Synthesis and Application of Imidazole Derivatives. Synthesis of 5-Methyl-7,8,9,10-tetrahydro-5*H*-azepino[1,2-*a*]benzimidazol-7-one and Related Compounds[1)]

Shunsaku OHTA,* Yoshihiro NARITA, Masao OKAMOTO, Shoko HATAKEYAMA, Keizo KAN, Teruyuki YUASA, and Kumiko HAYAKAWA

Kyoto Pharmaceutical University, Misasagi-nakauchicho 5, Yamashina-ku, Kyoto 607, Japan. *Received May 20, 1989*

5-Methyl-7,8,9,10-tetrahydro-5*H*-azepino[1,2-*a*]benzimidazol-7-one (6) was synthesized by treating 1-(3-carboxypropyl)-2,3-dimethylbenzimidazolium iodide (11) with 1,1′-carbonyldiimidazole in the presence of triethylamine. Refluxing 2-(5-chloro-2-oxopentyl)-1-methylbenzimidazole (4) in ethyl acetate did not afford 6 but gave (*Z*)-1-methyl-2-(2,3,4,5-tetrahydro-2-furylidenemethyl)benzimidazole (5), which was rearranged to the corresponding (*E*)-isomer (7) by heating in ethyl acetate in the presence of basic alumina. The structures of 5, 6 and 7 were determined by X-ray crystallography.

Keywords benzimidazole; azepino[1,2-*a*]benzimidazole; 2-(2-furylidenemethyl)benzimidazole; rearrangement; cyclization; X-ray crystallography; stereochemistry; 1-acylimidazole

Imidazole is an important heterocycle in the field of organic synthesis especially since Staab exploited the chemistry of 1-acylimidazoles in 1962.[2)] Recently, we have reported some applications of 2-acylimidazole to organic synthesis.[3)] The imidazole ring or benzimidazole ring is included in a variety of clinically useful drugs and biologically active substances,[4,5)] and the seven-membered azepine ring is also included in several psychotherapeutic drugs such as imipramine.

Thus, we wished to synthesize compounds which include both heterocycles in the molecule, expecting some interesting biological activities. This paper deals with a new synthetic route to the fused heterotricyclic system, azepino[1,2-*a*]benzimidazole. In the literature, the azepino[1,2-*a*]benzimidazole ring system has been constructed in relatively low yields mainly in the following ways[6)]: i) cyclization of 1-(2-substituted-phenyl)azepine derivatives[7)] ii) cyclization of 2-(ω-bromo-alkyl)benzimidazole derivatives,[8)] and iii) oxidative cyclization of 2-methylbenzimidazole and 1,2-dimethylbenzimidazole by treatment with dimethyl acetylenedicarboxylate (DMAD).[9)] We planned to construct the skeleton starting from commercially available benzimidazole derivatives, and we also wished to introduce a functional group such as a carbonyl group on the azepine ring in order to perform further derivatizations. The known routes i) and iii) to the ring system seem to be unsatisfactory for our requirements, so Deselm's procedure ii)[7)] was first examined.

The planned scheme is shown in Chart 1, and the key reaction is an intramolecular cyclization of the chloride (**4**) to **6**. Treatment of a solution of 2-lithiomethyl-1-methylbenzimidazole (**2**)[10)] in tetrahydrofuran (THF) with γ-butyrolactone gave 2-(5-hydroxy-2-oxopentyl)-1-methylbenzimidazole (**3**) in 95% yield. The ferric chloride test of the hydroxyketone (**3**) is positive, and the proton nuclear resonance spectrum (^{1}H-NMR) of the compound in $CDCl_3$ showed the signal of a vinylic proton in the enol form at 4.05 ppm (s, almost 1H). These data indicated that the enol form may be preferred to the keto-form (**3**). The enol form may arise from the electron attractive effect of the imidazole ring in addition to the conjugation and interaction (chelation) of the enol group with the imidazole ring. The hydroxyketone (**3**)

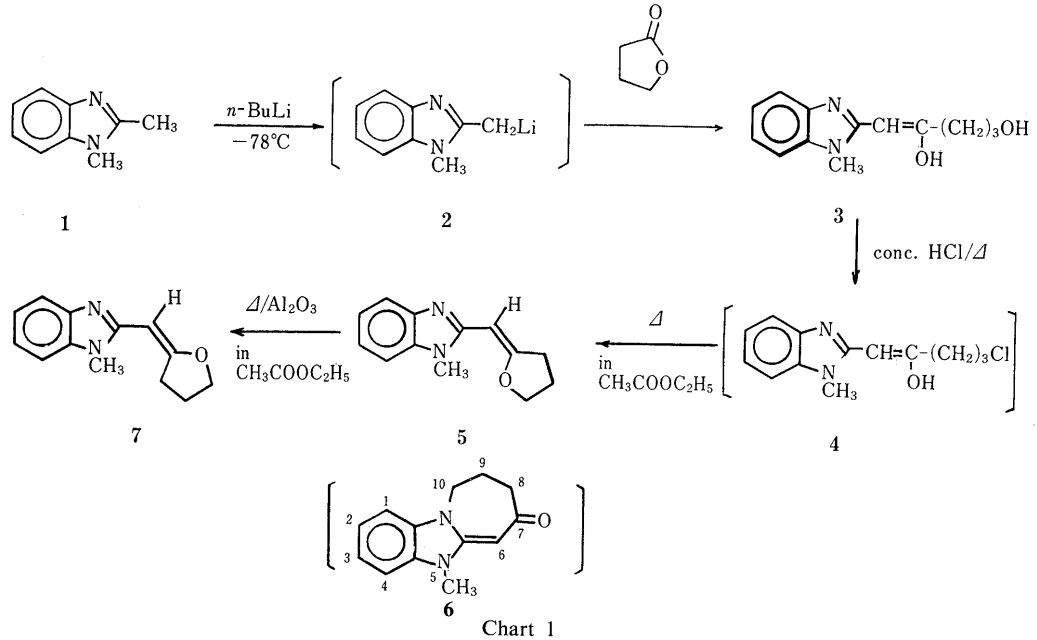
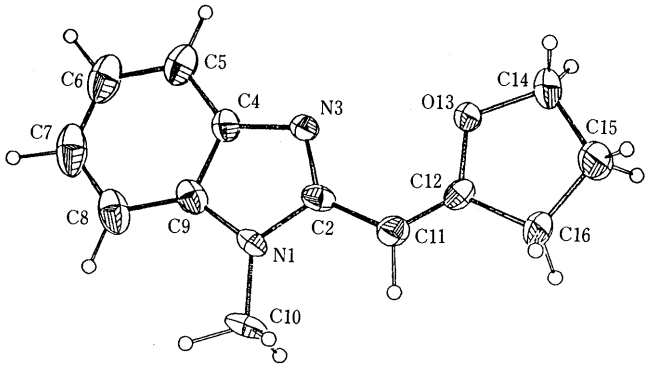


