[Chem. Pharm. Bull. 13(4) 465~472 (1965)]

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61. **Hideo Nakao and Genshun Sunagawa** : Studies on Seven-membered Ring Compounds. XVI.[*1] Synthesis of 2-Substituted Cycloheptimidazole Derivatives.

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Among imidazole and benzimidazole derivatives, there are many compounds of great importance and interest in biochemistry and pharmacology. However, there is no report concerning the biological effects of cycloheptimidazole derivatives which possess a condensed ring system of imidazole and cyclohpetatriene. One of the reasons is presumably that only few cycloheptimidazole derivatives have been synthesized. Therefore, the synthesis of cycloheptimidazole derivatives seems significant. The present paper is concerned with synthesis of 2-substituted cycloheptimidazole derivatives.

The synthesis of some 2-substituted cycloheptimidazoles has been previously reported by Murata, *et al.*,[1,2] starting from 2-methoxytropone (I) *via* 2-chloro- or 2-methylthiocycloheptimidazole. The first step in this process is the reaction of I with guanidine.[3] We attempted to apply this method to obtain 2-substituted cycloheptimidazole.

The reaction of I with methylguanidine afforded a small amount of 2-methylaminocycloheptimidazole (Ⅱ) besides a main product (A), m.p. 143°. This product (A) possessed the same composition $C_9H_9N_3$ as Ⅱ and its ultraviolet spectrum was similar to that of 1-methylcycloheptimidazol-2(1*H*)-one (Ⅲ) as shown in Fig. 1. Moreover, heating A with hydrochloric acid yielded Ⅲ. Therefore, A was confirmed to be 1-methyl-2-imino-1,2-dihydrocycloheptimidazole (Ⅳ). Similarly, reaction of I with ethylguanidine afforded two isomers, namely 2-ethylaminocycloheptimidazole (Ⅴ) and 1-ethyl-2-imino-1,2-dihydrocycloheptimidazole (Ⅵ), isolated as picrates. On the other hand, reaction of I with acetosulfaguanidine afforded only one product which was soluble in aqueous sodium

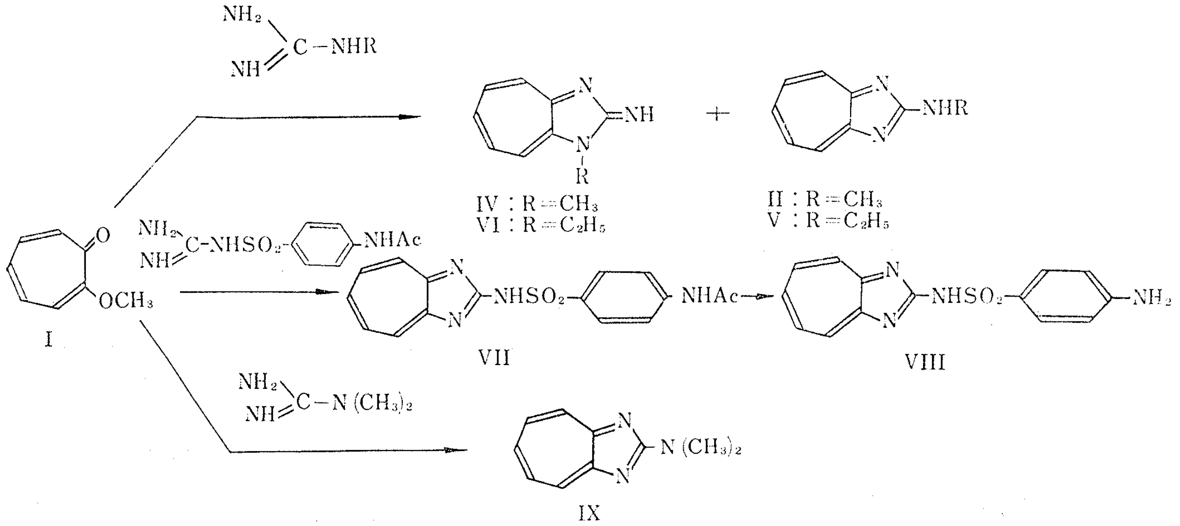


Chart 1.

[*1] Part XV. Nobuo Soma, Jun-ichi Nakazawa, Taiichiro Watanabe, Yoshio Sato, Genshun Sunagawa : This Bulletin, **13**, 457 (1965).

[*2] 1-2-58 Hiromachi, Shinagawa-ku, Tokyo (中尾英雄, 砂川玄俊).

1) T. Nozoe, T. Mukai, I. Murata : Proc. Japan Acad., **30**, 482 (1954).

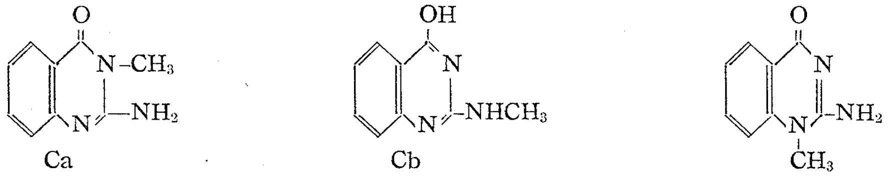
2) I. Murata : Bull. Chem. Soc. Japan, **33**, 56 (1960).

