2C\underline{H}_3$, $J$=7 Hz), 3.35 (q, 2H, $C\underline{H}_2CH_3$, $J$=7 Hz), 3.78 (s, 3H, $COOC\underline{H}_3$), 4.11 (s, 3H, $NC\underline{H}_3$), 5.67 (s, 2H, $C\underline{H}_2COOCH_3$), 7.60—7.78 (m, 2H, Ar-H), 7.93—8.10 (m, 2H, Ar-H). *Anal.* Calcd for $C_{13}H_{17}IN_2O_2$: C, 43.35; H, 4.75; N, 7.78. Found: C, 43.33; H, 4.81; N, 7.63.

**1-(1-Ethoxycarbonylethyl)-2-ethyl-3-methylbenzimidazolium Iodide (7d)** **7d** was obtained in a similar manner starting from **6d** (1.68 g, 6.8 mmol), MeI (2.2 ml, 34 mmol) and AcOEt (15 ml). The viscous crude product was used in the next step without further purification.

**1-Carboxymethyl-2,3-dimethylbenzimidazolium Iodide (8a)** A solution of **7a** (2.53 g, 7 mmol) in 4 N NaOH (2.0 ml, 8 mmol) was stirred for 1 h at room temperature. The solution was evaporated to dryness after neutralization with 2 N HCl (4.0 ml, 8 mmol), and the residual solid was recrystallized from MeOH–AcOEt to give colorless needles, mp 220—223 °C (dec.). Yield, 2.14 g (91.9%). IR $\nu_{max}$ cm$^{-1}$: 1740 (C=O). $^1$H-NMR (in DMSO-$d_6$) ppm: 2.88 (s, 3H, $=CC\underline{H}_3$), 4.05 (s, 3H, $NC\underline{H}_3$), 5.50 (s, 2H, $NC\underline{H}_2$), 7.58—7.70 (m, 2H, Ar-H), 7.95—8.08 (m, 2H, Ar-H). *Anal.* Calcd for $C_{11}H_{13}IN_2O_2$: C, 39.78; H, 3.94; N, 8.43. Found: C, 39.78; H, 4.05; N, 8.42.

**1-(1-Carboxyethyl)-2,3-dimethylbenzimidazolium Iodide (8b)** **8b** (yield, 9.75 g, 92.4%) was obtained in a similar manner starting from **7b** (11.40 g, 30.5 mmol) and 4 N NaOH (8.0 ml, 32 mmol). Colorless needles, mp 249—250 °C (dec.). IR $\nu_{max}$ cm$^{-1}$: 1760 (C=O). $^1$H-NMR (in DMSO-$d_6$) ppm: 1.80 (d, 3H, $CHC\underline{H}_3$, $J$=7 Hz), 2.93 (s, 3H, $=CC\underline{H}_3$), 4.03 (s, 3H, $NC\underline{H}_3$), 5.94 (q, 1H, $C\underline{H}CH_3$, $J$=7 Hz), 7.56—7.84 (m, 2H, Ar-H), 7.88—8.10 (m, 2H, Ar-H). *Anal.* Calcd for $C_{12}H_{15}IN_2O_2$: C, 41.64; H, 4.37; N, 8.09. Found: C, 41.80; H, 4.29; N, 8.18.

**1-Carboxymethyl-2-ethyl-3-methylbenzimidazolium Iodide (8c)** **8c** (yield, 458 mg, 92.2%) was obtained in a similar manner starting from **7c** (517 mg, 1.4 mmol) and 4 N NaOH (0.5 ml, 2 mmol). The crude product was recrystallized from 2-propanol to give pale yellow needles, mp 189—191 °C (dec.). IR $\nu_{max}$ cm$^{-1}$: 1740 (C=O). $^1$H-NMR (in DMSO-$d_6$) ppm: 1.26 (t, 3H, $CH_2C\underline{H}_3$, $J$=7 Hz), 3.35 (q, 2H, $C\underline{H}_2CH_3$, $J$=7 Hz), 4.10 (s, 3H, $NC\underline{H}_3$), 5.54 (s, 2H, $C\underline{H}_2COOH$), 7.53—7.77 (m, 2H, Ar-H), 7.88—8.10 (m, 2H, Ar-H). *Anal.* Calcd for $C_{12}H_{15}IN_2O_2$: C, 41.64; H, 4.37; N, 8.09. Found: C, 42.09; H, 4.43; N, 8.30.