Chart 1

TABLE I. Atomic Co-ordinates for Compounds **5**, **6** and **7**

Atom	*x*	*y*	*z*	*B*
Compound **5**				
N(1)	0.21676	−0.03266	0.49278	0.010317
C(2)	0.28774	0.05598	0.45849	0.012335
N(3)	0.26234	0.06911	0.33584	0.013454
C(4)	0.16951	−0.01418	0.28777	0.010247
C(5)	0.10172	−0.03740	0.16302	0.016356
C(6)	0.00713	−0.12566	0.14127	0.016356
C(7)	−0.02188	−0.18922	0.24162	0.011427
C(8)	0.04261	−0.16709	0.36665	0.010893
C(9)	0.13849	−0.07845	0.38600	0.009918
C(10)	0.23407	−0.07522	0.61774	0.019398
C(11)	0.37525	0.12215	0.55368	0.013925
C(12)	0.43144	0.21133	0.53697	0.008622
O(13)	0.42463	0.25452	0.42326	0.021443
C(14)	0.49190	0.35661	0.43198	0.035199
C(15)	0.56010	0.37223	0.56784	0.064286
C(16)	0.51494	0.28189	0.63917	0.019261
Compound **6**				
N(1)	0.8921	0.4292	0.7088	0.004367
C(2)	0.8122	0.3353	0.6696	0.005837
C(3)	0.7722	0.2451	0.7612	0.005699
C(4)	0.6901	0.1437	0.7404	0.008177
C(5)	0.6261	0.1053	0.6042	0.008266
C(6)	0.6885	0.1607	0.4885	0.018011
C(7)	0.6998	0.2723	0.4455	0.008680
N(8)	0.7815	0.3500	0.5356	0.006167
C(9)	0.8437	0.4560	0.4922	0.005740
C(10)	0.8416	0.5094	0.3664	0.007942
C(11)	0.9139	0.6166	0.3572	0.008720
C(12)	0.9849	0.6666	0.4673	0.008410
C(13)	0.9873	0.6117	0.5927	0.006250
C(14)	0.9131	0.5051	0.6010	0.005509
C(15)	0.9480	0.4486	0.8435	0.005866
O(16)	0.6602	0.0759	0.8382	0.009281
Compound **7**				
N(1)	0.39294	0.05406	0.81692	0.005490
C(2)	0.31001	0.11793	0.87666	0.005742
N(3)	0.20490	0.07924	0.93463	0.005755
C(4)	0.22110	−0.01557	0.91410	0.005050
C(5)	0.14463	−0.09111	0.96096	0.007677
C(6)	0.18801	−0.18132	0.92903	0.007677
C(7)	0.30563	−0.19592	0.84911	0.010016
C(8)	0.38298	−0.12183	0.80331	0.008528
C(9)	0.34014	−0.03426	0.83819	0.004521
C(10)	0.51537	0.07140	0.73841	0.007031
C(11)	0.33982	0.21773	0.87084	0.007187
C(12)	0.25405	0.28522	0.89606	0.007401
O(13)	0.29292	0.37631	0.88941	0.007896
C(14)	0.17656	0.43802	0.88847	0.011054
C(15)	0.07580	0.38126	0.97418	0.009533
C(16)	0.10931	0.27822	0.93235	0.006966

was converted to the chloride (**4**) by heating with concentrated hydrochloric acid. A solution of the free base of the crude chloride (**4**) in ethyl acetate was heated at 100 °C to precipitate crystals. The infrared (IR) spectrum of the corresponding free base (mp 142.5—144 °C) showed a strong absorption band at the ν C=O region (1660 cm^{-1}), and the ^{1}H-NMR spectrum showed the signal of the vinylic proton (t, 1H, J=1 Hz) at 5.32 ppm. We initially assigned the azepine structure (**6**) to the product, but the furylidene structure **5** or **7** may also be possible on the basis of the triplet signal at 5.32 ppm in the ^{1}H-NMR spectrum. So, we subjected the crystalline free base (mp 142.5—144 °C) of the product to X-ray structure analysis. As shown in Tables I, II and



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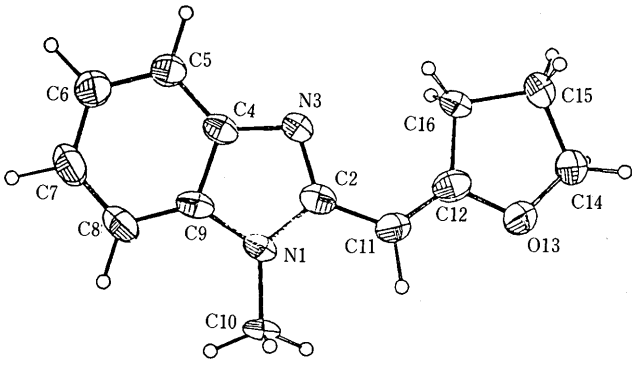

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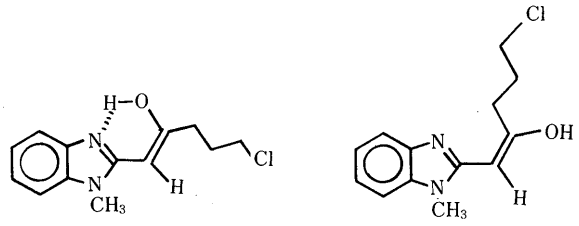
Fig. 1



(*Z*)-4′ (*E*)-4′

Chart 2

III and Fig. 1, the compound was identified as the (*Z*)-1-methyl-2-(1,2,3,4-tetrahydro-2-furylidenemethyl)benzimidazole (**5**). This structure (**5**) is consistent with the spectral data given above.