3) T. Nozoe, T. Mukai, K. Takase, I. Murata, K. Matsumoto : Proc. Japan Acad., **29**, 452 (1953).

hydroxide and thereby, was considered to be 2-(N-acetylsulfanilamido) cycloheptimidazole (VII). Hydrolysis of VII yielded the corresponding 2-sulfanilamidocycloheptimidazole (VIII).

The reaction of I with 1,1-dimethylguanidine afforded 2-(dimethylamino)cycloheptimidazole (IX), in good yield.

Moreover, the reaction of 2-bromo-7-methoxytropone (X) instead of I with substituted guanidine was attempted. In this respect, Matsumoto[4] reported that reaction of X with guanidine afforded 2-amino-4-bromocycloheptimidazole (XI). However, the reaction of X with methylguanidine afforded two kinds of products with the composition $C_9H_8N_3Br$ (B) and $C_9H_9ON_3$ (C), respectively. Since B showed the similar ultraviolet spectrum to II, it was considered to be 2-methylamino-4-bromocycloheptimidazole (XII). On the other hand, C was considered to be the rearranged product, benzene derivative, because its ultraviolet spectrum was different from that of cycloheptimidazole derivatives (Figs. 1 and 2). Therefore, the following three structures (Ca, Cb and Cc) for C could be proposed.



Ca Cb Cc

Chart 2.

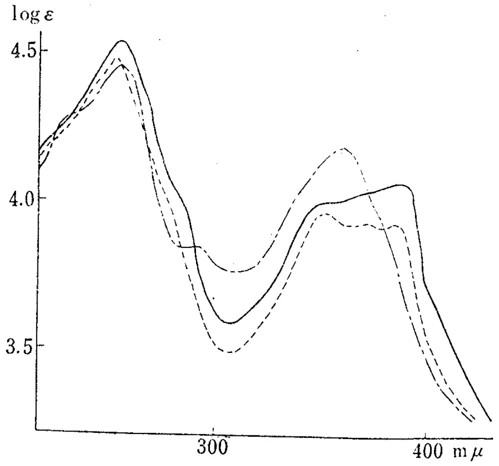


Fig. 1. Ultraviolet Spectra in Ethanol

——— A - - - - - III - - - - - II

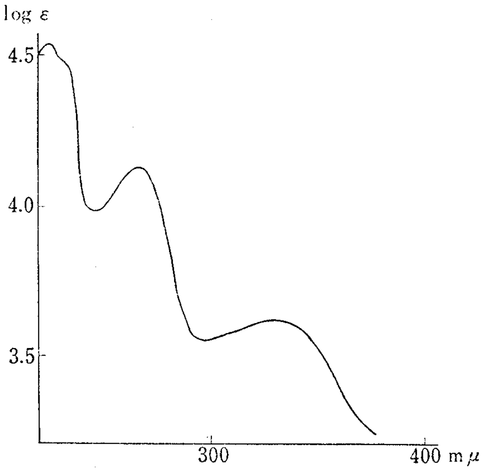


Fig. 2. Ultraviolet Spectrum of C in Ethanol

Among these three compounds, the synthesis of Ca and Cb has been reported by Grout, *et al.*[5] The melting point as well as the ultraviolet spectrum of Ca agreed with those of C. Therefore, C was confirmed to be 2-amino-3-methyl-4(3*H*)-quinazolinone (XIII) which is represented as structure Ca. Similarly, reaction of X with ethylguanidine afforded 2-ethylamino-4-bromocycloheptimidazole (XIV) and 2-amino-3-ethyl-4(3*H*)-quinazolinone (XV).

In the previous paper,[6] it was reported that the reaction of X with active methylene compounds generally affords rearranged product. In such reaction, the methoxy group of X was not involved in the reaction, and the rearranged product possessed a methoxy group. However, both XIII and XV possessed neither bromine nor a methoxy group.

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[4] K. Matsumoto: His Master Report (1955).

[5] R. J. Grout, M. W. Partridge: J. Chem. Soc., **1960**, 3540.

[6] Part XIII. G. Sunagwa, H. Nakao: This Bulletin, **13**, 443 (1965).

Therefore, this rearrangement reaction mechanism is apparently different from the previous known one in which the 3-position in X is attacked by the carbanion of active methylene compound. The formation of XIII or XV can be explained by Chart 3.

