[Chem. Pharm. Bull. 16(7)1308—1315(1968)]

UDC 547.785.5.07 : 547.517.07

Studies on Seven-membered Ring Compounds. XXVI.[1] Preparation and Some Reactions of 2-Alkoxycycloheptimidazoles[2]

GENSHUN SUNAGAWA and MITSUO WATATANI

Central Research Laboratories, Sankyo Co., Ltd.[3]

(Received October 3, 1967)

The preparation and some nucleophilic substitution reactions of 2-alkoxycycloheptimidazole derivatives were examined. Reaction of 2-methoxytropone derivatives with O-ethylisourea gave 2-ethoxycycloheptimidazoles (II, VIII to XIV) listed in Table I. The reaction of 2-methoxytroponeimine (V) with O-ethylisourea gave 2-aminocycloheptimidazole (VI) and 2-phenylcycloheptimidazole (VIII), besides 2-ethoxycycloheptimidazole (II). Reactions of II with sodium butoxide, aqueous ammonia, and dimethylamine gave 2-butoxy- (XXIX), 2-amino- (VI), and 2-dimethylaminocycloheptimidazole (XXX), respectively. Reaction of 4- and 6-bromo-2-ethoxycycloheptimidazole (VIII and IX) with dimethylamine resulted in displacement of the bromine atom on the seven-membered ring giving 4- and 6-dimethylamino-2-ethoxycycloheptimidazole (XXXI and XXXII), respectively. 2-Ethoxy-6-nitrocycloheptimidazole (XII) and IX gave 2,6-diethoxycycloheptimidazole (XXXIII) by their reaction with sodium ethoxide. Acid hydrolysis of 2-ethoxycycloheptimidazoles (VIII to XIV) gave cycloheptimidazol-2(1*H*)-ones (XXXV to XLIII) listed in Table II, whose substituents on the seven-membered ring remained unchanged. On the other hand, acid hydrolysis of XXXIII occurred preferentially at C-6 and 2-ethoxycycloheptimidazol-6(1*H*)-one (XLIV) was obtained.

During the course of synthetic studies on 1-substituted cycloheptimidazol-2(1*H*)-one, which shows a potent analgesic and antiphlogistic activity, 2-alkoxycycloheptimidazole derivatives were required as starting materials for cycloheptimidazol-2(1*H*)-ones having a substituent such as halogen atom or nitro group on their seven-membered ring, which could not be obtained by the common method, that is, hydrolysis of the corresponding 2-aminocycloheptimidazoles.[4,5] This paper deals with a new route for the preparation of 2-alkoxycycloheptimidazole derivatives by the reaction of 2-methoxytropones with O-alkylisourea, and with some reactions of the various 2-alkoxycycloheptimidazole derivatives thereby obtained.

Heating 2-methoxytropone (I) with O-ethylisourea in ethanol gave a condensation product as white crystals, $C_{10}H_{10}ON_2$, mp 101—102°, which was proved to be 2-ethoxycycloheptimidazole (II) from the similarity of its ultraviolet (UV) spectrum to that of 2-methoxycycloheptimidazole (III)[6,7] and its identification with the product obtained from 2-chlorocycloheptimidazole (IV) and sodium ethoxide. On the other hand, the reaction of 2-methoxytroponeimine (V), which can be regarded as a corresponding imino compound of I, with O-ethylisourea gave 2-aminocycloheptimidazole (VI) and 2-phenylcycloheptimidazole (VII), besides the expected II.