We carefully examined the cyclization reaction (**4**→**5**) again, but the corresponding (*E*)-isomer (**7**) could not be detected in the reaction mixture. The exclusive formation of the (*Z*)-isomer (**5**) from the chloride (**4**) may be explained by consideration of a six-membered chelating enol form (*Z*)-**4** rather than the unfavorable enol form (*E*)-**4**′ (Chart 2). When a solution of the (*Z*)-isomer (**5**) in ethyl acetate was heated at 90 °C for 2 h in the presence of basic alumina, interestingly, the starting material completely disappeared and a sole crystalline product (mp 110—111 °C) was formed. The spectral data of the product were very similar to those of **5** and the molecular formula was the same as that of **5**. We presumed that

TABLE II. Bond Lengths (Å) with the Estimated Standard Deviations ($\times 10^3$) in Parentheses

Atoms	Distance (Å)	Atoms	Distance (Å)	Atoms	Distance (Å)
Compound **5**					
N(1)–C(2)	1.393 (12)	N(1)–C(9)	1.376 (12)	N(1)–C(10)	1.474 (13)
C(2)–N(3)	1.341 (12)	C(2)–C(11)	1.456 (13)	N(3)–C(4)	1.391 (12)
C(4)–C(5)	1.420 (15)	C(4)–C(9)	1.434 (14)	C(5)–C(6)	1.397 (17)
C(6)–C(7)	1.442 (19)	C(7)–C(8)	1.415 (19)	C(8)–C(9)	1.404 (16)
C(11)–C(12)	1.306 (13)	C(12)–O(13)	1.372 (12)	C(12)–C(16)	1.534 (14)
O(13)–C(14)	1.475 (16)	C(14)–C(15)	1.514 (24)	C(15)–C(16)	1.522 (22)
Compound **6**					
N(1)–C(2)	1.362 (14)	N(1)–C(14)	1.394 (14)	N(1)–C(15)	1.468 (15)
C(2)–C(3)	1.420 (16)	C(2)–N(8)	1.384 (14)	C(3)–C(4)	1.399 (17)
C(4)–C(5)	1.556 (19)	C(4)–C(5)	1.556 (19)	C(5)–C(6)	1.530 (23)
C(6)–C(7)	1.529 (23)	C(7)–N(8)	1.480 (16)	N(8)–C(9)	1.405 (14)
C(9)–C(10)	1.397 (17)	C(9)–C(14)	1.390 (15)	C(10)–C(11)	1.397 (18)
C(11)–C(12)	1.412 (19)	C(12)–C(13)	1.405 (18)	C(13)–C(14)	1.398 (16)
Compound **7**					
N(1)–C(2)	1.366 (18)	N(1)–C(9)	1.390 (18)	N(1)–C(10)	1.477 (20)
C(2)–N(3)	1.332 (18)	C(2)–C(11)	1.460 (20)	N(3)–C(4)	1.378 (17)
C(4)–C(5)	1.406 (20)	C(4)–C(9)	1.439 (19)	C(5)–C(6)	1.396 (22)
C(6)–C(7)	1.434 (24)	C(7)–C(8)	1.393 (24)	C(8)–C(9)	1.365 (22)
C(11)–C(12)	1.330 (20)	C(12)–O(13)	1.363 (17)	C(12)–C(16)	1.531 (20)
O(13)–C(14)	1.468 (20)	C(14)–C(15)	1.529 (24)	C(15)–C(16)	1.557 (22)

TABLE III. Bond Angles with the Estimated Standard Deviations ($\times 10^2$) in Parentheses

