Studies on Heterocyclic Compounds. 10.[1] Synthesis of Some Imidazo[1,2-*a*]benzimidazoles with Potent Analgetic Activities

Haruo Ogura,* Hiroaki Takayanagi,

School of Pharmaceutical Sciences, Kitasato University, Shirogane, Minato-ku, Tokyo 108, Japan

Yukio Yamazaki, Shoichi Yonezawa,

Kodama Limited, Kanda Sakuma-cho, Chiyoda-ku, Tokyo 101, Japan

Hiromu Takagi, Shinsaku Kobayashi, Toshiharu Kamioka, and Katuo Kamoshita

Central Research Laboratories, Sankyo Company, Ltd., Shinagawa-ku, Tokyo 140, Japan. *Received February 10, 1972*

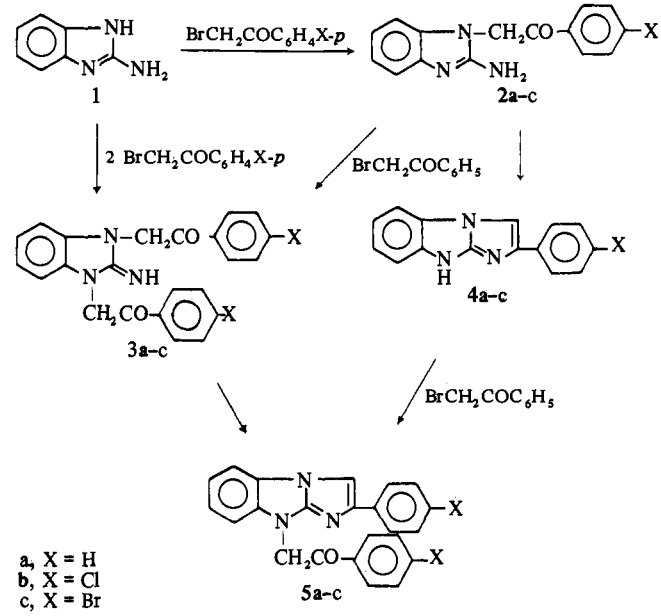
Imidazo[1,2-*a*]benzimidazole derivatives were synthesized in a search for a potent analgetic substance. Condensation of 2-aminobenzimidazole (**1**) and phenacyl bromide afforded 2-amino-1-phenacylbenzimidazole (**2**) and 2-imino-1,3-bis(phenacyl)benzimidazole (**3**). Cyclization of these open-chain compounds (**2**, **3**) afforded 2- and 2,9-substituted imidazo[1,2-*a*]benzimidazoles (**4**, **5**). The compound **5** was also obtained from the reaction of **4** and phenacyl bromide. Imidazo[1,2-*a*]benzimidazole (**9**) itself was prepared from 2-amino-1-(2,2-diethoxyethyl)benzimidazole (**8**) by its treatment with HCl. 9-Dialkylaminoalkyl derivatives (**12**) were prepared from **4** by reaction with dialkylaminoalkyl chloride. These compounds were also prepared by the cyclization of 1-dialkylaminoalkyl-2-imino-3-phenacylbenzimidazole (**11**), which was obtained by the reaction of 1-dialkylaminoalkyl-2-aminobenzimidazole (**10**) and phenacyl bromide. 9-Dialkylaminoalkyl derivatives showed a potent analgetic activity. Among these compounds, 2-(*p*-bromophenyl)-9-dimethylaminopropyl-9*H*-imidazo[1,2-*a*]benzimidazole (**12i**) was the most effective, and its ED_{50} and LD_{50} values were 6.0 mg/kg and 1100 mg/kg, respectively.

Previously, we reported the synthesis of tricyclic azole series, such as thiazolo[3,2-*a*]benzimidazoles,[2,3] thiazolo[2,3-*b*]benzothiazoles,[4] imidazo[2,1-*b*]benzothiazoles,[5] imidazo[2,1-*b*]benzoxazoles,[6] and pyrimido[1,2-*a*]benzazoles,[7] to obtain potential physiological compounds which have new ring systems. Hunger, *et al.*, already reported that 1-(dialkylaminoalkyl)benzimidazole derivatives[8] and, particularly, the 2-amino derivatives[9] showed potent analgetic activity. By virtue of the closer structural analogy of these compounds, imidazo[1,2-*a*]benzimidazole derivatives seemed hopeful as analgetic agents. The present paper describes the synthesis of imidazo[1,2-*a*]benzimidazole and its derivatives and their analgetic activity.