The reaction of substituted 2-methoxytropones with O-ethylisourea proceeded similarly to that of I giving the corresponding substituted 2-ethoxycycloheptimidazoles (VIII to XIV)

1) Part XXV: G. Sunagawa and M. Watatani, *Chem. Pharm. Bull.* (Tokyo), **16**, 1300 (1968).
2) A part of this work was presented at the Tohoku Local Meeting of the Chemical Society of Japan, Hirosaki, October, 1962.
3) Location: *Hiromachi, Shinagawa-ku, Tokyo.*
4) T. Nozoe, T. Mukai, and T. Asao, *Bull. Chem. Soc. Japan*, **35**, 1188 (1962).
5) H. Nakao, N. Soma, Y. Sato, and G. Sunagawa, *Chem. Pharm. Bull.* (Tokyo), **13**, 473 (1965).
6) T. Nozoe, T. Mukai, and I. Murata, *Proc. Japan Acad.*, **30**, 482 (1954).
7) I. Murata, *Sci. Repts. Res. Inst., Tohoku Univ.*, Ser. A, **12**, 272 (1960).

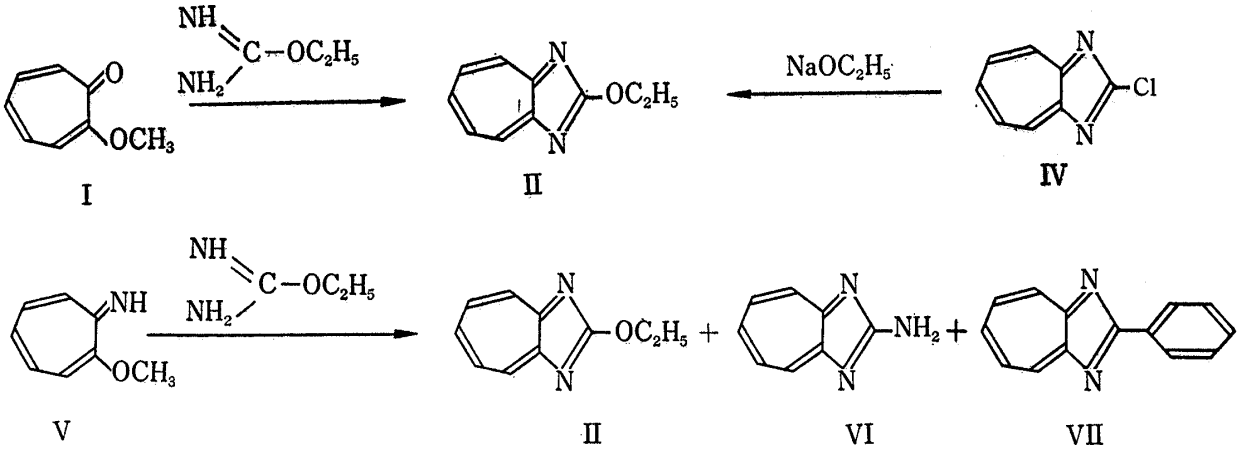
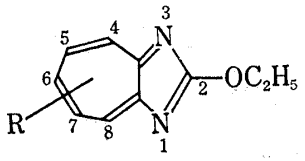


Chart 1

TABLE I. 2-Ethoxycycloheptimidazole Derivatives



Compound No.	R	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
II	H	102	$C_{10}H_{10}ON_2$	68.95	5.79	16.08	68.84	5.90	15.90
VIII	4-Br	142	$C_{10}H_9ON_2Br$	47.45	3.58	11.07	47.17	3.72	11.45
IX	6-Br	141	$C_{10}H_9ON_2Br$	47.45	3.58	11.07	47.39	3.59	10.76
X	4-Cl	142	$C_{10}H_9ON_2Cl$	57.56	4.35	13.43	57.18	4.71	13.37
XI	6-Cl	129	$C_{10}H_9ON_2Cl$	57.56	4.35	13.43	57.73	4.32	13.47
XII	6-NO_2	162	$C_{10}H_9O_3N_3$	54.79	4.14	19.17	54.78	4.23	19.02
XIII	4-CN	232	$C_{11}H_9ON_3$	66.32	4.55	21.10	66.03	4.51	21.14
XIV	4-$COOCH_3$	oil	$C_{18}H_{15}O_{10}N_5$ a)	46.86	3.28	15.18	47.24	3.48	15.35