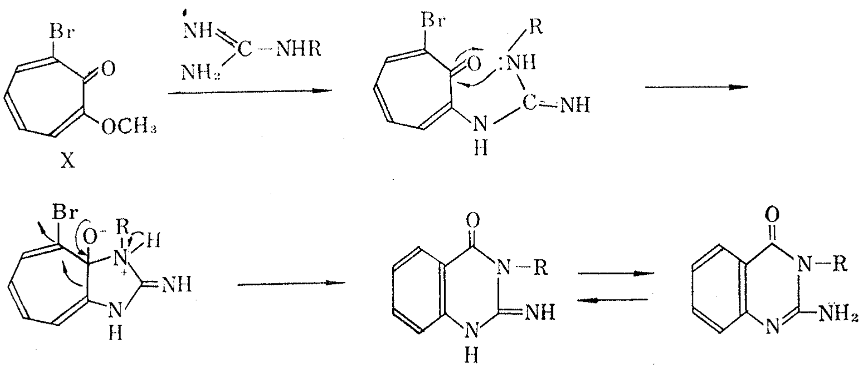
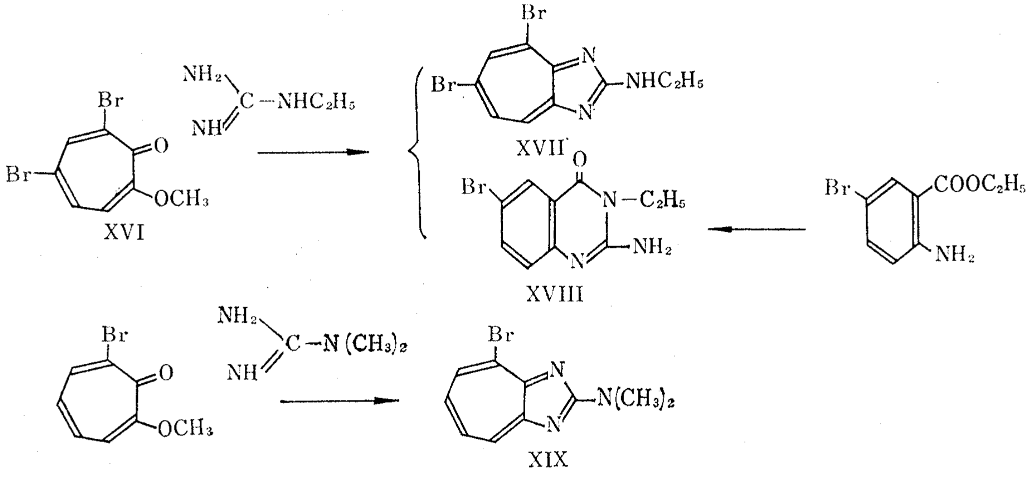


Chart 3.

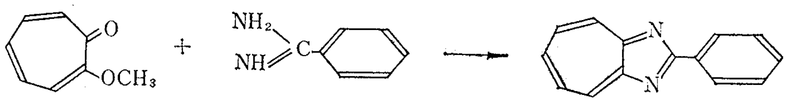
Further evidence for this mechanism was provided by the following additional reaction, in which 2-methoxy-5,7-dibromotropone (XVI) was allowed to react with ethylguanidine and afforded 2-ethylamino-4,6-dibromocycloheptimidazole (XVII) as well as the rearranged product, 2-amino-3-ethyl-6-bromo-4(3*H*)-quinazolinone (XVIII). The position of bromine in XVIII was decided by identity of this compound with an authentic sample prepared from methyl 2-amino-5-bromo-benzoate and ethylurea according to the Grout's method.[5] As described above, the reaction of X with monoalkylguanidine yielded quinazolinone derivative besides 2-alkylamino-4-bromo-cycloheptimidazole, but the reaction of X with 1,1-dimethylguanidine yielded only 2-dimethylamino-4-bromocycloheptimidazole (XIX), in good yield.



X

Chart 4.

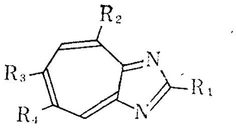
Furthermore, the reaction of I with amidine having a similar reaction center as guanidine was attempted. Aliphatic amidine such as acetamidine or phenylacetamidine did not react with I, but benzamidine reacted with I yielding 2-phenylcycloheptimidazole (XX). Similarly, the reaction of benzamidine with 2-chlorotropone, which did not react with guanidine afforded XX. Several other 2-substituted-cycloheptimidazole derivatives were prepared by the reaction of 2-methoxy- or 2-chlorotropone derivatives with aromatic amidines. The compounds synthesized are listed in Table I.

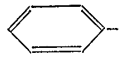
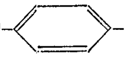
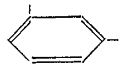
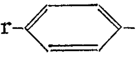
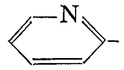


I XX

Chart 5.