Simonov and Kochergin[10] reported the synthesis of 2-phenyl-9-ethylimidazo[1,2-*a*]benzimidazole by the condensation of 2-amino-1-ethylbenzimidazole with phenacyl bromide. They also reported the synthesis of 9-diethylaminoethyl-2-phenyl-9*H*-imidazo[1,2-*a*]benzimidazole from 2-amino-1-diethylaminoethylbenzimidazole with phenacyl bromide.[11] Reaction of phenacyl bromides (R = H, Cl, Br) with 2-aminobenzimidazole (**1**) at room temperature gave 2-amino-1-phenacylbenzimidazole (**2a–c**) and 2-imino-1,3-bis(phenacyl)benzimidazole (**3a–c**). Compound **2a** was treated with excess reagent to obtain the bis compound (3a) (Scheme I). Both open-chain compounds (**2** and **3**) were readily cyclized with NaOH to give 2-substituted imidazo[1,2-*a*]benzimidazole (**4a–c**) or 2,9-disubstituted imidazo[1,2-*a*]benzimidazole (**5a–c**). Boiling of **3a–c** in MeOH resulted in cyclization to produce **5a–c**. The latter (**5**) was also obtained from **4** with phenacyl bromide (Tables II and III).

Recently, North and Day[12] reported a series of 1-alkyl-2,3-dihydroimidazo[1,2-*a*]benzimidazoles and examined the prototropic tautomerism. It was found that 1-alkylation takes place under strongly basic conditions and 9-alkylation occurs under neutral conditions. There is the possibility of protonation of compound **4** at either 1H or 9H. For further confirmation of the position of the alkylation, the following experiments were adopted. *o*-Aminophenylurea (**6**)[12]

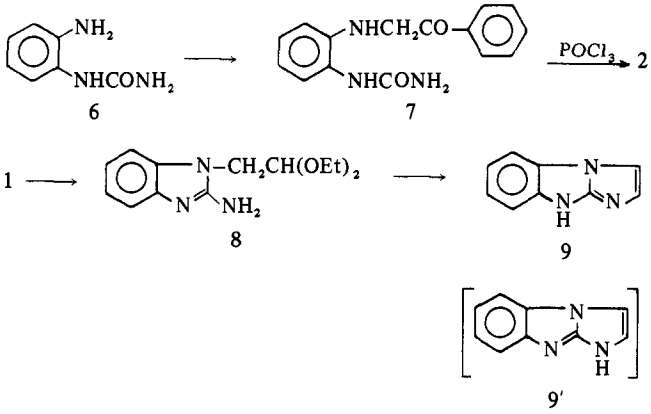
Scheme I



was treated with phenacyl bromide in MeOH, and the resulting compound (**7**) was cyclized with phosphoryl chloride to yield 2-amino-1-phenacylbenzimidazole (**2**) (Scheme II). This proved that the alkylation of **1** occurred at the imidazole ring nitrogen rather than the amino group at C-2 position. The compound (**2**) showed a sharp singlet absorption at δ 6.05 ppm due to the methylene protons in the phenacyl group. Similar absorption was observed at 6.10 ppm in the bis compound (**3**). This evidence indicated that two phenacyl groups in **3** were condensed to the 1 and 3 positions in the imidazole ring and not to the imino group at C-2.

Synthesis of imidazo[1,2-*a*]benzimidazole (**9**) itself was attempted as follows. Compound **8** was prepared from the reaction of bromoacetal and 2-aminobenzimidazole (**1**).

Scheme II

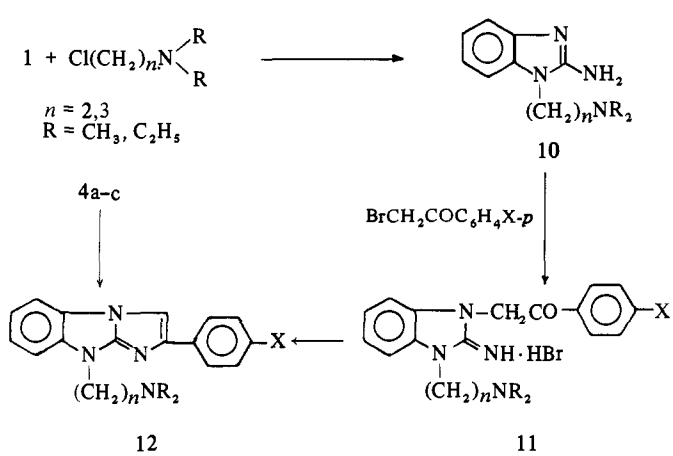


Treatment of **8** with 2 *N* HCl produced a skeletal compound (**9**), which was confirmed by its nmr and mass spectrum.