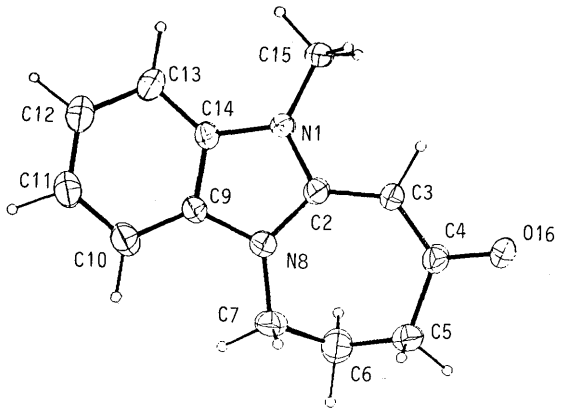
Atoms	Angle (°)	Atoms	Angle (°)
Compound **5**			
C(2)–N(1)–C(9)	107.08 (74)	C(2)–N(1)–C(10)	127.39 (78)
C(9)–N(1)–C(10)	125.33 (79)	N(1)–C(2)–N(3)	112.61 (78)
N(1)–C(2)–C(11)	119.40 (80)	N(3)–C(2)–C(11)	127.99 (85)
C(2)–N(3)–C(4)	104.91 (75)	N(3)–C(4)–C(5)	129.14 (88)
N(3)–C(4)–C(9)	110.00 (80)	C(5)–C(4)–C(9)	120.79 (89)
C(4)–C(5)–C(6)	116.98 (101)	C(5)–C(6)–C(7)	121.18 (115)
C(6)–C(7)–C(8)	122.83 (125)	C(7)–C(8)–C(9)	114.89 (112)
N(1)–C(9)–C(4)	105.39 (80)	N(1)–C(9)–C(8)	131.29 (95)
C(4)–C(9)–C(8)	123.31 (95)	C(2)–C(11)–C(12)	126.39 (89)
C(11)–C(12)–O(13)	123.85 (86)	C(11)–C(12)–C(16)	125.65 (87)
O(13)–C(12)–C(16)	110.50 (77)	C(12)–O(13)–C(14)	112.28 (84)
O(13)–C(14)–C(15)	104.89 (118)	C(14)–C(15)–C(16)	108.87 (136)
C(12)–C(16)–C(15)	103.16 (102)		
Compound **6**			
C(2)–N(1)–C(14)	109.6 (90)	C(2)–N(1)–C(15)	125.7 (90)
C(14)–N(1)–C(15)	124.8 (90)	N(1)–C(2)–C(3)	121.3 (100)
N(1)–C(2)–N(8)	107.7 (90)	C(3)–C(2)–N(8)	131.0 (100)
C(2)–C(3)–C(4)	129.6 (110)	C(3)–C(4)–C(5)	125.3 (110)
C(3)–C(4)–O(16)	119.8 (120)	C(5)–C(4)–O(16)	114.8 (110)
C(4)–C(5)–C(6)	113.7 (120)	C(5)–C(6)–C(7)	113.7 (140)
C(6)–C(7)–N(8)	111.7 (120)	C(2)–N(8)–C(7)	129.0 (100)
C(2)–N(8)–C(9)	108.4 (90)	C(7)–N(8)–C(9)	122.6 (90)
N(8)–C(9)–C(10)	130.0 (100)	N(8)–C(9)–C(14)	107.2 (90)
C(10)–C(9)–C(14)	122.8 (100)	C(9)–C(10)–C(11)	115.6 (110)
C(10)–C(11)–C(12)	121.8 (120)	C(11)–C(12)–C(13)	122.1 (120)
C(12)–C(13)–C(14)	115.3 (110)	N(1)–C(14)–C(9)	107.2 (90)
N(1)–C(14)–C(13)	130.4 (100)	C(9)–C(14)–C(13)	122.4 (100)
Compound **7**			
C(2)–N(1)–C(9)	107.60 (110)	C(2)–N(1)–C(10)	128.32 (117)
C(9)–N(1)–C(10)	124.05 (116)	N(1)–C(2)–N(3)	113.31 (118)
N(1)–C(2)–C(11)	120.19 (122)	N(3)–C(2)–C(11)	126.55 (126)
C(2)–N(3)–C(4)	104.79 (108)	N(3)–C(4)–C(5)	130.29 (123)
N(3)–C(4)–C(9)	110.54 (114)	C(5)–C(4)–C(9)	119.12 (123)
C(4)–C(5)–C(6)	117.72 (132)	C(5)–C(6)–C(7)	120.86 (148)
C(6)–C(7)–C(8)	122.06 (157)	C(7)–C(8)–C(9)	116.17 (151)
N(1)–C(9)–C(4)	103.74 (114)	N(1)–C(9)–C(8)	132.20 (136)
C(4)–C(9)–C(8)	124.05 (135)	C(2)–C(11)–C(12)	124.20 (134)
C(11)–C(12)–O(13)	119.36 (129)	C(11)–C(12)–C(16)	129.73 (133)
O(13)–C(12)–C(16)	110.92 (116)	C(12)–O(13)–C(14)	109.87 (112)
O(13)–C(14)–C(15)	105.05 (128)	C(14)–C(15)–C(16)	103.40 (128)
C(12)–C(16)–C(15)	102.63 (116)		

the product is the (*E*)-isomer (**7**). The structure of the product was also determined by X-ray structure analysis as the expected (*E*)-1-methyl-2-(2,3,4,5-tetrahydro-2-furylidenemethyl)benzimidazole (**7**) as shown in Tables I, II and III and Fig. 1. The exclusive rearrangement of the (*Z*)-isomer (**5**) into the (*E*)-isomer (**7**) is probably due to the relative thermodynamic stability of **7** because of a possible electrostatic repulsion between the lone-pair electrons of the imidazole nitrogen and the furylidene oxygen in **5**.

Next, we planned to construct the azepino[1,2-*a*]benzimidazole skeleton by intramolecular acylation of an appropriate derivative of the 1-(3-carboxypropyl)-2,3-dimethylbenzimidazolium salt. 2-Methylbenzimidazole (**8**) was alkylated by treatment with sodium hydride in the presence of ethyl 4-bromobutyrate to give 1-(3-ethoxycarbonylpropyl)-2-methylbenzimidazole (**9**) in 90.6% yield. The ester (**9**) was hydrolyzed by treatment with 1 eq of sodium hydroxide in ethanol, and the reaction mixture was neutralized with an equimolar amount of 2 N hydrochloric acid to give the corresponding crystalline free carboxylic acid (**10**) in 82.5% yield. A suspension of the acid (**10**) in *tert*-butanol was refluxed in the presence of an excess amount of methyl iodide to afford easily the corresponding quaternary salt (**11**) in 93.2% yield. A suspension of the salt (**11**) in acetonitrile was treated with *N*,*N*′-carbonyldiimidazole (CDI) in the presence of an equimolar amount of triethylamine to give the desired azepino[1,2-*a*]benzimidazole (**6**) *via* **12** in 59.7% yield as pale yellow crystals [mp 177—178.5 °C (dec.)]. The ^{1}H-NMR spectrum of the product is consistent with either the azepino[1,2-*a*]benzimidazole structure (**6**) or the furylidene structure (**5** or **7**). The IR spectrum ($CHCl_3$) rather supports the furylidene structure (**5** or **7**) on the basis of the absence of any ν C=O absorption band in the 1800—1600 cm^{-1} region. The structure of the product could be determined by X-ray structure analysis as **6** or **6**′.[11] As shown in Table II, the bond lengths of N1–C2, C2–C3, C3–C4 and C4–O16

