Diazepines I. A New Synthesis of 6-Phenyl-4*H*-imidazo[1,2-*a*][1,4]benzodiazepines

Takeshi Hara, Kazuhiko Itoh and Nobuhiro Itoh

Teijin Institute for Biomedical Research, 4-3-2 Asahigaoka, Hino, Tokyo 191, Japan

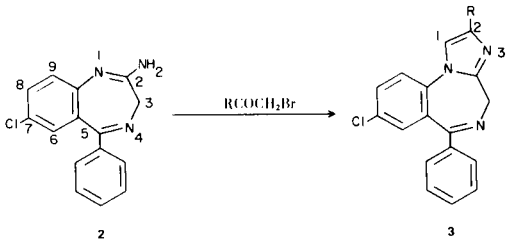
Received July 26, 1976

6-Phenyl-4*H*-imidazo[1,2-*a*][1,4]benzodiazepines are obtained on reaction of 2-amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine with α-bromoketones. In the cases of 3-bromo-2-butanone and of 3-bromo-2-pentanone, 2-alkylimidazobenzodiazepine but not 1,2-dialkyl compound is the major product. A mechanism for the imidazole ring formation is presented.

J. Heterocyclic Chem., 13, 1233 (1976).

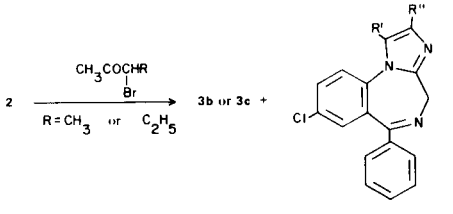
Considerable attention has been directed in recent years to the synthesis of tricyclic diazepine compounds possessing useful anxiolytic activity (1,2). This paper describes a new synthesis of 6-phenyl-4*H*-imidazo[1,2-*a*]-[1,4]benzodiazepines (2) by the action of the amidine moiety of the 2-aminobenzodiazepine **2** with α-bromoketones. Although this type of reaction for the formation of imidazole ring has been known for many years (3), it has not yet been studied in detail, particularly with respect

Scheme I



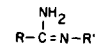
2 3

a R = CH_3
b R = C_2H_5
c R = $CH_2CH_2CH_3$
d R = $CH(CH_3)_2$
e R = $CH_2C_6H_5$



6

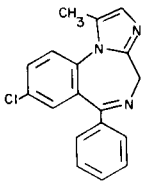
a R' = CH_3, R'' = CH_3
b R' = C_2H_5, R'' = CH_3



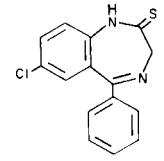
1

to *N*-substituted amidine (*viz.* **1**).

The 2-aminobenzodiazepine **2** (4) was heated with bromoacetone in ethanol to give the imidazobenzodiazepine **3a** (Scheme I). Even if one reasonably assumes that the nitrogen atom which makes a nucleophilic attack on bromoacetone is that of the 2-amino group, there are still two possible structures **3a** and **4** for the product imidazobenzodiazepine, corresponding to two possible sites of attack, namely the carbonyl group and the α-carbon atom. The reaction product was determined to be **3a** but not **4** through the comparison of the nmr spectrum of the product with that of **4** prepared according to reported procedure (2b), treating the thioamide **5** with propargylamine in the presence of *p*-toluenesulfonic acid. The