Compounds **12a–i** were prepared by two methods. Treatment of the sodium salt of 2-substituted imidazo[1,2-*a*]-benzimidazole (**4a–c**) with dialkylaminoalkyl chloride afforded the desired compounds in a good yield. Another procedure involved the treatment of the sodium salt of **1** with dialkylaminoalkyl chloride to afford 2-amino-1-dialkylaminoalkylbenzimidazoles (**10a–c**). These compounds (**10a–c**) were treated with phenacyl bromide to yield 1-dialkylaminoalkyl-2-imino-3-phenacylbenzimidazole (**11a–f**) hydrobromide. Although 1-dimethylaminoethyl- and 1-diethylaminoethyl-2-imino-3-phenacylbenzimidazoles (**11a,b** and **11c,d**) were cyclized to the compounds (**12b,c,e,f**) by heating, compounds **11e, f** were not cyclized under the same conditions and starting material was recovered. Further treatment of **11e, f** with concd H_2SO_4 or polyphosphoric acid was not successful.

Pharmacology. It was already reported that 2-phenyl-9-diethylaminoethyl-9*H*-imidazo[1,2-*a*]benzimidazole (**12d**) showed a hypotensive activity in cats.[11] Tests on analgetic and taming activities and toxicity of 2-aryl-9-dialkylaminoalkyl-9*H*-imidazo[1,2-*a*]benzimidazoles are summarized in Table I. The analgetic effect of the hydrochlorides of these compounds was tested by the acetic acid induced writhing syndrom in mice,[13] and the ED_{50} was calculated by the method of Litchfield-Wilcoxon.[14] According to these results, ED_{50} value (po) of **12i** was 6.0 (2.6–13.8) mg/kg, which was the most effective in this system. The LD_{50} value (po) of **12i** was about ten times more potent and less toxic than that of some known analgetic drugs, benzydamine and mepirizole, and these compounds (**12**) do not show morphine-like narcotic activity. From our experiments, it has been concluded that substituents at both C-2 and N-9 positions have an effect on activity and toxicity of the compounds mentioned above. Concerning the C-2 position, the *p*-bromophenyl group is more effective than the phenyl group. Concerning the N-9 position, the dimethylaminopropyl group is more effective than the diethylaminoethyl group.

Scheme III



Experimental Section†

General Procedure for 2-Amino-1-phenacylbenzimidazoles (2a–c) and 2-Imino-1,3-bis(phenacyl)benzimidazoles (3a–c) (Table II). To a solution of 2-aminobenzimidazole (1, 0.1 mole) in MeOH (100 ml) phenacyl bromide (0.1 mole) was added. After standing at room temperature for 10 days, light pale brown prisms precipitated. The product was recrystallized from MeOH to obtain the bis compound 3·HBr as white prisms.

This compound (3a·HBr) was also prepared from 2a (0.01 mole) and phenacyl bromide (0.01 mole) in MeOH. 3a·HBr was obtained in 75% yield, and the product was identified by means of ir spectral comparison and mixed mp examination.

3·HBr was converted into a free base (3) by dissolving in MeOH and adding 10% $NaHCO_3$ until the precipitation was completed. The product was recrystallized from MeOH to obtain white needles.

The filtrate obtained by removal of the bis compound 3·HBr was cooled to 0° and 2-amino-1-phenacylbenzimidazole (2·HBr) was obtained as white needles, which were recrystallized from MeOH to obtain an analytical sample. This was converted to its free base (2) with 10% $NaHCO_3$ by the same method as described above.

General Procedure for 2-Substituted 9*H*-Imidazo[1,2-*a*]benzimidazole (4a–c) (Table III). (a) To a solution of 2·HBr in MeOH, 10% NaOH was added until the precipitation was completed. The collected precipitates were recrystallized from DMF to obtain 4 as white needles in 85% yield.