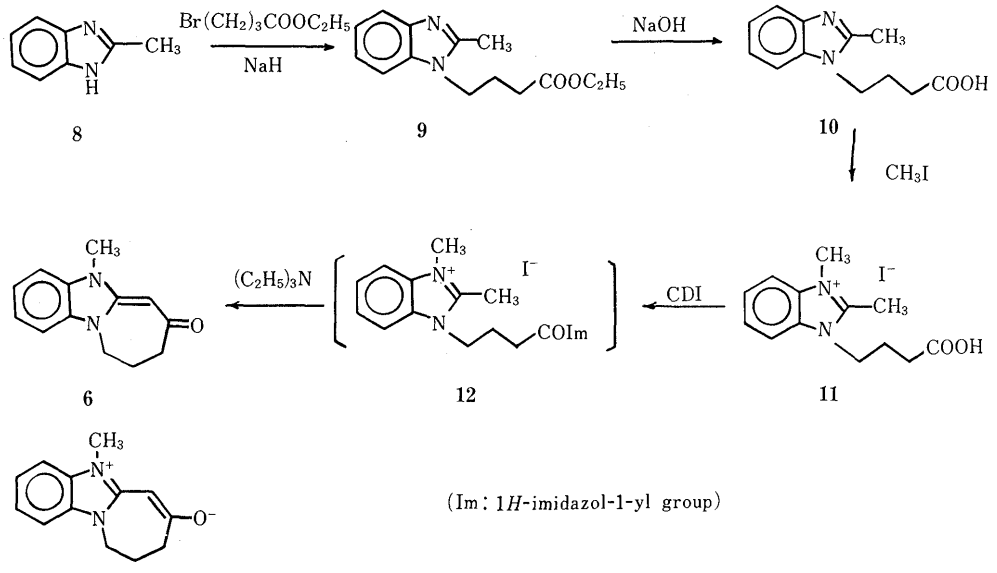
of compound **6** were observed as 1.326, 1.420, 1.399 and 1.269 Å, respectively. These N–C, C–C and C–O bond lengths are all intermediate values compared with the normal covalent bond lengths of N–C (1.47 Å)—N=C (1.30 Å), C–C (1.54 Å)—C=C (1.35 Å) and C–O (1.43 Å)—C=O (1.22 Å), respectively. These observed values and the absence of the carbonyl group absorption in the IR spectrum can be explained by consideration of the dipole structure (**6′**) for the product rather than the keto-form (**6**). In the description below, however we use the keto structure (**6**) for the convenience.

We wished to prepare the 5-benzyl analogue (**16**) in order to introduce an appropriate alkyl substituent at the 5-position *via* the debenzylated intermediate **17**. The ester (**9**) was converted to the corresponding quaternary salt (**13**) by treatment with benzyl bromide. The salt (**13**) was hydrolyzed with sodium hydroxide solution to give the carboxylic acid (**14**) in 70.6% yield, and this was converted to the 5-benzyl-1,2,3,4-tetrahydro-5*H*-azepino-[1,2-*a*]benzimidazol-7-one (**16**) in 62.3% yield from **14** in a similar manner to that used in the reaction of **11**→**6**. Unfortunately, several attempts to achieve the hydrogenolytic removal of the benzyl group of **16** to provide



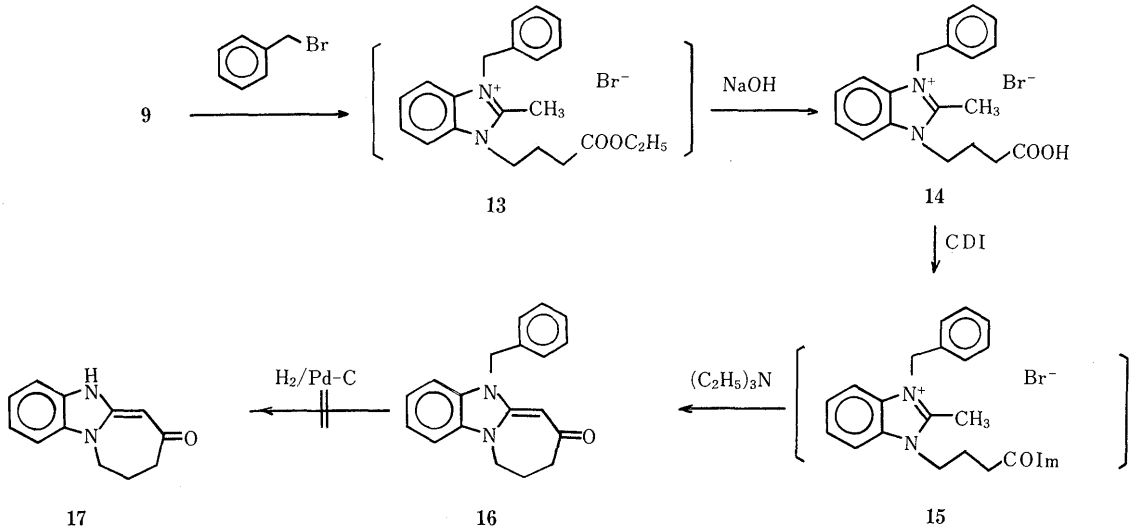
6 (6′)

Fig. 2



8 **9** **10** **11** **12** **6** **6′**

Chart 3



9 **13** **14** **15** **16** **17**

Chart 4

the corresponding azepinone (**17**) were all unsuccessful.

Other derivatizations of the azepino[1,2-*a*]benzimidazole (**6**) and application of the present cyclization procedure for the synthesis of pyrido- and pyrrolobenzimidazole derivatives are under investigation.

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 at 300 MHz on a Varian XL-300 spectrometer, and the chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard. Abbreviations of ^{1}H-NMR signal patterns are as follows: s (singlet); d (doublet); t (triplet); quar (quartet); quin (quintet); m (multiplet); br (broad). The ultraviolet (UV) spectra were obtained on a Shimadzu UV-200S spectrometer. Mass spectra (MS) were obtained on a Hitachi M-80 spectrometer. All solvents were removed under reduced pressure by using a rotary evaporator in the usual work-up procedure. Unless otherwise stated, anhydrous sodium sulfate was used as a drying agent. A Kugel-Rohr apparatus was used for vacuum distillations of crude oily products. Silica gel (Merck Art. 7734) was used in column chromatography.

2-(5-Hydroxy-2-oxopentyl)-1-methylbenzimidazole (3) *n*-BuLi (45.4 ml of 1.6 M hexane solution; 71.0 mmol) was added at −78 °C to a solution of 1,2-dimethylbenzimidazole (10.36 g, 71.0 mmol), and tetramethylethylenediamine (TMEDA, 12.8 ml, 85.2 mmol) in tetrahydrofuran (THF, 100 ml). The solution was stirred at room temperature for 1 h, and then cooled again to −78 °C followed by addition of γ-butyrolactone (5.45 ml, 71 mmol). The mixture was stirred for 1 h at room temperature, then 10% HCl (100 ml) and ethyl acetate (100 ml) were added to it. The aqueous layer was basified by addition of powdered K_2CO_3 to liberate a free base, which was extracted several times into $CHCl_3$. Removal of the solvent gave a crystalline residue, recrystallization of which gave colorless needles. mp 89.5—91.0 °C. Yield, 15.63 g (95.0%). IR ν_{max}^{KBr} cm^{-1}: 1715 (C=O). ^{1}H-NMR (in $CDCl_3$; enol form) δ: 1.81—2.77 (m, 4H, -(C$\underline{H}_2$)$_2$-OH), 3.28 (d-like, 1H, =C(O$\underline{H}$)-CH$_2$-, J=2 Hz), 3.51—3.89 (s+m, 5H, N-C$\underline{H}_3$ + =C(OH)C$\underline{H}_2$-), 4.05 (s, 1H, -C$\underline{H}$=C(OH)-), 7.15—7.34 (m, 3H, aromatic protons), 7.64—7.75 (m, 1H, aromatic proton). High-resolution MS *m/z*: Calcd for $C_{13}H_{16}N_2O_2$=232.1212. Found=232.1215.