4



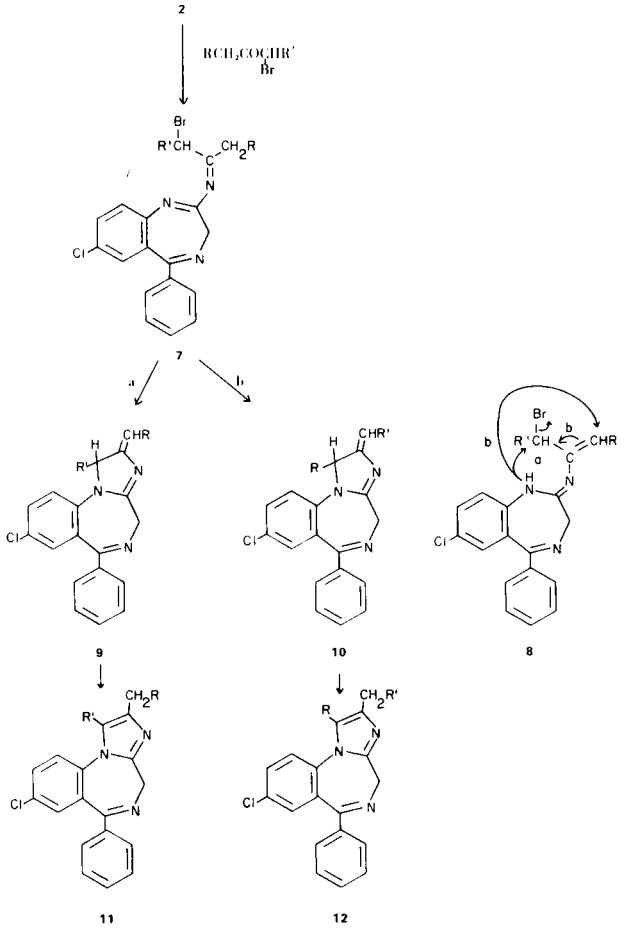
5

imidazole ring proton of **3a** (C_1-H) resonates at a lower magnetic field than that (C_2-H) of **4** (δ 7.05 *vs.* 6.83), and regarding the methyl proton signal the opposite is observed (δ 2.25 *vs.* 2.35). These can be attributed to the anisotropic deshielding effect of the benzene ring of the benzodiazepine skeleton on C_1-H and C_1-CH_3. Similarly are prepared the imidazobenzodiazepines **3b,c,d,e.** In the nmr spectra of all of these imidazobenzodiazepines **3a-e**, the methylene protons of the diazepine ring exhibit two

broad singlets at ambient temperature, whereas, those of **4** show a clear AB quartet. Examination of molecular model suggests that this contrast is due to the fact that whereas, in the case of **4**, there is steric interaction between the 1-substituent with the hydrogen atom of the benzene ring, the compounds **3a-e** have no such steric interaction making the seven-membered ring of **3a-e** more flexible than that of **4**. Thus, examination of the methylene proton signals contributes to the determination of the position of the substituent on the imidazole ring.

In order to synthesize 1,2-dialkyl-6-phenyl-4*H*-imidazo[1,2-*a*][1,4]benzodiazepines, **2** was treated with 3-bromo-2-butanone and with 3-bromo-2-pentanone. Although the reactions afforded the expected **6a,b** (Scheme I), the major products were **3b** and **3c**. As in the case of **4**, the methylene protons of the diazepine ring of **6a,b** exhibited, in the nmr spectra, a clear AB quartet supporting the existence of a substituent at the 1-position. Isomerization of 3-bromo-2-butanone to 1-bromo-2-butanone by the aid of a basic substance prior to the reaction with **2** is excluded by the experiments where 3-bromo-2-butanone was heated with triethylamine and with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in refluxing ethanol; the gas chromatographic analysis of the mixture did not detect any 1-bromo-2-butanone.