(b) A solution of the free base (2) was warmed in MeOH under reflux for 24 hr. Evaporation of MeOH under a reduced pressure gave 4 as white needles in 90% yield. The product was identified with that obtained in a by means of ir spectral comparison and mixture melting point determination.

General Procedure for 2-Substituted 9-Phenacyl-9*H*-imidazo[1,2-*a*]benzimidazoles (5a–c) (Table III). (a) A solution of 3·HBr (0.02 mole) in EtOH (100 ml) was heated under reflux for 10 hr. The cyclized compound 5a–c·HBr was obtained as white needles in a good yield.

(b) This compound (5a·HBr) was also obtained from 4a (0.01 mole) and phenacyl bromide (0.01 mole) in MeOH by heating under reflux for 5 hr. After evaporation of MeOH, 5a·HBr was obtained in 80% yield as white needles. The product was identified with that obtained in a by means of ir spectrum and mixture melting point determination. 5a–c·HBr were converted to their free base (5a–c) by dissolving in MeOH and adding 5% NaOH until the precipitation was completed. The precipitate was recrystallized from EtOH.

General Procedure for 2-Phenacylaminophenylurea (7) (Table IV). A solution of *o*-aminophenylurea (6, 0.05 mole) and phenacyl bromide (0.05 mole) in MeOH (200 ml) was heated under reflux for 5 min. Cooling of the reaction mixture afforded 7 as white needles.

General Procedure for 2-Amino-1-phenacylbenzimidazole (2a–c) (Table IV). A solution of 7 (0.01 mole) in $POCl_3$ (5 ml) was warmed at 90° for 10 min. When cooled, the reaction mixture was poured into ice water, and the precipitate was recrystallized from MeOH. 2·HCl was obtained as white needles.

7a–c·HCl were converted to their free base (2a–c) by dissolving in MeOH and adding 5% $NaHCO_3$ until the precipitation was completed. The precipitate was recrystallized from MeOH and was identified with that obtained in the first experiment by means of ir spectrum and mixture melting point determination.

2-Amino-1-(2,2-diethoxyethyl)benzimidazole (8). To a solution of Na (1.1 g) in abs MeOH (30 ml), 1 (6.0 g) and 2-bromoacetaldehyde diethylacetal (10.0 g) were added. After heating under reflux for 30 hr, the solvent was removed under reduced pressure, and the

†Melting points are uncor. Nmr spectra were measured with a Varian T-60 spectrometer and Me_4Si was used as an internal standard. Mass spectra were detd on a Japan Electron Optics JMS-01S high-resolution mass spectrometer, and all spectral data were consistent with the proposed structures. Elemental analyses (C, H, N) of the compounds gave values corresponding to their formula within ±0.4%.

Table I. Pharmacological Results of Imidazo[1,2-*a*]benzimidazole Derivatives

Compound	Analgetic activity: Writhing method ED_{50}, mg/kg, po	Analgetic activity: Hot plate method ED_{50}, mg/kg, po	Taming activity ED_{50}, mg/kg, po	Acute toxicity LD_{50}, mg/kg, po
12d	17.3 (10.2-29.5)[a]	18.5 (9.8-35.0)	52 (36-75)	590 (531-608)
12f	11.5 (5.8-23.0)	12.0 (6.3-23.0)	48 (36-66)	640 (533-767)
12h	10.0 (6.1-16.5)	7.2 (4.1-13.0)	64 (53-78)	780 (650-936)
12i	6.0 (2.6-13.8)	9.0 (4.3-19.0)	38 (28-52)	1100 (915-1320)
Chlorpromazine	2.8 (1.1-7.2)	3.8 (2.2-6.7)	4 (3-6)	97 (63-131)
Benzydamine	94.0 (61.4-144)	>200		660 (520-838)
Mepirizol	68.0 (50-93)	94.0 (73-121)		820 (738-923)

[a]Figures in parenthesis are 95% confidence limits.