Table I. 2-Phenyl- and 2-(2-Pyridyl)cycloheptimidazole Derivatives



Compound	R_1	R_2	R_3	R_4	m.p. (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
XXI	-	H	Br	H	221	$C_{14}H_9N_2Br$	58.97	3.18	9.83	58.70	3.32	9.74
XXII	〃	Br	H	〃	153	〃	58.97	3.18	9.83	59.00	3.42	9.93
XXIII	〃	CN	〃	〃	192	$C_{15}H_9N_3$	77.90	3.92	18.17	77.70	3.88	18.25
XXIV	CH_3--	H	〃	〃	181	$C_{15}H_{12}N_2$	81.79	5.49	12.72	81.48	5.58	12.63
XXV	〃	CN	〃	〃	217	$C_{16}H_{11}N_3$	78.35	4.52	17.13	78.14	4.65	17.25
XXVI	〃	H	NO_2	〃	263	$C_{15}H_{11}O_2N_3$	67.91	4.18	15.84	67.95	4.10	15.69
XXVII	CH_3O--	〃	H	〃	160	$C_{15}H_{12}ON_2$	76.25	5.12	11.86	76.38	5.17	11.87
XXVIII	〃	CN	〃	〃	265	$C_{16}H_{11}ON_3$	73.55	4.24	—	73.65	4.32	—
XXIX	NO_2 -	H	〃	〃	267	$C_{14}H_9O_2N_3$	66.92	3.61	16.73	66.55	3.48	16.82
XXX	〃	〃	〃	i-Pr	163	$C_{17}H_{15}O_2N_3$	69.61	5.15	14.33	69.78	5.12	14.45
XXXI	NO_2--	〃	〃	H	>290	$C_{14}H_9O_2N_3$	66.92	3.61	16.73	66.62	3.74	16.45
XXXII	Br--	〃	〃	〃	204	$C_{14}H_9N_2Br$	58.97	3.18	9.83	58.76	3.26	10.00
XXXIII	-	〃	〃	〃	186	$C_{13}H_9N_3$	75.34	4.38	20.28	75.03	4.35	20.44
XXXIV	〃	CN	〃	〃	235	$C_{14}H_8N_4$	72.40	3.47	24.13	72.52	3.65	23.92

It has been known that cycloheptimidazole derivatives do not undergo electrophilic substitution reaction, because the electron-rich 1-and 3-positions are occupied with nitrogen atoms. The only example of such electrophilic substitution reaction has been reported by Ebine,[7] who obtained 2-amino-4,6,8,-tribromocycloheptimidazole by the bromination of 2-aminocycloheptimidazole in pyridine. However, it was expected that 2-dimethylaminocycloheptimidazole (IX) having an electron donating group *i.e.* dimethylamino group, would undergo easily electrophilic substitution reaction at the 4(8)- and 6-positions for the attribution of the resonance effect (Chart 6). Thereafter, bromination

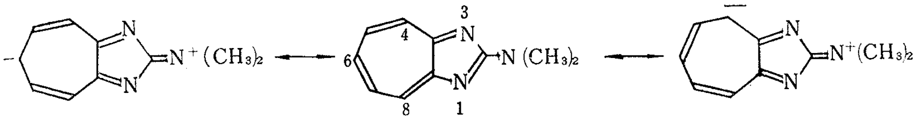


Chart 6.

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[7] S. Ebine: This work was presented at the 16th Annual Meeting of the Chemical Society of Japan, 1962.

and nitration reactions were examined. When the bromination of IX was carried out by bromine in chloroform, a monobromo derivative was produced. This product was not identical with the 4-bromo derivative (XIX). The brominated position was proved to be the 6-position by identity of the product with 2-dimethylamino-6-bromocycloheptimidazole (XXXV), prepared from 2-methoxy-5-bromotropone and 1,1-dimethylguanidine. The bromination of XXXV yielded a dibromo derivative, which was identical with 2-dimethylamino-4,6-dibromocycloheptimidazole (XXXVI), prepared from 2-methoxy-5,7-dibromotropone (XVI) and 1,1-dimethylguanidine. XXXVI was also obtained by the bromination of XIX. The bromination of XXXVI yielded a tribromo derivative, which seemed to be 2-dimethylamino-4,6,8-tribromocycloheptimidazole (XXXVII). From this series of bromination, it became clear that IX was brominated step by step in the order of 6,4(8)-positions. On the other hand, the nitration of IX with fuming nitric acid yielded a mononitro derivative. The nitro group was proved to be introduced at the 6-position by identity of the product with 2-dimethylamino-6-nitrocycloheptimidazole (XXXVIII), prepared from 2-methoxy-5-nitrotropone (XXXIX) and 1,1-dimethylguanidine.