a) picrate: mp 142°

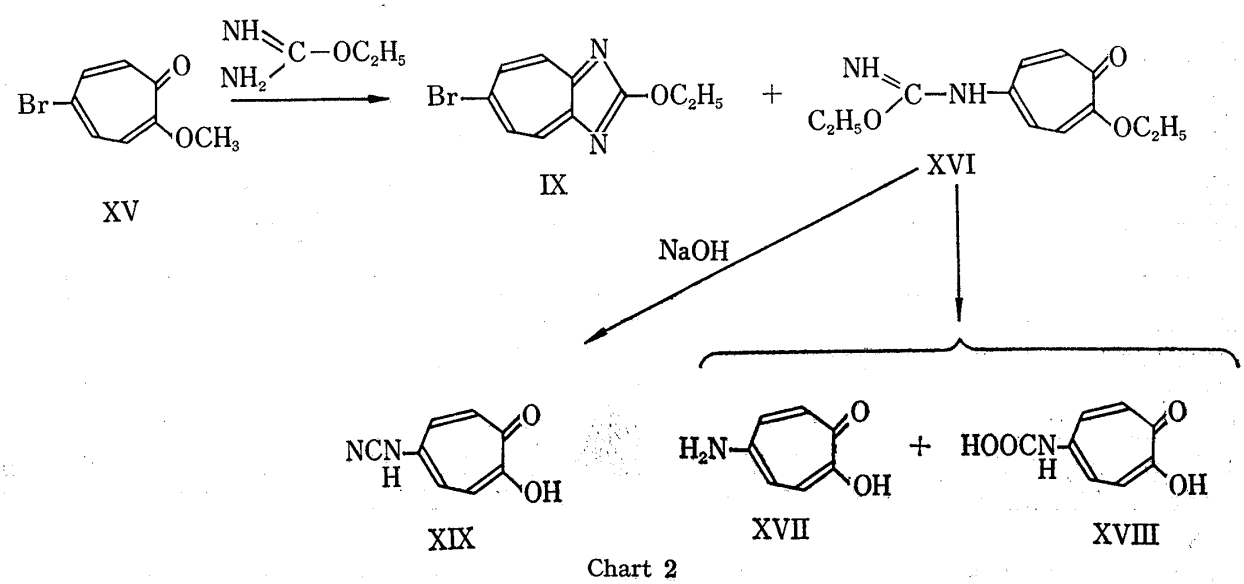


Chart 2

listed in Table I. Among these, the reaction of 5-bromo-2-methoxytropone (XV) was accompanied by a side reaction giving O-ethyl-N-(2-ethoxytropon-5-yl)isourea (XVI). The structure of XVI was proved from its elemental analysis, the similarity of its UV spectrum to that of 5-acetamido-2-methoxytropone, and the nuclear magnetic resonance (NMR) spectrum which indicated the presence of two ethoxyl groups. Further chemical proof for the structure of XVI was obtained by its acid hydrolysis to 5-aminotropolone (XVII) and 5-tropolonylcarbamic acid (XVIII). Alkaline hydrolysis of XVI yielded 5-cyanaminotropolone (XIX).

Methyl 7-methoxy-2-troponecarboxylate (XX), which was used as the starting material in the above condensation reaction, was obtained by the methylation of 3-tropolonecarboxylic acid (XXI) with diazomethane, together with methyl 2-methoxy-3-troponecarboxylate (XXII). The structure of XX was established by its amination to 7-aminotropone-2-carboxamide (XXIII), which was identified with the product obtained from 7-methoxytropone-2-carbonitrile (XXIV)[8] by its amination and successive hydrolysis. The structure of XXII was established by the reaction similar to that shown in Chart 3.