**1-(1-Carboxyethyl)-2-ethylbenzimidazolium Iodide (8d)** **8d** (yield, 2.33 g, 94.5%, calculated from **6d**) was obtained in a similar manner starting from **7d** [prepared from 1.68 g (6.8 mmol) of **6d**] and 2 N NaOH (4.0 ml, 8 mmol). Recrystallization from MeOH–AcOEt gave colorless prisms, mp 255—257 °C (dec.). IR $\nu_{max}$ cm$^{-1}$: 1750 (C=O). $^1$H-NMR (in DMSO-$d_6$) ppm: 1.28 (t, 3H, $CH_2C\underline{H}_3$, $J$=7 Hz), 1.82 (d, 3H, $CHC\underline{H}_3$, $J$=7 Hz), 3.38 (q, 2H, $C\underline{H}_2CH_3$, $J$=7 Hz), 4.07 (s, 3H, $NC\underline{H}_3$), 5.96 (q, 1H, $C\underline{H}CH_3$, $J$=7 Hz), 7.57—7.88 (m, 3H, Ar-H), 7.95—8.11 (m, 1H, Ar-H). *Anal.* Calcd for $C_{13}H_{17}IN_2O_2$: C, 43.35; H, 4.76; N, 7.78. Found: C, 43.36; H, 4.67; N, 7.79.

**1-Carboxymethyl-2,3-dimethylbenzimidazolium Chloride (9a)** A solution of **8a** (14.54 g, 43.8 mmol) in MeOH (50 ml) was passed through a column (i.d. 3.5 cm) of Amberlyst A-21 ($Cl^-$ form; 75 g) and the column was washed with 250 ml of MeOH. The combined MeOH solution was evaporated and the residue was recrystallized from MeOH–AcOEt to give colorless needles, mp 240—242 °C (dec.). Yield, quantitative. IR $\nu_{max}$ cm$^{-1}$: 1740 (C=O). $^1$H-NMR (in DMSO-$d_6$) ppm: 2.89 (s, 3H, $=CC\underline{H}_3$), 4.06 (s, 3H, $NC\underline{H}_3$), 5.54 (s, 2H, $NC\underline{H}_2$), 7.57—7.69 (m, 2H,

Ar-H), 7.96—8.07 (m, 2H, Ar-H). *Anal.* Calcd for $C_{11}H_{13}ClN_2O_2$: C, 54.89; H, 5.44; N, 11.64. Found: C, 54.64; H, 5.55; N, 11.40.

**4-Methyl-4*H*-pyrrolo[1,2-*a*]benzimidazol-2(1*H*)-one (11a)** a) CDI (1.49 g, 9.2 mmol) was added to a solution of **9a** (2.00 g, 8.3 mmol) in DMF (16 ml) at room temperature under an $N_2$ atmosphere. The mixture was stirred for 1 h, then $Et_3N$ (3.5 ml, 25 mmol) was added and the whole was heated at 70 °C for 5 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by chromatography on silica gel (solvent: $CHCl_3$–MeOH, 5:1). Crystals obtained from the main fraction were recrystallized from $C_6H_6$ to give pale yellow needles, mp 199—201 °C. Yield, 574 mg (35.3%). IR $\nu_{max}$ $cm^{-1}$:1570 (C=O or C=C). $^1$H-NMR (in $CDCl_3$) ppm: 3.55 (s, 3H, $NCH_3$), 4.14 (s, 2H, $NCH_2$), 4.80 (s, 1H, >C=CH–), 7.11 (br s, 4H, Ar-H). UV $\lambda_{max}^{EtOH}$ nm (log $\varepsilon$): 241 (4.31), 322 (4.30), 332 (4.40). LRMS *m/z*: 186 ($M^+$). *Anal.* Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.94; H, 5.35; N, 15.04.

b) A mixture of **14** (183 mg, 0.64 mmol), 5% Pd–C (100 mg) and 2-propanol (2.0 ml) was stirred for 1 h at room temperature under an $H_2$ atmosphere (1 atm). The catalyst was removed by filtration and the filtrate was concentrated. The residue was diluted with water (1 ml), basified with solid $K_2CO_3$, and extracted with AcOEt (10 ml). Removal of the solvent of the extract after drying gave a solid mass, which was recrystallized from $C_6H_6$ to give pale yellow needles, mp 199—201 °C. Yield, quantitative. The product was identical (IR, TLC, mp, and mixed-melting-point test) with **11a** obtained by method a.