(*Z*)-1-Methyl-2-(2,3,4,5-tetrahydro-2-furylidenemethyl)benzimidazole (5) A solution of **3** (13.8 g, 59.5 mmol) in concentrated HCl (200 ml) was heated at 100 °C for 2 h, and then evaporated. A solution of the residue in water (100 ml) was basified by addition of solid K_2CO_3 followed by extractions with ethyl acetate (100, 50, 50 ml). The combined organic layer was refluxed for 2 h at 100 °C, and cooled to give crystalline precipitates, which were collected by suction. A solution of the precipitates (the hydrochloride of **5**) in water (50 ml) was basified by addition of powdered K_2CO_3. The liberated free base was extracted with ethyl acetate. After removal of the solvent, the residue was recrystallized from ethyl acetate to give colorless prisms. mp 142.5—144 °C. Yield, 10.82 g (85.2%). IR ν_{max}^{KBr} cm^{-1}: 1660 (C=C). ^{1}H-NMR (300 MHz in $CDCl_3$) δ: 2.07 (quin, 2H, -CH$_2$C$\underline{H}_2$CH$_2$-, J=7 Hz), 2.81 (t, 2H, =C-C$\underline{H}_2$-, J=9 Hz), 3.62 (s, 3H, N-C$\underline{H}_3$), 4.49 (t, 2H, -OC$\underline{H}_2$-, J=7 Hz), 5.32 (t, 1H, -C$\underline{H}$=C-, J=1 Hz), 7.15—7.19 (m, 3H, aromatic protons), 7.75—7.79 (m, 1H, aromatic proton). ^{13}C-NMR (75 MHz in $CDCl_3$) δ: 164.60 (-C=C≺), 150.48, 143.71, 121.34 (2C), 119.18, 119.18 and 108.37 (aomatic carbons), 134.89 (-N=C-N≺), 83.46 (-C$\underline{H}$=C), 73.83 (-OC$\underline{H}_2$-), 32.05 (=C-C$\underline{H}_2$-), 29.68 (N-C$\underline{H}_3$), 24.01 (-CH$_2$C$\underline{H}_2$CH$_2$-). UV λ_{max}^{EtOH} nm (log ε): 242 (4.23), 308 (4.35), 321 (4.12). *Anal.* Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.64; H, 6.74; N, 12.84.

(*E*)-1-Methyl-2-(2,3,4,5-tetrahydro-2-furylidenemethyl)benzimidazole (7) A solution of **5** (1.00 g, 4.67 mmol) in ethyl acetate (50 ml) was refluxed for 2 h at 90 °C under a nitrogen atmosphere in the presence of basic alumina (10 g; Merck, 70—230 mesh). After removal of the alumina by filtration, the solvent was evaporated to leave a crystalline residue, which was recrystallized from ether to give colorless prisms. mp 110—111 °C. Yield, 1.00 g (quantitative). IR ν_{max}^{KBr} cm^{-1}: 1660 (C=C). ^{1}H-NMR (300 MHz in $CDCl_3$) δ: 2.13 (quin, 2H, -CH$_2$C$\underline{H}_2$CH$_2$-, J=7 Hz), 3.32 (t, 2H, =C-C$\underline{H}_2$-, J=8 Hz), 3.61 (s, 3H, N-C$\underline{H}_3$), 4.23 (t, 2H, -COC$\underline{H}_2$-, J=7 Hz), 5.84 (t, 1H, -C$\underline{H}$=C-, J=2 Hz), 7.16—7.20 (m, 3H, aromatic protons), 7.65—7.68 (m, 1H, aromatic proton). ^{13}C-NMR (75 MHz in $CDCl_3$) δ: 168.77 (-C=C≺), 152.41, 143.58, 121.50, 121.13, 118.27 and 108.39 (aromatic carbons), 135.35 (-N=C-N-), 84.88 (-C$\underline{H}$=C≺), 71.32 (-OC$\underline{H}_2$-), 30.27 (=C-C$\underline{H}_2$-), 29.45 (N-C$\underline{H}_3$), 24.62 (-CH$_2$C$\underline{H}_2$CH$_2$-). UV λ_{max}^{EtOH} nm (log ε): 241 (4.26), 304 (4.39). *Anal.* Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.85; H, 6.36; N, 12.74.

1-(3-Ethoxycarbonylpropyl)-2-methylbenzimidazole (9) 2-Methylbenzimidazole (8.00 g, 60.6 mmol) was added under a nitrogen atmosphere at 0 °C to a suspension of 97% NaH (1.65 g, 66.7 mmol) in THF (60 ml), and then ethyl 4-bromo-*n*-butyrate (13.0 g, 66.7 mmol) was added dropwise to the mixture at 0 °C followed by stirring for 2 h at room temperature. After careful addition of water (10 ml), the mixture was extracted with ethyl acetate (100 ml × 3). Evaporation of the solvent gave an oily residue, which was distilled under vacuum to give a pale yellow oil. bp 153—158 °C (2 mmHg). Yield, 13.50 g (90.6%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (C=O). ^{1}H-NMR (in $CDCl_3$) δ: 1.24 (t, 3H, -CH$_2$C$\underline{H}_3$, J=7 Hz), 2.02—2.43 (m, 4H, -C$\underline{H}_2$CH$_2$CO-), 2.60 (s, 3H, -C$\underline{H}_3$), 4.00—4.23 (m, 4H, ≻N-C$\underline{H}_2$- and -OC$\underline{H}_2$-), 7.14—7.32 (m, 3H, aromatic protons), 7.62—7.73 (m, 1H, aromatic proton). High-resolution MS *m/z*: Calcd for $C_{14}H_{18}N_2O_2$=246.1368. Found=246.1369.