Table II. 2-Amino-1-phenacylbenzimidazoles (2a-c) and 2-Imino-1,3-bis(phenacyl)benzimidazoles (3a-c)

Compound	Mp, °C dec	Yield, %	Formula
2a	282-285		$C_{15}H_{13}ON_3$
2a·HBr	308-311	35	$C_{15}H_{13}ON_3 \cdot HBr$
2b	273		$C_{15}H_{12}ON_3Cl$
2b·HBr	310-312	25	$C_{15}H_{12}ON_3Cl \cdot HBr$
2c	285-286		$C_{15}H_{12}ON_3Br$
2c·HBr	279-280	28	$C_{15}H_{12}ON_3Br \cdot HBr$
3a	218		$C_{23}H_{19}O_2N_3$
3a·HBr	283-284	40	$C_{23}H_{19}O_2N_3 \cdot HBr$
3b	205-207		$C_{23}H_{17}O_2N_3Cl_2$
3b·HBr	260	33	$C_{23}H_{17}O_2N_3Cl_2 \cdot HBr$
3c	222-224		$C_{23}H_{17}O_2N_3Br_2$
3c·HBr	265	38	$C_{23}H_{17}O_2N_3Br_2 \cdot HBr$

Table III. 2-Substituted and 2,9-Disubstituted 9*H*-Imidazo[1,2-*a*]benzimidazoles

Compound	Mp, °C dec	Yield, %	Formula
4a	269-270	85	$C_{15}H_{11}N_3$
4b	275-276	92	$C_{15}H_{10}N_3Cl$
4c	279-280	96	$C_{15}H_{10}N_3Br$
5a	218		$C_{23}H_{17}ON_3$
5a·HBr	268-269	95	$C_{23}H_{17}ON_3 \cdot HBr$
5b	208-209		$C_{23}H_{15}ON_3Cl_2$
5b·HBr	218-219	97	$C_{23}H_{15}ON_3Cl_2 \cdot HBr$
5c	240-242		$C_{23}H_{15}ON_3Br_2$
5c·HBr	239-240	98	$C_{23}H_{15}ON_3Br_2 \cdot HBr$

Table IV. 2-Phenacylaminophenylurea (7) and 2-Amino-1-phenacylbenzimidazoles (2)

Compound	Mp, °C	Yield, %	Formula
7a	186-188	40	$C_{15}H_{15}O_2N_3$
7b	191-192	36	$C_{15}H_{14}O_2N_3Cl$
7c	187-189	35	$C_{15}H_{14}O_2N_3Br$
2a·HCl	214-215 dec	93	$C_{15}H_{13}ON_3 \cdot HCl$
2b·HCl	274-275 dec	85	$C_{15}H_{13}ON_3Cl \cdot HCl$
2c·HCl	217-218 dec	84	$C_{15}H_{12}ON_3Br \cdot HCl$

residue was extracted with ether. After evaporation of ether, the residual crystals were recrystallized from $CHCl_3$-petr ether to 8 (8.4 g, 75%) as white needles, mp 137-139°. *Anal.* ($C_{12}H_{19}O_2N_3$) C, H, N.

Imidazo[1,2-*a*]benzimidazole (9). A solution of 8 (1.0 g) in 2 *N* HCl (5 ml) was left overnight at room temperature. The reaction solution was made alkaline with 10% $NaHCO_3$ to give 9 (0.6 g, 95%) as white needles (from 50% MeOH): mp 190° dec; nmr δ 7.5-8.1 ppm (CF_3COOH); ir ν^{KBr} 1613 cm^{-1} (aromatic ring); mass *m/e*, 157 (M^+). *Anal.* ($C_9H_7N_3$) C, H, N.

General Procedure for 2-Amino-1-dialkylaminoalkylbenzimidazoles (10a-c) (Table V). To a solution of 2-aminobenzimidazole (133 g, 1 mole) and Na (23 g, 1 g-atom) in abs EtOH (500 ml), a solution of dialkylaminoalkyl chloride (1 mole) in abs EtOH (500 ml) was added. After refluxing for 8 hr, separated NaCl was filtered off, the filtrate was evaporated under a reduced pressure, and the residue was washed with H_2O. The crude substance was recrystallized from Me_2CO to a pure compound as white needles.

General Procedure for 3-Substituted 1-Dialkylaminoalkyl-2-iminobenzimidazole (11a-f·HBr) (Table V). A solution of 2-amino-1-dialkylaminoalkylbenzimidazole (0.1 mole) and para-substituted phenacyl bromide (0.1 mole) in MeOH was warmed under reflux for 10 min. After evaporation of the solvent, residual crystalline product was washed with Me_2CO and then recrystallized from MeOH to a pure compound as white needles.