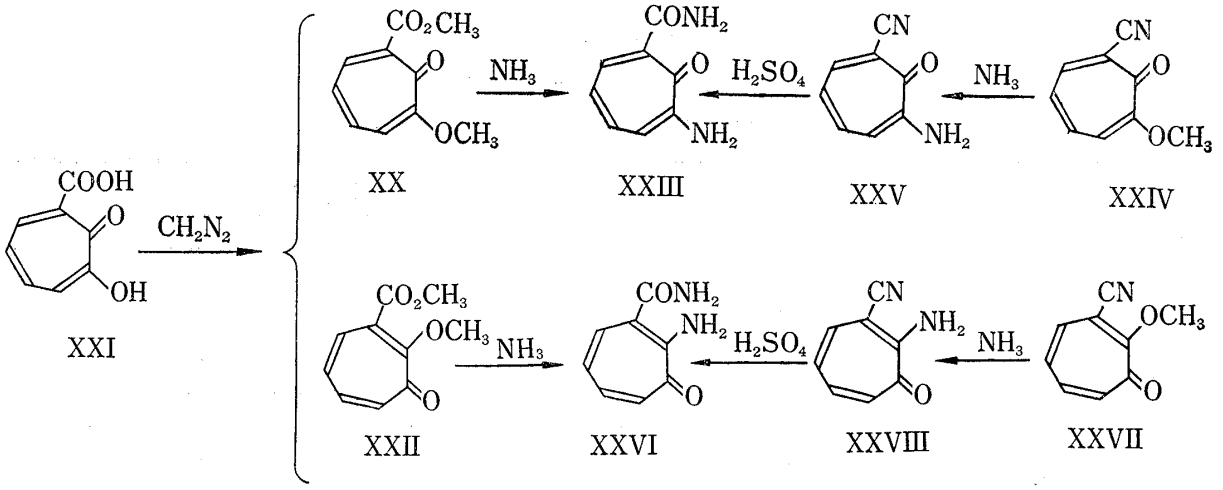


Chart 3

Next, nucleophilic substitution reaction of 2-ethoxycycloheptimidazoles was examined. When II was heated with sodium butoxide in butanol, transetherification occurred and 2-butoxycycloheptimidazole (XXIX) was obtained. Heating of XXIX with sodium ethoxide in ethanol reconverted it to the starting material, II. Heating of II in aqueous ammonia or dimethylamine resulted in the displacement of the ethoxyl group to give 2-aminocycloheptimidazole (VI) and 2-dimethylaminocycloheptimidazole (XXX). On the other hand, when 4-bromo-(VIII) and 6-bromo-2-ethoxycycloheptimidazole (IX) were allowed to react with dimethylamine, the displacement of the bromine atom on the seven-membered ring occurred and 4-dimethylamino-(XXXI) and 6-dimethylamino-2-ethoxycycloheptimidazole (XXXII) were obtained. The reaction of IX with sodium ethoxide also resulted in the displacement of the bromine atom of the seven-membered ring giving 2,6-diethoxycycloheptimidazole (XXXIII). The nitro group in 2-ethoxy-6-nitrocycloheptimidazole (XII) underwent displacement even at room temperatures and XXXIII was obtained. The displacement of the nitro group on the seven-membered ring with ethoxyl group had not hitherto been observed.

The reaction of IX with *p*-(dimethylamino)phenyllithium gave 6-bromo-4-(*p*-dimethylaminophenyl)-2-ethoxycycloheptimidazole (XXXIV), instead of the expected substitution product. The structure of XXXIV was proved from its satisfactory elemental analysis and

8) T. Nozoe, K. Kitahara, K. Takase, and I. Murata, *Bull. Chem. Soc. Japan*, **37**, 1292 (1964).