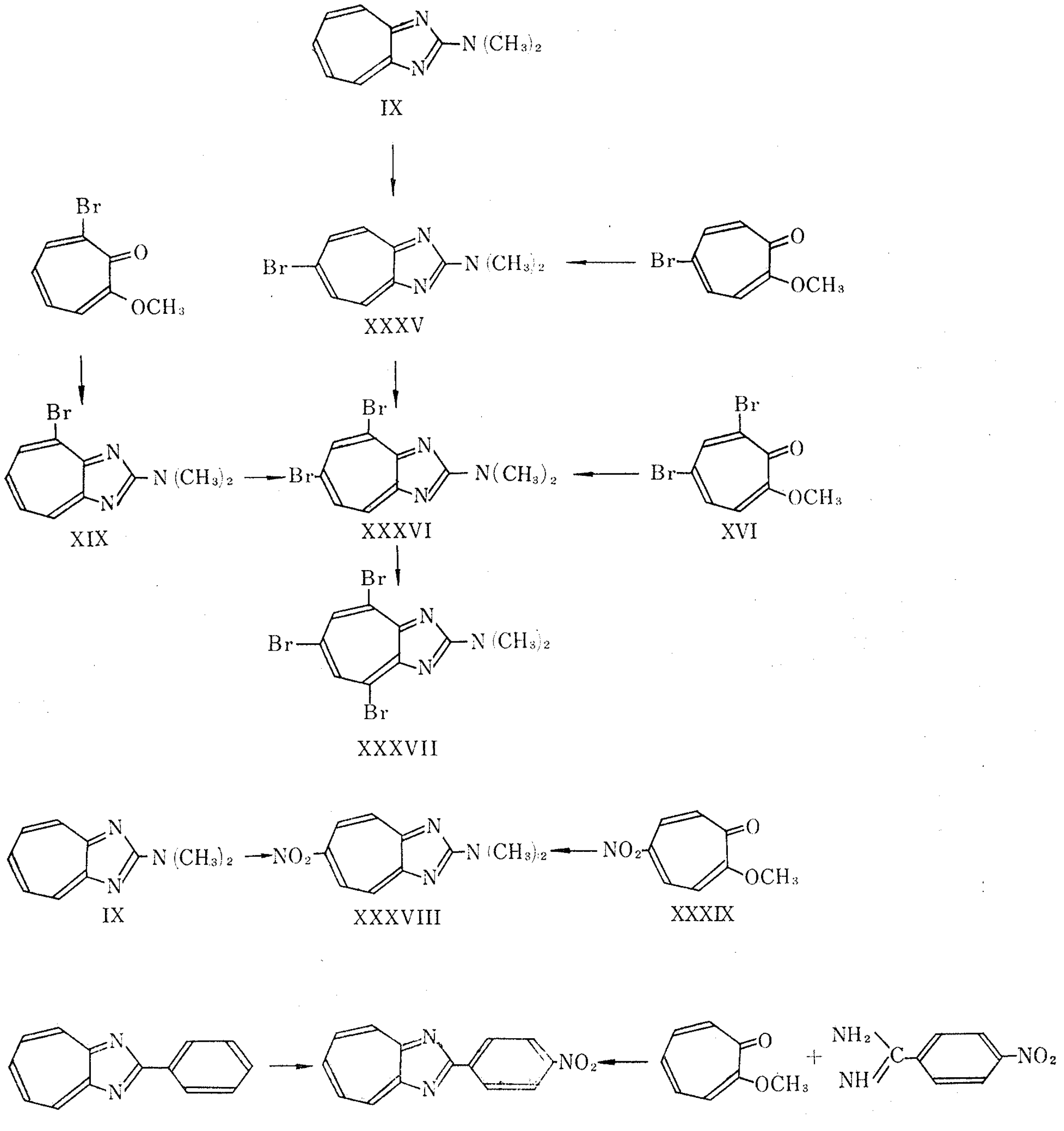


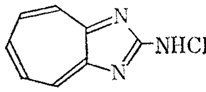
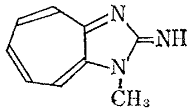
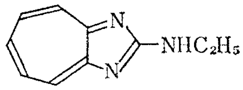
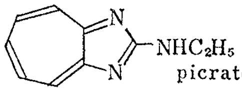
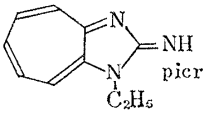
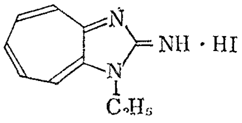
Chart 7.

In order to compare the bromination and nitration of Ⅸ with those of 2-phenylcycloheptimidazole (XX), experiments were carried out under same conditions which were performed for Ⅸ. In this respect, bromination of XX did not occur at all, whereas the nitration afforded a mononitro derivative. However, this compound was identical with 2-(*p*-nitrophenyl)cycloheptimidazole (XXXI). These results have made it clear that XX does not undergo electrophilic substitution reaction at the seven-membered ring.

Experimental

Reaction of 2-Methoxytropone (I) with Monoalkylguanidine——To a solution of Na (230 mg.) in EtOH (15 ml.) was added monoalkylguanidine sulfate (1.22 g.) and the mixture was stirred for 10 min. Then 2-methoxytropone (1.3 g.) was added and the mixture was stirred under reflux for 1 hr. After removal of the EtOH under reduced pressure, H_2O was added and the mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was extracted with 10% HCl. The acidic layer was made alkaline with 10% NaOH and then extracted with $CHCl_3$. After concentration of the $CHCl_3$ extract under reduced pressure, the residual oil was purified by alumina chromatography. The first eluate gave 1-alkyl-2-imino-1,2-dihydrocycloheptimidazol and the second gave a small amount of 2-(alkylamino)cycloheptimidazole. The reaction products are shown in Table Ⅱ.