**1,4-Dimethyl-4*H*-pyrrolo[1,2-*a*]benzimidazol-2(1*H*)-one (11b) 11b** (yield, 581 mg, 56.2%) was obtained in a similar manner to method a as used for **11a** starting from **8b** (1.79 g, 5.2 mmol), CDI (924 mg), DMF (10 ml) and $Et_3N$ (2.15 ml, 15.5 mmol). The crude product was recrystallized from $C_6H_6$ to give pale yellow needles, mp 159—162 °C (dec.). IR $\nu_{max}$ $cm^{-1}$:1550, 1570 (C=O or C=C). $^1$H-NMR (in $CDCl_3$) ppm: 1.62 (d, 3H, $CHCH_3$, $J$=6 Hz), 3.55 (s, 3H, $NCH_3$), 4.20 (q, 1H, $CHCH_3$, $J$=6 Hz), 4.75 (s, 1H, >C=CH–), 7.12 (br s, 4H, Ar-H). HRMS *m/z*: Calcd for $C_{12}H_{12}N_2O$: 200.0949. Found: 200.0932 ($M^+$).

**3,4-Dimethyl-4*H*-pyrrolo[1,2-*a*]benzimidazol-2(1*H*)-one (11c) 11c** (yield, 187 mg, 70.6%) was obtained in a similar manner to that described for **11a** starting from **8c** (458 mg, 1.3 mmol), CDI (236 mg, 1.5 mmol), DMF (3 ml) and $Et_3N$ (0.55 ml, 4 mmol). The crude product was recrystallized from $C_6H_6$ to give pale yellow needles, mp 216—218 °C. IR $\nu_{max}$ $cm^{-1}$:1540, 1560 (C=O or C=C). $^1$H-NMR (in $CDCl_3$) ppm: 2.00 (s, 3H, $=CCH_3$), 3.71 (s, 3H, $NCH_3$), 4.05 (s, 2H, $NCH_2$), 7.08 (br s, 4H, Ar-H). LRMS *m/z*: 200 ($M^+$). *Anal.* Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.70; H, 6.08; N, 13.84.

**1,3,4-Trimethyl-4*H*-pyrrolo[1,2-*a*]benzimidazol-2(1*H*)-one (11d) 11d** (yield, 468 mg, 81.3%) was obtained in a similar manner to that used for **11a** starting from **8d** (969 mg, 2.7 mmol), CDI (480 mg, 3.0 mmol), DMF (6 ml) and $Et_3N$ (1.1 ml, 8.1 mmol). The crude product was recrystallized from $C_6H_6$ to give pale yellow needles, mp 166—167.5 °C. IR $\nu_{max}$ $cm^{-1}$: 1550, 1570 (C=O or C=C). $^1$H-NMR (in $CDCl_3$) ppm: 1.58 (d, 3H, $CHCH_3$, $J$=7 Hz), 2.00 (s, 3H, $=CCH_3$), 3.73 (s, 3H, $NCH_3$), 4.11 (q, NCH, $J$=7 Hz), 7.08 (s, 4H, Ar-H). LRMS *m/z*: 214 ($M^+$). *Anal.* Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.55; H, 6.56; N, 13.06.

**1,1,3,4-Tetramethyl-4*H*-pyrrolo[1,2-*a*]benzimidazol-2(1*H*)-one (11e)** A LDA solution (0.98 mmol, prepared in a usual manner) was added dropwise at −78 °C under an $N_2$ atmosphere to a solution of **11d** (200 mg, 0.93 mmol), and the mixture was stirred for 1 h at −78 °C. $CH_3I$ (63 $\mu$l, 0.93 mmol) was added to the mixture, followed by stirring for 1 h. The reaction was quenched by addition of water (5 ml), and the product was extracted with AcOEt (5 ml × 3). The combined organic phase was evaporated to give a solid residue, which was recrystallized from $C_6H_6$ to give pale yellow prisms, mp 163—164.5 °C. Yield, 156 mg (73.2%). IR $\nu_{max}$ $cm^{-1}$: 1550, 1570 (C=O or C=C). $^1$H-NMR (in $CDCl_3$) ppm: 1.51 (s, 6H, $>C(CH_3)_2$), 2.01 (s, 3H, $=CCH_3$), 3.74 (s, 3H, $NCH_3$), 7.08 (br s, 4H, Ar-H). LRMS *m/z*: 228 ($M^+$). *Anal.* Calcd for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.27. Found: C. 73.70; H, 7.10; N, 12.30.