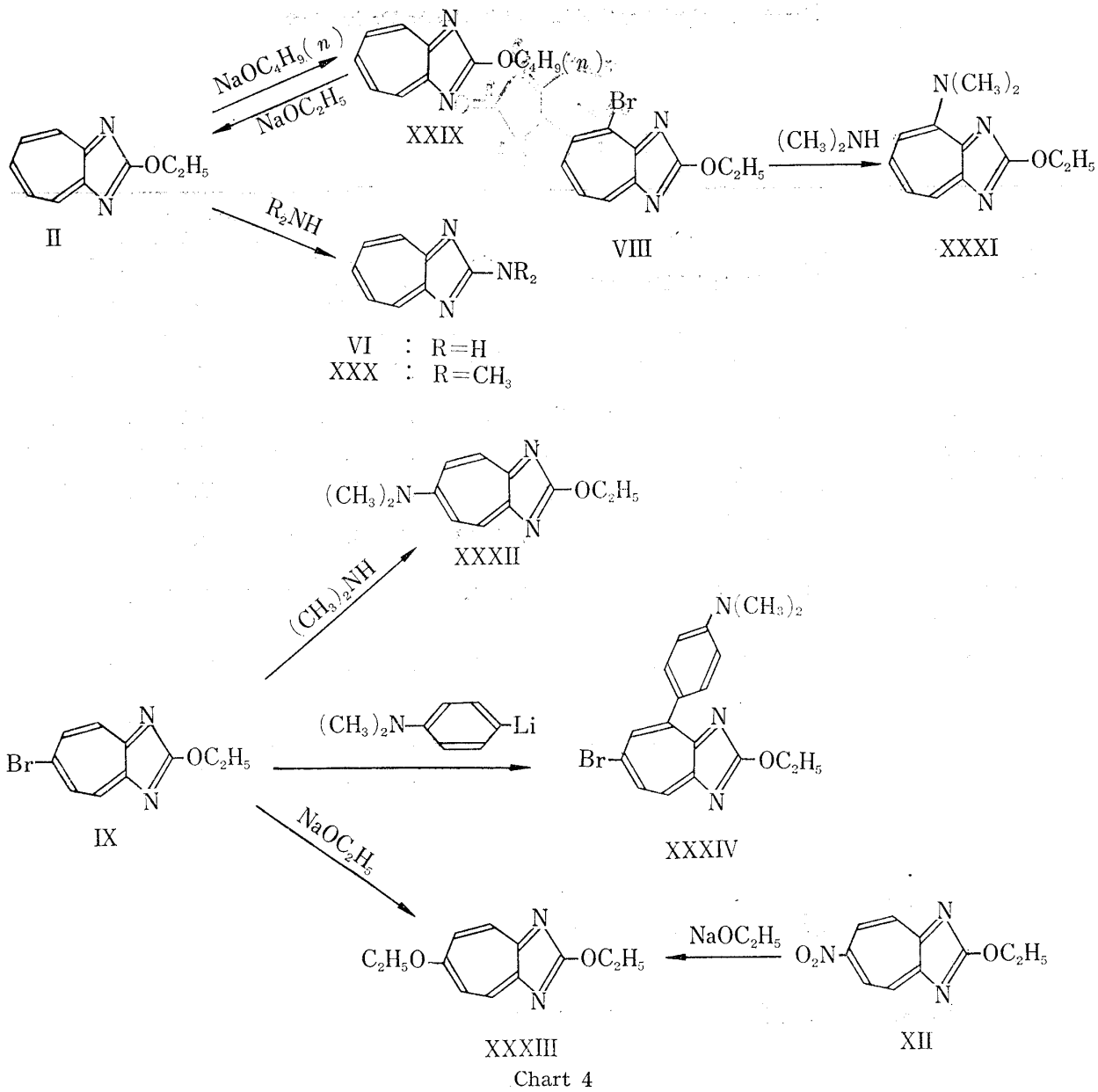


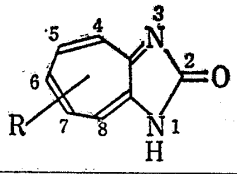
Chart 4

the similarity of its UV spectrum to that of 2,6-dichloro-4-(*p*-dimethylaminophenyl)cycloheptimidazole.[1] Furthermore, the structure of XXXIV is also supported by the fact that the addition of alkyl- or aryl-lithium toward azulene occurred at C-4 of azulene.[9]