Table Ⅱ. Reaction Products

Compound	m.p. (°C) (decomp.)	Formula	Analysis (%)					
			Calcd.			Found		
			C	H	N	C	H	N
	174	$C_9H_9N_3$	67.90	5.70	—	67.61	6.00	—
	(143)	〃	67.90	5.70	26.40	67.78	5.79	26.60
	124	$C_{10}H_{11}N_3$	69.34	6.40	24.26	69.29	6.50	24.17
 picrate	242	$C_{16}H_{14}O_7N_6$	47.76	3.51	20.89	47.69	3.46	20.92
 picrate	242	〃	47.76	3.51	20.89	47.70	3.58	20.58
	240	$C_{10}H_{12}N_3I$	39.89	4.02	13.95	39.62	4.00	13.92

2-Ethylaminocycloheptimidazole (V)——A solution of 2-chlorocycloheptimidazole (500 mg.) in 10% ethanolic ethylamine (10 ml.) was heated at 100° for 2 hr. in a sealed tube. After removal of the solvent, 5 ml. of H_2O was added and the mixture was made alkaline with 10% NaOH and then extracted with $CHCl_3$. Concentration of the organic extract gave a solid which on recrystallization from cyclohexane gave pale yellow crystals, m.p. 124°. Yield, 200 mg. Picrate, m.p. 242°.

2-(N-Acetylsulfanilamido)cycloheptimidazole (VII)——To a solution of Na (150 mg.) in EtOH (20 ml.) was added acetosulfaguanidine (1.3 g.) and 2-methoxytropone (0.7 g.). The mixture was stirred under reflux for 1.5 hr. After cooling, the separated crystals were collected and poured into 20 ml. of H_2O. The mixture was filtered off to remove insoluble matter and the filtrate was adjusted to pH 3 with 10% HCl.

The separated crystals were collected and recrystallized from dimethylformamide to give 0.8 g. of yellow crystals, m.p. 297°(decomp.). *Anal.* Calcd. for $C_{16}H_{14}O_3N_4S$: C, 56.14; H, 4.12; N, 16.37. Found : C, 56.05; H, 3.98; N, 16.34.

2-Sulfanilamidocycloheptimidazole (VIII)——A mixture of VII (0.8 g.) and 7% HCl (10 ml.) was heated on a steam bath for 1 hr. After treatment of the mixture with charcoal, the filtrate was adjusted to pH 4 with aqueous Na_2CO_3 solution. The separated crystals were recrystallized from dimethylformamide to yield 0.4 g. of yellow crystals, m.p. 283°. *Anal.* Calcd. for $C_{14}H_{12}O_2N_4S$: C, 56.00; H, 4.03; N, 18.66. Found : C, 55.99; H, 3.81; N, 18.68.

2-Dimethylaminocycloheptimidazole (IX)——To a solution of Na (850 mg.) in EtOH (50 ml.) was added 5 g. of dimethylguanidine sulfate and the mixture was stirred for 10 min. Then 2-methoxytropone (5 g.) was added and the mixture was stirred under reflux for 4 hr. After cooling, the mixture was filtered off to remove insoluble matter and the filtrate was concentrated under reduced pressure. To the residue was added 20 ml. of H_2O and the mixture was extracted with $CHCl_3$. Concentration of the $CHCl_3$ extract gave a solid, which on recrystallization from ligroin gave pale yellow prisms, m.p. 136°. Yield, 3.5 g. *Anal.* Calcd. for $C_{10}H_{11}N_3$: C, 69.34; H, 6.40; N, 24.26. Found : C, 69.13; H, 6.37; N, 24.26. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε) : 239 (4.31), 263 (4.37), 298 (3.71), 370 (4.23).

Reaction of 2-Bromo-7-methoxytropone (X) with Alkylguanidine——a) To a solution of Na (642 mg.) in 90 ml. of EtOH was added 3.3 g. of methylguanidine sulfate and the mixture was stirred for 30 min. Then 6 g. of X was added and the mixture was stirred under reflux for 9 hr. After removal of the solvent under reduced pressure, 50 ml. of H_2O was added and the mixture was extracted with $CHCl_3$. The extract was concentrated to separate crystals, which were collected by filtration and recrystallized from EtOH to give 0.5 g. of 2-amino-3-methyl-4(3*H*)-quinazolinone (XIII), m.p. 240°. *Anal.* Calcd. for $C_9H_9ON_3$: C, 61.70; H, 5.18; N, 23.99. Found : C, 61.47; H, 5.16; N, 24.08. Picrate, m.p. 282°.

The filtrate was concentrated again to 10 ml. and chromatographed on alumina to give 0.5 g. of 2-methylamino-4-bromocycloheptimidazole (XII), m.p. 178°. *Anal.* Calcd. for $C_9H_8N_3Br$: C, 45.40; H, 3.39; N, 17.65. Found : C, 45.23; H, 3.40; N, 17.71.