**1,1,3-Trichloro-4-methyl-4*H*-pyrrolo[1,2-*a*]benzimidazol-2(1*H*)-one (14)** A mixture of **8a** (1.00 g, 3 mmol) and $SOCl_2$ (10 ml) was refluxed at 80 °C for 2 h in a usual manner. Excess reagent was removed by evaporation under reduced pressure and the residue was washed with dry $C_6H_6$ (10 ml). The resulting residue was basified with 5% $NaHCO_3$ (5 ml) and the product was extracted with AcOEt (5 ml × 3). The organic phase was evaporated after drying and the residue was purified by column chromatography on silica gel (solvent, AcOEt). Removal of the solvent of the main fraction gave a solid residue, which was recrystallized from MeOH to give pale yellow needles, mp 219—220.5 °C (dec.). Yield, 475 mg (54.8%). IR $\nu_{max}$ $cm^{-1}$: 1580, 1620, 1710 (C=O or C=C). $^1$H-NMR (in $CDCl_3$) ppm: 3.88 (s, 3H, $NCH_3$), 7.21—7.46 (m, 4H, Ar-H). UV $\lambda_{max}^{EtOH}$ nm (log $\varepsilon$): 247 (4.12), 293 (3.54), 379 (3.86). LRMS *m/z*: 288 ($M^+$). *Anal.* Calcd for $C_{11}H_7Cl_3N_2O \cdot 1/2H_2O$: C, 44.25; H, 2.70; N, 9.38. Found: C, 44.75; H, 2.77; N, 9.47.

**6-Acetyl-5-methyl-9,10-dihydro-5*H*-azepino[1,2-*a*]benzimidazol-7(8*H*)-one (19)** A mixture of **2a** (R = $CH_3$, 2.14 g, 10 mmol) and acetic anhydride (10 ml) was stirred for 4 h at 100 °C under an $N_2$ atmosphere. The volatile portion of the mixture was removed by evaporation under reduced pressure. Water (10 ml) was added to the residue and the mixture was stirred for 30 min then basified with powdered $K_2CO_3$. The mixture was extracted with $CHCl_3$ (100 ml), and the extract was dried. Evaporation of the solvent gave a crystalline residue, which was purified by column chromatography on silica gel (solvent, AcOEt–MeOH, 5:1) to give a crystalline mass. The product was recrystallized from AcOEt to give slightly brown prisms; yield, 1.74 g (68%). *Anal.* Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.21; H, 6.36; N, 10.91.

**6-Benzoyl-5-methyl-9,10-dihydro-5*H*-azepino[1,2-*a*]benzimidazol-7(8*H*)-one (20)** A mixture of **2a** (R = $CH_3$, 2.14 g, 10 mmol) and benzoic anhydride (11.30 g, 50 mmol) was stirred for 18 h at 80 °C under an $N_2$ atmosphere. After the mixture was cooled, water (50 ml) was added, the whole was basified with $K_2CO_3$, and the product was extracted with $CHCl_3$ (100 ml × 3). The extract was concentrated after drying to give a crystalline residue. Product: pale yellow needles; yield, 1.76 g (57%). *Anal.* Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.18; H, 5.69; N, 8.85.

**5-Methyl-6-(3-oxobutyl)-9,10-dihydro-5*H*-azepino[1,2-*a*]benzimidazol-7(8*H*)-one (21)** Methyl vinyl ketone (1.25 ml, 15 mmol) was added to a solution of **2a** (R = $CH_3$, 2.14 g, 10 mmol) in EtOH (20 ml), and the mixture was stirred for 5 h at room temperature. Removal of the solvent gave a viscous residue, which was purified by column chromatography on silica gel (solvent, $CHCl_3$–MeOH, 10:1). The main fraction gave a crystalline residue. Product: slightly brown needles; yield, 1.30 g (46%). *Anal.* Calcd for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.86; H, 7.14; N, 9.87.