General Procedure for 2-Substituted 9-Dialkylaminoalkyl-9*H*-imidazo[1,2-*a*]benzimidazole (12b,c,e,f·HBr) (Table VI). 11·HBr (0.1 mole) was heated at 190-210° (bath temp) for 10 min. When cooled, the crude compound obtained by filtration was recrystallized from EtOH to a pure compound as white needles.

General Procedure for 2-Aryl-9-dialkylaminoalkylimidazo[1,2-*a*]benzimidazole (12a-i·HCl) (Table VI). 2-Substituted 9*H*-imidazo[1,2-*a*]benzimidazole (4a-c) was added in small portions to liquid NH_3 (150 ml) containing $NaNH_2$ (0.624 g, 16 mmoles) under a continuous stirring. After evaporation of NH_3, dry toluene (150 ml) was added to dissolve the Na salt. A solution of dialkylaminoalkyl chloride (15 mmoles) in dry toluene (50 ml) was added with stirring. After stirring for 3 hr at 90°, the reaction mixture was allowed to stand overnight, H_2O was added, and extracted with benzene. After evaporation of the dried organic layer, the resulting substance was dissolved in Et_2O. HCl gas was passed through the ether solution until precipitation was completed. The crystalline precipitate was recrystallized from Me_2CHOH-MeOH to obtain the products as white needles.

Pharmacological Method. Tests for analgetic and taming activities and acute toxicity of imidazo[1,2-*a*]benzimidazole derivatives were carried out on groups of 5 or 10 male mice (ddY strain, weighing 20-25 g) with more than three doses of test compound. The test compounds were given orally as solution or suspension in 0.85% sa-

Table V. Substituted Benzimidazoles (10 and 11)

Compound	$(CH_2)_n$	R	X	Mp, °C	Yield, %	Formula
10a	CH_2CH_2	CH_3		146-148	34	$C_{11}H_{16}N_4$
b	CH_2CH_2	C_2H_5		146-147	30	$C_{13}H_{20}N_4$
c	$CH_2CH_2CH_2$	CH_3		148-149.5	32	$C_{12}H_{18}N_4$
11a	CH_2CH_2	CH_3	Cl	219 dec	72	$C_{19}H_{21}ON_4Cl \cdot HBr$
b	CH_2CH_2	CH_3	Br	164 dec	70	$C_{19}H_{21}ON_4Br \cdot HBr$
c	CH_2CH_2	C_2H_5	Cl	196-197 dec	95	$C_{21}H_{25}ON_4Cl \cdot HBr$
d (HBr)	CH_2CH_2	C_2H_5	Br	208-209 dec	63	$C_{21}H_{25}ON_4Br \cdot HBr$
e	$CH_2CH_2CH_2$	CH_3	Cl	189-191 dec	75	$C_{20}H_{23}ON_4Cl \cdot HBr$
f	$CH_2CH_2CH_2$	CH_3	Br	173-174 dec	80	$C_{20}H_{23}ON_4Br \cdot HBr$

Table VI. 2-Substituted 9-Dialkylaminoalkyl-9*H*-imidazo[1,2-*a*]benzimidazoles (12)

Compd	$(CH_2)_n$	R	X	Mp, °C	Yield, %	Formula
12b	CH_2CH_2	CH_3	Cl	190–192	70	$C_{19}H_{19}N_4Cl \cdot HBr$
c	CH_2CH_2	CH_3	Br	218–219	65	$C_{19}H_{19}N_4Br \cdot HBr$
e (HBr)	CH_2CH_2	C_2H_5	Cl	197–199	75	$C_{21}H_{23}N_4Cl \cdot HBr$
f	CH_2CH_2	C_2H_5	Br	187–189	78	$C_{21}H_{23}N_4Br \cdot HBr$
12a	CH_2CH_2	CH_3	H	260–263 dec	65	$C_{19}H_{20}N_4 \cdot 2HCl$
b	CH_2CH_2	CH_3	Cl	271–272 dec	71	$C_{19}H_{19}N_4Cl \cdot 2HCl$
c	CH_2CH_2	CH_3	Br	268–270 dec	62	$C_{19}H_{19}N_4Br \cdot 2HCl$
d	CH_2CH_2	C_2H_5	H	268–269 dec[a]	70	$C_{21}H_{24}N_4 \cdot 2HCl$
e (2HCl)	CH_2CH_2	C_2H_5	Cl	258–259 dec	68	$C_{21}H_{23}N_4Cl \cdot 2HCl$
f	CH_2CH_2	C_2H_5	Br	245–248 dec	65	$C_{21}H_{23}N_4Br \cdot 2HCl$
g	$CH_2CH_2CH_2$	CH_3	H	266–267 dec	92	$C_{20}H_{22}N_4 \cdot 2HCl$
h	$CH_2CH_2CH_2$	CH_3	Cl	261–263 dec	62	$C_{20}H_{21}N_4Cl \cdot 2HCl$
i	$CH_2CH_2CH_2$	CH_3	Br	249–250 dec	56	$C_{20}H_{21}N_4Br \cdot 2HCl$