b) By the same procedure as described in a), 3.8 g. of ethylguanidine sulfate and 6 g. of X were allowed to react in the presence of Na (642 mg.). The $CHCl_3$ layer was extracted with 10% HCl. From the $CHCl_3$ layer, 0.5 g. of 2-ethoxy-7-bromotropone, m.p. 109°, was obtained. The HCl extract was made alkaline with 10% NaOH and extracted with $CHCl_3$. The $CHCl_3$ extract was concentrated to 10 ml. and chromatographed on alumina. The first eluate gave 50 mg. of 2-ethylamino-4-bromocycloheptimidazole (XIV), m.p. 120°. *Anal.* Calcd. for $C_{10}H_{10}N_3Br$: C, 47.64; H, 4.00; N, 16.67. Found : C, 48.31; H, 4.18; N, 16.70. The second eluate gave 180 mg. of 2-amino-3-ethyl-4(3*H*)-quinazolinone (XV), m.p. 187°. *Anal.* Calcd. for $C_{10}H_{11}ON_3$: C, 63.47; H, 5.86; N, 22.21. Found : C, 63.67; H, 5.89; N, 22.20.

c) By the same procedure as described in a), 0.7 g. of dimethylguanidine sulfate and 1.1 g. of X were allowed to react in the presence of sodium ethoxide. From the $CHCl_3$ extract, 0.5 g. of 2-dimethylamino-4-bromocycloheptimidazole (XIX), m.p. 117°, was obtained. *Anal.* Calcd. for $C_{10}H_{10}N_3Br$: C, 47.64; H, 4.00; N, 16.67. Found : C, 47.88; H, 4.02; N, 16.21.

Reaction of 2-Methoxy-5,7-dibromotropone (XVI) with Ethylguanidine——To a solution of Na (214 mg.) in 30 ml. of EtOH was added 1.26 g. of ethylguanidine sulfate and the mixture was stirred for 30 min. Then 2.7 g. of XVI was added and the mixture was stirred under reflux for 9 hr. After removal of the solvent under reduced pressure, 50 ml. of H_2O was added and the mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was concentrated to give a brown solid, which was dissolved in $CHCl_3$ and chromatographed on alumina. From the first eluate with $CHCl_3$-benzene (1:1), 150 mg. of 2-ethylamino-4,6-dibromocycloheptimidazole (XVII) was obtained, m.p. 178°. *Anal.* Calcd. for $C_{10}H_9N_3Br_2$: C, 36.28; H, 2.74; N, 12.70. Found : C, 36.33; H, 2.71; N, 12.78.

From the second eluate with EtOH, 0.5 g. of crude crystals were obtained. These crystals were recrystallized from EtOH to give 70 mg. of crystals, m.p. 228°, which were identical with 2-amino-3-ethyl-6-bromo-4(3*H*)-quinazolinone (XVIII). *Anal.* Calcd. for $C_{10}H_{10}N_3OBr$: C, 44.79; H, 3.76; N, 15.67. Found : C, 44.68; H, 3.88; N, 15.71.

2-Ethylamino-6-bromo-4-quinazolinol and 2-Amino-3-ethyl-6-bromo-4(3*H*)-quinazolinone (XVIII)—— By applying the Grout's method,[5] the reaction of ethylurea (2.1 g.) with methyl 2-amino-5-bromobenzoate (5.5 g.) yielded 2 g. of colorless crystals, m.p. above 280° and 0.5 g. of colorless needles, m.p. 228°. The former is 2-ethylamino-6-bromo-4-quinazolinol hydrochloride. The latter is 2-amino-3-ethyl-6-bromo-4(3*H*)-quinazolinone (XVIII). *Anal.* Calcd. for $C_{10}H_{10}N_3OBr$: C, 44.79; H, 3.76; N, 15.67. Found : C, 44.68; H, 3.68; N, 15.63.

Reactions of Amidine with 2-Methoxy- and 2-Chlorotropone——a) To a solution of Na (230 mg.) in 15 ml. of EtOH was added 1.6 g. of benzamidine hydrochloride. After stirring for 10 min., 1.3 g. of 2-methoxytropone was added, and the mixture was stirred under reflux for 3 hr. After removal of the solvent, the residue was extracted with $CHCl_3$. The $CHCl_3$ layer was extracted with 10% HCl. The acidic layer was made alkaline with 10% NaOH and then extracted again with $CHCl_3$. Concentration of the $CHCl_3$ extract gave crude crystals, which were recrystallized from EtOH to give 1 g. of 2-phenylcycloheptimidazole (XX), m.p. 161°. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε) : 252 (4.44), 272 (4.39), 342 (4.34), 354 (4.35).

b) By the same procedure as described in a), the reaction of 2-chlorotropone (390 mg.) with *p*-methylbenzamidine hydrochloride (470 mg.) in the presence of sodium ethoxide yielded 50 mg. of 2-(*p*-tolyl)-cycloheptimidazole, m.p. 181°.

c) A solution of 2-methoxy-5-bromotropone (0.9 g.) and benzamidine (0.9 g.) in 13 ml. of benzene was stirred under reflux for 2 hr. The mixture was cooled and the separated crystals were collected and recrystallized from benzene to give 0.3 g. of 2-phenyl-6-bromocycloheptimidazole, m.p. 221° (decomp.).