**5-Methyl-6-(*N*-phenylcarbamoyl)-9,10-tetrahydro-5*H*-azepino[1,2-*a*]-benzimidazol-7(8*H*)-one (22)** Phenyl isocyanate (1.63 ml, 10 mmol) was added to a solution of **2a** (R = $CH_3$, 2.14 g, 10 mmol) in $CHCl_3$ (8 ml), and the mixture was stirred for 3 h at room temperature. The solvent was removed by evaporation to give a viscous material, which was purified by column chromatography on silica gel (solvent: AcOEt–MeOH, 10:1). Removal of the solvent gave a crystalline residue, which was recrystallized. Product: colorless needles; yield, 1.75 g (82%). *Anal.* Calcd for $C_{20}H_{19}N_3O_2$: C, 72.05; H, 5.74; N, 12.61. Found: C, 71.87; H, 5.64; N, 12.84.

**6-(*N*-Butylcarbamoyl)-5-methyl-9,10-tetrahydro-5*H*-azepino[1,2-*a*]-benzimidazol-7(8*H*)-one (23)** **23** (yield, 0.66 g, 35%) was obtained in a similar manner starting from **2a** (R = $CH_3$, 1.28 g, 6 mmol), *n*-butyl isocyanate (1.06 ml, 9 mmol) and $CHCl_3$ (5 ml). Product: colorless needles. *Anal.* Calcd for $C_{18}H_{23}N_3O_2$: C, 67.81; H, 7.46; N, 13.20. Found: C, 67.80; H, 7.76; N, 12.80.

**5-Methyl-6-(*N*-phenylthiocarbamoyl)-7,8,9,10-tetrahydro-6*H*-azepino-[1,2-*a*]benzimidazol-7-one (24)** **24** (yield, 0.57 g, 31%) was obtained in a similar manner starting from **2a** (R = $CH_3$, 1.07 g, 5 mmol), phenyl isothiocyanate (0.66 ml, 5.5 mmol) and $CHCl_3$ (5 ml). *Anal.* Calcd for $C_{20}H_{19}N_3OS$: C, 68.74; H, 5.48; N, 12.03. Found: C, 68.61; H, 5.31; N, 11.91.

**5-Methyl-6-phenylazo-9,10-tetrahydro-5*H*-azepino[1,2-*a*]benzimidazol-7(8*H*)-one Hydrochloride (25·HCl)** A mixture of aniline (0.92 ml, 10 mmol), 2 N HCl (15 ml, 30 mmol), EtOH (22.5 ml) and isoamyl nitrite (1.35 ml, 10 mmol) was stirred at 0 °C for 15 min. The reaction mixture was added dropwise to an ice-cooled solution of **2a** (R = $CH_3$, 2.14 g, 10 mmol) in EtOH (5 ml) under stirring, then the resulting mixture was stirred at room temperature for 1 h. The volatile portion of the reaction mixture was evaporated off. A solution of the residue in EtOH (30 ml) was passed through a column of Amberlyst A-21 -HCl form (30 g; Rohm & Haas Ltd.). The resin was washed with ethanol (50 ml), and the combined ethanolic solution was evaporated to give a crystalline residue. Product: yellow needles. Yield, 2.56 g (72%). *Anal.* Calcd for $C_{19}H_{19}ClN_4O$: C, 58.38; H, 5.92; N, 14.33. Found: C, 58.41; H, 5.72; N, 14.22.

**6-(4-Methoxyphenylazo)-5-methyl-9,10-dihydro-5*H*-azepino[1,2-*a*]-benzimidazol-7(8*H*)-one Hydrochloride (26·HCl)** **26**·HCl (yield, 1.64 g, 36%) was obtained in a similar manner starting from **2a** (R = $CH_3$, 2.14 g, 10 mmol) in EtOH (5 ml), *p*-anisidine (1.23 g, 10 mmol) in EtOH (22.5 ml), isoamyl nitrite (1.35 ml, 10 mmol) and 2 N HCl (15 ml, 30 mmol). Product:

yellow needles. *Anal.* Calcd for $C_{20}H_{21}ClN_4O_2$: C, 52.47; H, 5.06; N, 12.23. Found: C, 52.64; H, 4.69; N, 12.28.