Scheme II



A possible mechanistic sequence (Scheme II) for the imidazole ring formation is one in which the 2-amino group of aminobenzodiazepine **2** reacts with the carbonyl group of α-bromoketone to form the shiff-base **7**, which then cyclizes with loss of hydrogen bromide to give **9** and/or **10** with **8** (5) as the probable intermediate. Tautomerization of **9** and **10** gives **11** and **12**, respectively. This sequence accounts for the formation of **3b** [**12** (R = H, R′ = CH_3)] and **3c** [**12** (R = H, R′ = C_2H_5)] together with **6a** [**11** (R = H, R′ = CH_3)] and **6b** [**11** (R = H, R′ = C_2H_5)], respectively in the reaction of **2** with 3-bromo-2-butanone and with 3-bromo-2-pentanone, respectively. In the case where the formation of two isomeric imidazobenzodiazepines is possible, such isomer as having no or a smaller substituent at the 1-position is predominant because of the steric interaction, at the transition state of the conversion of **8** to **9** or **10**, of the potential 1-substituent with the hydrogen atom on the 9-position of the starting aminobenzodiazepine. In other words, the nitrogen atom of the seven-membered ring attacks preferentially the carbon atom having no or a smaller substituent [the conversion (a) (Scheme II) predominates when R′ < R, whereas the conversion (b) when R < R′]. The above reasoning is supported by the experimental observation that the product ratio of **3c** and **6b** (4.6:1) (Experiment number 7, Table I) is larger than that of **3b** and **6a** (2.3:1) (Experiment number 6, Table I).

EXPERIMENTAL

Melting points were taken on a Yanagimoto hot-stage apparatus and are uncorrected. Instrumental data were obtained from Hitachi EPI-510 infrared spectrophotometer, a Varian EM 360 nuclear magnetic resonance spectrometer except in the case otherwise noted with tetramethylsilane as an internal standard, and a LKB 9000 mass spectrometer.

General Procedure for 6-Phenyl-4*H*-imidazo[1,2-*a*][1,4]benzodiazepines.

A mixture of 4.0 ~ 8.4 mmoles of 2-amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine (4), α-bromoketone, and ethanol was heated at reflux. The solvent was evaporated under reduced pressure, and to the residual material were added ethyl acetate (or methylene chloride) and water. Without separating two layers, the water layer was made alkaline with saturated aqueous sodium bicarbonate solution. The separated organic layer was washed with water and dried over anhydrous sodium sulfate. The material obtained on evaporation of the solvent was chromatographed on silica gel with benzene-ethyl acetate as the eluant. Imidazobenzodiazepine thus obtained was recrystallized from organic solvent. The more detailed reaction conditions and the product(s) are listed in Table I, and the melting points and the analytical data of the 6-phenyl-4*H*-imidazo[1,2-*a*][1,4]benzodiazepines are shown in Table II.

The spectral data are written below.

8-Chloro-2-methyl-6-phenyl-4*H*-imidazo[1,2-*a*][1,4]benzodiazepine (**3a**).

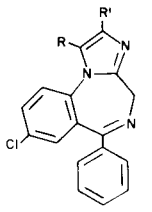
Ir (potassium bromide) cm^{-1}: 1604, 1575, 1526, 1486, 1445, 1430, 1313, 1299; nmr (deuteriochloroform) δ: 2.25 (3H, s, CH_3), 4.4 (1H, broad s) and 5.1 (1H, broad s) (CH_2N), 7.05 (1H, s, -CH=), 7.15-7.85 (8H, m, C_6H_5 and C_6H_3).

8-Chloro-2-ethyl-6-phenyl-4*H*-imidazo[1,2-*a*][1,4]benzodiazepine (**3b**).

Ir (potassium bromide) cm^{-1}: 1613, 1575, 1525, 1487, 1445, 1429, 1315, 1305; nmr (deuteriochloroform) δ: 1.25 (3H, t, J = 7.4 Hz, CH_3), 2.64 (2H, q, J = 7.4 Hz, CH_2CH_3), 4.2 (1H, broad s) and 5.1 (1H, broad s) (CH_2N), 7.07 (1H, s, -CH=), 7.16-7.7 (8H, m, C_6H_5 and C_6H_3).