[a] Reported,[11] mp 205–206°.

line containing 0.5% tragacanth. The ED_{50} and LD_{50} were calculated by the method of Litchfield and Wilcoxon.[14]

The analgetic effects were assayed by the following two methods. The first was antagonism of acetic acid induced writhing method.[13] Thirty minutes after drug administration, 0.2 ml of 0.6% acetic acid solution was injected ip. Writhing was checked from 5 to 15 min after acetic acid injection. The analgetic ED_{50} was estimated as the dose which reduced writhing number to 50% of that of control animals over a period of 10 min. The second was a modification of the hot plate method by Eddy, *et al.*[15] The apparatus, which was reported by Takagi, *et al.*,[16] was used, and the bath temperature was kept constantly at 55 ± 1°. Animals showed a reaction time from 5 to 10 sec. The pain responses were determined before and 15, 30, 45, and 60 min after drug administration. The dose which increased the reaction time to 75% longer than that observed before drug administration was considered to be analgetic. The ED_{50} was calculated as the dose which caused analgesia in 50% of the animals.

The taming effect was measured by the antifighting behavior method. The paired animals were stimulated by an electric current (60 V DC, 1 mA, 3 cps) which was applied through a grid to the feet of the animals, according to the method of Tedeschi, *et al.*[17] The ED_{50} was determined by the ability to abolish the fighting behavior in 50% of the paired mice. Median lethal dose (LD_{50}) was determined 1 week after the administration.

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Synthesis and Antiprotozoal Activity of Methylnitro Derivatives of 2,2′-Biimidazole

Piero Melloni, Emanuele Dradi, Willy Logemann,*
Chemical Laboratories, Carlo Erba Research Institute, Milan, Italy

Ivo de Carneri, and Franca Trane
Microbiology Laboratories, Carlo Erba Research Institute, Milan, Italy.
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Several mono- and dinitro derivatives of *N*-methyl- and *N,N′*-dimethyl-2,2′-biimidazole have been synthesized. These compounds were tested for *in vitro* and *in vivo* activity against *Trichomonas vaginalis, Entamoeba histolytica,* and *Giardia muris.* Most compounds exhibited good *in vitro* activity against *T. vaginalis.* Only a few were active *in vivo.* The most active compounds were 1,1′-dimethyl-5-nitro-2,2′-biimidazole (12) and 1,1-dimethyl-5,5′-dinitro-2,2′-biimidazole (14).

Many compounds presently used as drugs for the treatment of protozoal infections contain a nitroimidazole moiety. A few examples are metronidazole[1] (**1**), tinidazole[2] (**2**), flunidazole[3] (**3**), and nitrimidazine[4] (**4**). Since it has previously been observed that molecular doubling can lead to enhancement of activity[5] we decided to investigate the 2,2′-biimidazole[6] ring structure **5**. In this paper we wish to report the synthesis of several nitro derivatives of **5** and their respective antitrichomonas and antiamoebic activities.

2,2′-Biimidazole (**5**) was selectively monomethylated with 1 equiv of Me_2SO_4 to yield predominantly **6**. Some dimethylated biimidazole **7** was always present as a side product regardless of how much excess 2,2′-biimidazole was used. In excess Me_2SO_4 **7** was formed exclusively.

The nitration of **5** was carried out in $AcOH-Ac_2O$. If only 1 equiv of nitric acid was used the major product was 4-nitro-2,2′-biimidazole (**8**). Using an excess of HNO_3 the major product is the symmetrical dinitro compound **9**. It is of interest that nitration of **5** with an equivalent of a sulfonitric mixture also gave **8**. Contrary to Lehmstedt and Zumstein[7]