**5-Methyl-6-phenylselenenyl-9,10-dihydro-5*H*-azepino[1,2-*a*]benzimidazol-7(8*H*)-one (27)** A mixture of **2a** (R = $CH_3$, 1.07 g, 5 mmol), phenylselenenyl chloride (0.96 g, 5 mmol) and $CHCl_3$ (10 ml) was stirred for 2.5 h at room temperature, and the solvent was evaporated under reduced pressure. The viscous residue was purified by chromatography on silica gel (solvent: AcOEt–MeOH, 5 : 1). The solvent was evaporated to give a crystalline mass, which was recrystallized from AcOEt–*n*-hexane to give pale yellow powder; yield, 1.38 g (75%). *Anal.* Calcd for $C_{19}H_{18}N_2OSe$: C, 61.79; H, 4.91; N, 7.59. Found: C, 61.64; H, 5.12; N, 7.27.

**8-(1-Hydroxy-1-methylethyl)-5-methyl-9,10-tetrahydro-5*H*-azepino-[1,2-*a*]benzimidazol-7(8*H*)-one (17a)** Powdered **2a** (R = $CH_3$, 1.07 g, 5 mmol) was added at −78 °C under an $N_2$ atmosphere to a solution of LDA (5.1 mmol), which was prepared in a usual manner, and the mixture was stirred for 15 min. Acetone (0.39 ml, 5.25 mmol) was added to the mixture, and the reaction was quenched after 1 h by addition of water (10 ml). The resulting mixture was extracted with AcOEt (100 ml) followed by washing of the organic phase with brine. Evaporation of the solution after drying with $Na_2SO_4$ gave a crystalline residue, which was recrystallized from AcOEt to give colorless needles; yield, 0.78 g (58%). *Anal.* Calcd for $C_{16}H_{20}N_2O_2$: C, 82.51; H, 5.86; N, 7.40. Found: C, 82.27; H, 6.10; N, 7.18.

**5-Methyl-8-(diphenylhydroxymethyl)-9,10-tetrahydro-5*H*-azepino[1,2-*a*]benzimidazol-7(8*H*)-one (17b)** **17b** (yield, 0.80 g, 50%) was obtained in a similar manner starting from **2a** (R = $CH_3$, 0.86 g, 4.0 mmol), LDA (4.2 mmol) and benzophenone (0.74 g, 4.2 mmol). *Anal.* Calcd for $C_{26}H_{24}N_2O_2$: C, 78.76; H, 6.10; N, 7.07. Found: C, 78.53; H, 6.10; N, 7.14.

**5-Methyl-8-diphenylmethylene-9,10-tetrahydro-5*H*-azepino[1,2-*a*]benzimidazol-7(8*H*)-one (18b)** The hydroxy ketone (**17b**, 0.60 g, 1.5 mmol) was stirred in $SOCl_2$ (0.58 ml, 8 mmol) for 5 min at room temperature. Excess reagent was removed by evaporation under reduced pressure. The residue was treated with water (5 ml) and $CHCl_3$ (25 ml), and the aqueous phase was basified with powdered $K_2CO_3$ under shaking. The $CHCl_3$ phase was separated and dried with $Na_2SO_4$, followed by evaporation under reduced pressure to give a crystalline residue. Recrystallization of the crude product gave pale yellow needles; yield, 0.39 g (67%), mp 255—257 °C. IR (KBr) $cm^{-1}$: 1560 (C=O). $^1$H-NMR (80 MHz in $CDCl_3$) ppm: 2.99 (t, 2H, $-CH_2C\underline{H}_2C-$, $J$ = 6 Hz), 3.46 (s, 3H, $-NC\underline{H}_3$), 3.85 (t, 2H, $-NC\underline{H}_2-$, $J$ = 6 Hz), 5.15 (s, 1H, $C=C\underline{H}CO-$), 6.96—7.41 (m, 14H, aromatic protons). *Anal.* Calcd for $C_{26}H_{22}N_2O$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.53; H, 7.46; N, 10.21.

**References and Notes**

1) Examples of the imidazole-contained drug: cimetidine, clotrimazole, miconazole, ozagrel, nizofenone, histidine, histamine; examples of the benzimidazole-contained drug: omeprazole, cremizole, mebendazole, cyanocobalamine.
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