Table I

Synthesis of 6-Phenyl-4*H*-imidazo[1,2-*a*][1,4]benzodiazepines



3, 6

Experiment Number	Reaction Conditions: α-Bromoketone employed	Reaction Conditions: Molar Ratio of α-Bromoketone/ Aminobenzodiazepine	Reaction Conditions: Reaction Period (hours)	Product	Product: R	Product: R'	Yield (%)
1	CH_3COCH_2Br	1.2	23	**3a**	H	CH_3	22
2	$CH_3CH_2COCH_2Br$	6	5	**3b**	H	CH_2CH_3	35
3	$CH_3CH_2CH_2COCH_2Br$	4	3.8	**3c**	H	$CH_2CH_2CH_3$	14
4	$(CH_3)_2CHCOCH_2Br$	5	5	**3d**	H	$CH(CH_3)_2$	20
5	$C_6H_5CH_2COCH_2Br$	3	4	**3e**	H	$CH_2C_6H_5$	20
6	$CH_3COCHBrCH_3$	6	7	**3b**	H	CH_2CH_3	12
				6a	CH_3	CH_3	5.2
7	$CH_3COCHBrCH_2CH_3$	3	5	**3c**	H	$CH_2CH_2CH_3$	13
				6b	CH_2CH_3	CH_3	2.8

Table II

Physical and Analytical Data for 6-Phenyl-4*H*-imidazo[1,2-*a*][1,4]benzodiazepines

Compound Number	M.p. (°C) (Recrystallization solvent) (a)	Formula	*Anal.*	C (%)	H (%)	N (%)	Mass Spec.	M^+, m/e
3a	174-176 (B-H)	$C_{18}H_{14}ClN_3$	Calcd.	70.24	4.59	13.69		
			Found	70.30	4.39	13.27		
3b	147-149 (A-H)	$C_{19}H_{16}ClN_3$	Calcd.	70.91	5.02	13.06	Calcd.	321.10333
			Found	71.09	4.83	12.74	Found	321.10381 ± 0.00963
3c	158-159 (B-H)	$C_{20}H_{18}ClN_3$	Calcd.	71.53	5.40	12.51	Calcd.	335.11899
			Found	71.56	5.48	12.29	Found	335.11810 ± 0.01005
3d	138-140 (B-H)	$C_{20}H_{18}ClN_3$	Calcd.	71.53	5.40	12.51	Calcd.	335.11899
			Found	71.81	5.49	12.23	Found	335.11580 ± 0.01005
3e	143-145 (A-H)	$C_{24}H_{18}ClN_3$	Calcd.	75.09	4.73	10.95	Calcd.	383.11899
			Found	74.77	4.63	10.98	Found	383.11924 ± 0.01149
6a	152-153 (B-H)	$C_{19}H_{16}ClN_3$	Calcd.	70.91	5.02	13.06	Calcd.	321.10333
			Found	70.80	4.78	12.68	Found	321.10480 ± 0.00963
6b	136-137 (B-H)	$C_{20}H_{18}ClN_3$					Calcd.	335.11899
							Found	335.11780 ± 0.01005

(a) B-H = benzene-*n*-hexane, A-H = ethyl acetate-*n*-hexane.

8-Chloro-6-phenyl-2-propyl-4*H*-imidazo[1,2-*a*][1,4]benzodiazepine (**3c**).

Ir (potassium bromide) cm^{-1}: 1609, 1571, 1522, 1488, 1445, 1429, 1316, 1304; nmr (deuteriochloroform) δ: 1.00 (3H, t, J = 7.0 Hz, CH_3), 1.74 (2H, sextet, J = 7.0 Hz, CH_2CH_3), 2.63 (2H, J = 7.0 Hz, $CH_2CH_2CH_3$), 4.25 (1H, broad s) and 5.20 (1H, broad s) (CH_2N), 7.12 (1H, s, -CH=), 7.33-7.6 (8H, m, C_6H_5 and C_6H_3).

8-Chloro-2-isopropyl-6-phenyl-4*H*-imidazo[1,2-*a*][1,4]benzodiazepine (**3d**).