1-(3-Carboxypropyl)-2-methylbenzimidazole (10) A 4 N NaOH solution (15.0 ml, 60 mmol) was added to a solution of **9** (10.00 g, 40.7 mmol) in EtOH (20 ml), and the solution was stirred for 30 min at room temperature. The mixture was neutralized by addition of 2 N HCl (30.1 ml, 60.2 mmol) followed by evaporation to give a crystalline residue. The residue was recrystallized from methanol to give colorless needles. mp 202.5—204 °C. Yield, 7.30 g (82.5%). IR ν_{max}^{KBr} cm^{-1}: 3450 (OH), 1720 (COOH). ^{1}H-NMR (DMSO-d_6) δ: 1.92 (quin, 2H, -CH$_2$C$\underline{H}_2$CH$_2$-, J=6 Hz), 2.30 (t, 2H, -C$\underline{H}_2$CO-, J=6 Hz), 2.53 (s, 3H, -C$\underline{H}_3$), 4.19 (t, 2H, N-C$\underline{H}_2$-, J=7 Hz), 7.09—7.27 (m, 2H, aromatic protons), 7.41—7.60 (m, 2H, aromatic protons). UV λ_{max}^{EtOH} nm (log ε): 252 (3.88), 275 (3.78), 282 (3.85). MS *m/z*: 218 (M$^+$). *Anal.* Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 65.92; H, 6.66; N, 12.81.

1-(3-Carboxypropyl)-2,3-dimethylbenzimidazolium Iodide (11) A suspension of **10** (3.16 g, 14.5 mmol) in *tert*-BuOH (50 ml) was refluxed for 2 h at 80 °C in the presence of methyl iodide (4.8 ml, 72.5 mmol). The resulting precipitates were collected by suction followed by recrystallization from methanol. Colorless needles, mp 226—228 °C (dec.). Yield, 4.87 g (93.2%). IR ν_{max}^{KBr} cm^{-1}: 1735 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.99 (quin, 2H, -CH$_2$C$\underline{H}_2$CH$_2$-, J=6 Hz), 2.41 (t, 2H, -C$\underline{H}_2$CO-, J=6 Hz), 2.89 (s, 3H, -C$\underline{H}_3$), 3.89 (s, 3H, N-C$\underline{H}_3$), 4.51 (t, 2H, N-C$\underline{H}_2$-, J=7 Hz), 7.58—7.74 (m, 2H, aromatic protons), 7.89—8.09 (m, 2H, aromatic protons). *Anal.* Calcd for $C_{13}H_{17}IN_2O_2$: C, 43.35; H, 4.76; N, 7.78. Found: C, 43.32; H, 4.68; N, 7.90.

5-Methyl-7,8,9,10-tetrahydro-5*H*-azepino[1,2-*a*]benzimidazol-7-one Hydrochloride (6-HCl) CDI (2.20 g, 13.6 mmol) was added to a stirred suspension of **11** (4.40 g, 12.3 mmol) in acetonitrile (30 ml) under a nitrogen atmosphere, and the mixture was stirred for 1 h. The solution was refluxed for 12 h at 70 °C in the presence of triethylamine (5.1 ml, 36.9 mmol). The volatile portion of the resulting mixture was removed under reduced pressure followed by additions of water (30 ml) and ethyl acetate (90 ml) to the residue. The organic layer was dried over Na_2SO_4 after washing with saturated aqueous NaCl. Removal of the solvent under reduced pressure gave a viscous residue, a methanolic solution of which was passed through a column of 100 g of Amberlyst A-21 HCl form (Organo).[12] Evaporation of the eluate under reduced pressure gave a crystalline residue, which was recrystallized from 2-propanol. Colorless needles, mp 240 °C (dec.). Yield, 1.85 g (59.7%). The free base was obtained for measurement of the spectral data listed below in the usual manner, and it was recrystallized from benzene to give pale yellow needles. mp 177—178.5 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1550, 1570 (C=C and C=O). ^{1}H-NMR (in $CDCl_3$) δ: 2.08—2.35 (m, 2H, -CH$_2$C$\underline{H}_2$CH$_2$-), 2.81 (t, 2H, C$\underline{H}_2$CO-, J=6 Hz), 3.39 (s, 3H, N-C$\underline{H}_3$), 4.08 (t, 2H, N-C$\underline{H}_2$-, J=6 Hz), 5.00 (s, 1H, =C$\underline{H}$CO-), 6.96—7.28 (m, 4H, aromatic protons). UV λ_{max}^{EtOH} nm (log ε): 234 (4.02), 252 (4.03), 322 (4.45), 333 (4.40). MS *m/z*: 214 (M$^+$). *Anal.* Calcd for $C_{13}H_{15}ClN_2O$ (hydrochloride): C, 62.28; H, 6.03; N, 11.17. Found: C, 62.16; H, 6.04; N, 11.15.

3-Benzyl-1-(3-carboxylpropyl)-2-methylbenzimidazolium Bromide (14) A mixture of **9** (7.92 g, 32.2 mmol), benzyl bromide (4.59 ml, 38.6 mmol) and ethanol (8 ml) was stirred for 2 h at 60 °C. Removal of the solvent under reduced pressure gave a crystalline residue, which was recrystallized from $CHCl_3$ to give the ester (**13**) as colorless needles. mp 230—232 °C. Yield, 10.39 g (77.3%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (C=O). ^{1}H-NMR (in $CDCl_3$) δ: 1.17 (t, 3H, -CH$_2$C$\underline{H}_3$, J=7 Hz), 2.20—2.39 (m, 2H, ≻NCH$_2$C$\underline{H}_2$CH$_2$-), 2.63 (t, 2H, -C$\underline{H}_2$CO-, J=7.5 Hz), 3.26 (s, 3H, N=C-C$\underline{H}_3$), 4.18—3.91 (quar, 2H, -C$\underline{H}_2$CH$_3$, J=7 Hz), 4.76 (t=2H, >N-C$\underline{H}_2$-, J=8 Hz), 5.87 (s, 2H, C$_6$H$_5$C$\underline{H}_2$-), 7.32 (s, 5H, C$_6$H$_5$-), 7.40—

8.04 (m, 4H, aromatic protons).