2-Dimethylamino-6-bromocycloheptimidazole (XXXV)——a) To a solution of Ⅸ (300 mg.) in 3 ml. of $CHCl_3$ was added dropwise a solution of bromine (280 mg.) in 2 ml. of $CHCl_3$ with stirring. The separated crystals were collected and the crystals were poured into 5 ml. of water. The mixture was adjusted to pH 8 with aqueous Na_2CO_3 solution. The insoluble solid was collected and recrystallized from benzene to give 50 mg. of yellow needles, m.p. 209°. *Anal.* Calcd. for $C_{10}H_{10}N_3Br$: C, 47.63; H, 4.00; N, 16.67. Found : C, 47.90; H, 3.83; N, 16.33.

b) Following the method used for the preparation of Ⅸ, the reaction of 2-methoxy-5-bromotropone (1.08 g.) with 1,1-dimethylguanidine sulfate (0.7 g.) in the presence of sodium ethoxide gave 0.8 g. of yellow needles, m.p. 209°, which were identical with the compound prepared by the method a).

2-Dimethylamino-4,6-dibromocycloheptimidazole (XXXVI)——a) Following the method a) for the preparation of XXXV, the bromination of XIX (250 mg.) with bromine (160 mg.) in $CHCl_3$ gave a crude product, which was purified by alumina chromatography followed by recrystallization from ligroin to give 50 mg. of yellow crystals, m.p. 161°. *Anal.* Calcd. for $C_{10}H_9N_3Br_2$: C, 36.28; H, 2.74; N, 12.69. Found : C, 36.30; H, 2.80; N, 12.47.

b) XXXVI was also obtained by the bromination of XXXV (96 mg.). Yield, 30 mg.

c) According to the method of preparing Ⅸ, the reaction of 2-methoxy-5,7-dibromotropone (1 g.), 1,1-dimethylguanidine sulfate (470 mg.) and Na (80 mg.) in EtOH gave a crude product, which was recrystallized from EtOH to give 0.4 g. of yellow crystals, m.p. 161°.

2-Dimethylamino-4,6,8-tribromocycloheptimidazole (XXXVII)——According to the method a) used for XXXVI, the reaction of XXXVI (200 mg.) with bromine (100 mg.) yielded 5 mg. of yellow needles, m.p. 200°. *Anal.* Calcd. for $C_{10}H_8N_3Br$: C, 29.23; H, 1.97; N, 10.25. Found : C, 29.37; H, 2.25; N, 10.21.

2-Dimethylamino-6-nitrocycloheptimidazole (XXXVIII)——a) To a solution of Na (40 mg.) in 60 ml. of EtOH was added 230 mg. of 1,1-dimethylguanidine sulfate. After stirring for 10 min., to the mixture was added 300 mg. of 2-methoxy-5-nitrotropone, and the mixture was stirred under reflux for 3 hr. After cooling the reaction mixture, the separated crystals were collected, washed with water and recrystallized from EtOH to give 150 mg. of red needles, m.p. 276°. *Anal.* Calcd. for $C_{10}H_{10}O_2N_4$: C, 55.04; H, 4.62; N, 25.68. Found : C, 54.91; H, 4.82; N, 25.40.

b) 200 mg. of Ⅸ was dissolved in 2 ml. of fuming nitric acid and the mixture was heated at 70° for 15 min. and poured into 10 ml. of water and then made alkaline with 10% NaOH. The separated crystals were collected and recrystallized from EtOH to give 30 mg. of red needles, m.p. 276°, which were identical with the sample obtained by the method a). UV λ_{max}^{EtOH} mμ (log ε) : 254 (4.56), 329 (3.70), 435 (4.52).

Nitration of 2-Phenylcyclcloheptimidazole (XX)——500 mg. of XX was dissolved in 4 ml. of fuming nitric acid and the solution was heated on a steam bath for 2 hr. and then poured into 30 ml. of water. The mixture was made alkaline with 10% NaOH and the separated crystals were collected and recrystallized from EtOH to give 100 mg. of yellow crystals, m.p. above 290°. This compound was proved to be identical with 2-(*p*-nitrophenyl)cycloheptimidazole (XXXI) by the comparison of the infrared spectrum.

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Summary

In order to obtain 2-substituted cycloheptimidazole, the reaction of 2-methoxytropone (I) with substituted guanidine and amidine was carried out. Reaction of I with monoalkylguanidine afforded a small amount of 2-alkylaminocycloheptimidazole besides 1-alkyl-2-imino-1,2-dihydrocycloheptimidazole. Reaction of 2-bromo-7-methoxytropone with monoalkylguanidine afforded 2-alkylamino-4-bromocycloheptimidazole and rearranged product, 2-amino-3-alkyl-4(3*H*)-quinazolinone. However, reaction of dialkylguanidine with I and 2-bromo-7-methoxytropone afforded only one product, 2-dimethylamino- and 2-dimethylamino-4-bromocycloheptimidazole, respectively. Reaction of aromatic amidine with I or 2-chlorotropone afforded 2-phenyl- and 2-pyridylcycloheptimidazole derivatives. Among cycloheptimidazole derivatives, 2-dimethylaminocycloheptimidazole has been found to undergo easily electrophilic substitution reaction, bromination and nitration.

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