Ir (potassium bromide) cm^{-1}: 1608, 1596, 1576, 1552, 1486, 1469, 1449, 1428, 1384; nmr (deuteriochloroform) (6) δ: 1.26 (6H, d, J = 6.0 Hz, 2 x CH_3), 2.90 (1H, apparent quintet, J = 6.0 Hz, $CH(CH_3)_2$), 4.2 (1H, broad s) and 5.1 (1H, broad s) (CH_2N), 7.01 (1H, s, -CH=), 7.2-7.6 (8H, m, C_6H_5 and C_6H_3).

2-Benzyl-8-chloro-6-phenyl-4*H*-imidazo[1,2-*a*][1,4]benzodiazepine (**3e**).

Ir (potassium bromide) cm^{-1}: 1608, 1572, 1523, 1485, 1444, 1425, 1312; nmr (deuteriochloroform) δ: 3.95 (2H, s, $CH_2C_6H_5$), 4.25 (1H, broad s) and 5.15 (1H, broad s) (CH_2N), 6.90 (1H, s, -CH=), 7.0-7.9 (13H, m, 2 x C_6H_5 and C_6H_3).

8-Chloro-1,2-dimethyl-6-phenyl-4*H*-imidazo[1,2-*a*][1,4]benzodiazepine (**6a**).

Ir (potassium bromide) cm^{-1}: 1607, 1572, 1525, 1485, 1443, 1419, 1315; nmr (deuteriochloroform) δ: 2.18 (3H, s, 2-CH_3), 2.28 (3H, s, 1-CH_3), ν_A 5.30 and ν_B 3.98 (2H, AB system, J = 14 Hz, CH_2N), 7.3-7.6 (8H, m, C_6H_5 and C_6H_3).

8-Chloro-1-ethyl-2-methyl-6-phenyl-4*H*-imidazo[1,2-*a*][1,4]benzodiazepine (**6b**).

Ir (potassium bromide) cm^{-1}: 1605, 1555, 1525, 1480, 1415, 1310; nmr (deuteriochloroform) δ: 0.99 (3H, t, J = 8 Hz, CH_2CH_3), 2.25 (3H, s, 2-CH_3), 2.80 (2H, t, J = 8 Hz, CH_2CH_3), ν_A 5.25 and ν_B 3.97 (2H, AB system, J = 13 Hz, CH_2N), 7.2-7.7 (8H, m, C_6H_5 and C_6H_3).

Acknowledgment.

The authors wish to thank Misses K. Tatebe and M. Sasaki for microanalyses, Mr. M. Asano for mass spectra and Dr. T. Wakabayashi for valuable discussion. Particular appreciation is expressed to Dr. T. Noguchi, Dr. S. Tsunoda and Mr. S. Ishimoto for their advice and support during the course of this investigation.

REFERENCES AND NOTES

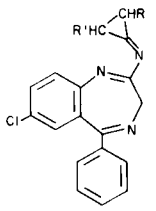
(1a) J. B. Hester, Jr., A. D. Rudzik and B. V. Kamdar, *J. Med. Chem.*, **14**, 1078 (1971); (b) K. Megro, H. Tawada and Y. Kuwada, *Chem. Pharm. Bull.*, **21**, 1619 (1973).

(2a) J. B. Hester, Jr. and A. R. Hanze (to Upjohn), U.S. Patent 3,917,627 (1975); (b) (to Centre d'Etudes pour l'Industrie Pharmaceutique), German Patent 2,321,705 (1973).

(3) K. Hofmann, "The Chemistry of Heterocyclic Compounds. Imidazole and Its Derivatives," Part I, Interscience Publishers, Inc., New York, N. Y., 1953, p. 43.

(4) K. Megro, H. Tawada and Y. Kuwada, *Yakugaku Zasshi* **93**, 1253 (1973).

(5) The process from the deprotonation from the CH_2R group of **7** to the five-membered ring formation may be concerted. The



13

possibility that the species **13** is the intermediate is excluded by the observation that **6a** was not obtained by the reaction of **2** with 1-bromo-2-butanone and that **6b** by the reaction with 1-bromo-2-pentanone.

(6) The spectrum was recorded on a JEOL JNM-MH-100 spectrometer.