The ester (**13**; 17.88 g, 42.9 mmol) was stirred for 30 min at room temperature in 4 N NaOH (50 ml, 200 mmol). The solution was neutralized by addition of 2 N HCl (100 ml, 200 mmol) followed by evaporation under reduced pressure to give **14** as a crystalline residue. Recrystallization of the crystals from 2-propanol gave colorless needles, mp 234—236 °C. Yield, 11.70 g (70.6% from **13**). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1700 (COOH). ^{1}H-NMR (in DMSO-d_6) δ: 2.03—2.15 (m, 2H, $\geq NCH_2C\underline{H}_2CH_2-$), 2.38—2.54 (m, 2H, $\geq NCH_2CH_2C\underline{H}_2-$), 2.98 (s, 3H, $-N=C-C\underline{H}_3$), 4.54 (t, 2H, $\geq NC\underline{H}_2-$, $J=8$ Hz), 5.81 (s, 2H, $C_6H_5C\underline{H}_2-$), 7.37 (s, 5H, $C_6\underline{H}_5-$), 7.55—8.15 (m, 4H, aromatic protons). *Anal.* Calcd for $C_{19}H_{21}BrN_2O_2$: C, 58.62; H, 5.44; N, 7.20. Found: C, 58.50; H, 5.52; N, 7.02.

5-Benzyl-7,8,9,10-tetrahydroazepino[1,2-*a*]benzimidazol-7-one (16) CDI (285 mg, 1.76 mmol) was added to a suspension of **14** (570 mg, 1.46 mmol) in acetonitrile (2.9 ml). The mixture was stirred for 30 min at 60 °C, then triethylamine (0.62 ml, 4.4 mmol) was added. The whole was refluxed for 1.5 h at 60 °C, then the solvent was evaporated off under reduced pressure. Water (20 ml) and ethyl acetate (20 ml) were added to the residue, and the ethyl acetate layer was dried over Na_2SO_4. Evaporation of the solvent gave a crystalline residue, which was recrystallized from ethyl acetate to give slightly brown needles. mp 110—112 °C. Yield, 265 mg (62.3%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1575, 1515 (C=C and C=O). ^{1}H-NMR (in $CDCl_3$) δ: 2.16—2.37 (m, 2H, $\geq NCH_2C\underline{H}_2CH_2-$), 2.18 (t, 2H, $-C\underline{H}_2CO-$, $J=8$ Hz), 4.14 (t, 2H, $\geq N-C\underline{H}_2-$), 5.05 (s, 1H, $\geq C=C\underline{H}CO-$), 5.08 (s, 2H, $C_6H_5-C\underline{H}_2-$), 7.01—7.64 (m, 9H, aromatic protons). *Anal.* Calcd for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.58; H, 6.30; N, 9.42.

Crystallographic Measurements The crystal data of **5**, **6** and **7** were collected on a Rigaku Denki AFC-5UD diffractometer using Cu-K_α radiation. The intensities of all the reflections with 2θ values from 5° to 130° of (hkl), ($\bar{h}kl$), ($hk\bar{l}$) and ($\bar{h}k\bar{l}$) were measured by the ω–2θ scanning technique [ω-interval = $(1.2+0.5\tan\theta)°$] at a scan rate of 4°/min for **5** and 8°/min for **6** and **7**. In total, 1897, 6354 and 1911 independent non-zero reflections were obtained in the measurements of **5**, **6** and **7**, respectively.

Crystal Data for **5**: $C_{13}H_{14}N_2O$. $M_r=214.27$. Monoclinic. $a=7.567(1)$, $b=13.580(1)$, $c=10.967(1)$ Å. $\beta=98.93°$ (1). $V=1113.4(2)$ Å^3. $D_x=1.278$ g/cm^3. $z=4$. Space group, $P2_1/c$. Crystal dimensions, $0.4\times0.3\times0.2$ mm.

Crystal Data for **6**: $(C_{13}H_{14}N_2)_3\cdot4H_2O$. $M_r=714.86$. Triclinic. $a=14.572(5)$, $b=14.399(6)$, $c=10.398(4)$ Å. $\alpha=80.00(8)$, $\beta=101.89(5)$, $\gamma=118.27°$ (3). $V=1873(1)$ Å^3. $D_x=1.267$ g/cm^3. $z=2$. Space group, $P\bar{1}$. Crystal dimensions, $0.45\times0.30\times0.25$ mm.

Crystal Data for **7**: $C_{13}H_{14}N_2O$. $M_r=214.27$. Monoclinic. $a=10.096(1)$, $b=14.297(1)$, $c=7.860(1)$ Å. $\beta=98.00°$ (1). $V=1123.4(2)$ Å^3. $D_x=1.267$ g/cm^3. $z=4$. Space group, $P2_1/c$. Crystal dimensions, $0.5\times0.5\times0.3$ mm.

Structure Analysis and Refinement for 5, 6 and 7 The structures were solved by direct methods using MULTAN 78, RANTAN and MULTAN78, respectively, and refined by the block-diagonal least-squares method with anisotropic factors. The final R-values for **5**, **6** and **7** were 0.152, 0.124 and 0.150, respectively. ORTEP drawings of the molecules, the atomic parameters, bond lengths, and bond angles are given in Figs. 1, 2 and Tables I, II and III, respectively.

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References and Notes

1) A part of the present work was presented at the 36th Kinkishibu Annual Meeting of the Pharmaceutical Society of Japan, November 1986.
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4) Examples of imidazole drugs: Micronazole, Ketoconazole, Clotrimazole, Nitronidazole, Cimetidine, Dazoxybene.
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11) The X-ray structure analysis of **6** met with some difficulty in the preparation of a suitable crystal and instability of the crystals on storage and measurement (they became colored and gradually became muddy). The R-factor of the X-ray analysis was relatively low (12.4%) in spite of the use of a collodion coated crystal.
12) We have conveniently applied the procedure (the method using Amberlyst A-21-HCl resin) to general conversion of organic bases into their hydrochlorides.