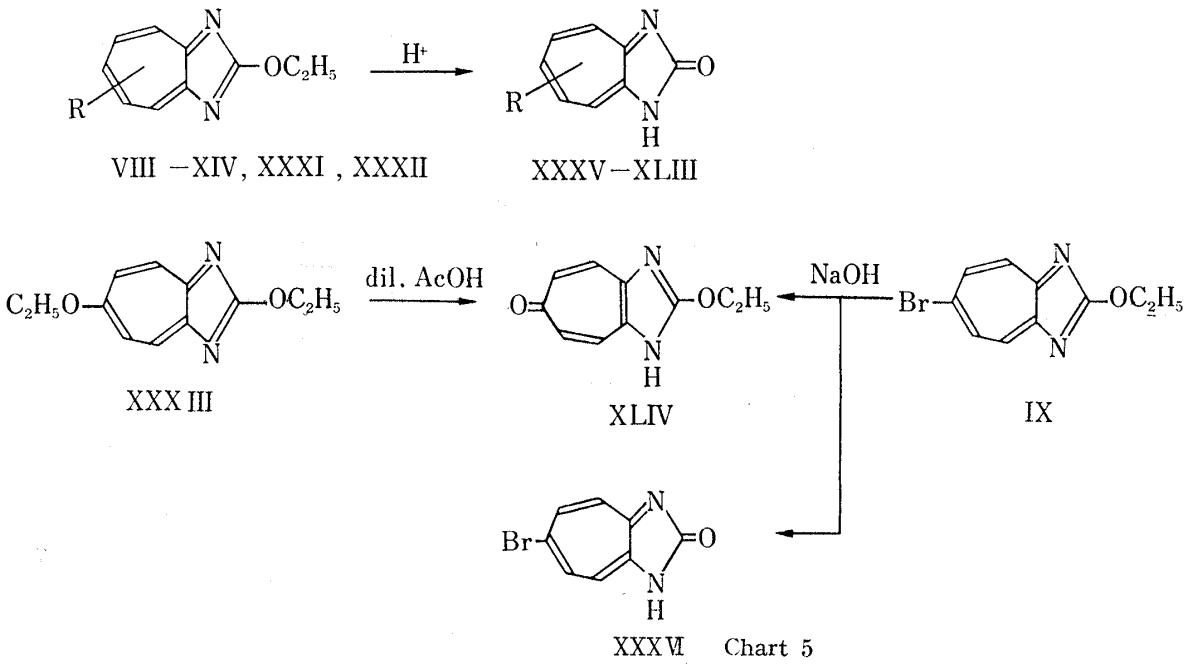
Finally, acid hydrolysis of the substituted 2-ethoxycycloheptimidazoles obtained as above was examined. These compounds were easily hydrolyzed even under a mild condition, such as warming with dilute hydrochloric acid, and substituted cycloheptimidazol-2(1*H*)-ones listed in Table II were obtained. In this acid hydrolysis, the substituents on the seven-membered ring of 2-ethoxycycloheptimidazole derivatives remained unchanged, while these substituents were more easily displaced than ethoxyl group at C-2 by nucleophilic agents such as amines or alkoxides, as described above. The acid hydrolysis of VIII and IX with dilute hydrochloric acid was accompanied by the halogen exchange and 4-(and 6)-chlorocycloheptimidazol-2(1*H*)-one (XXXVII and XXXVIII) were obtained, respectively. The hydrolysis of XXXIII with dilute acetic acid took place at the ethoxyl group on the seven-membered ring giving 2-ethoxycycloheptimidazol-6(1*H*)-one (XLIV). The structure

9) K. Hafner and H. Weldes, *Angew. Chem.*, **67**, 302 (1955); *Ann.*, **606**, 90 (1957).

Table II. Cycloheptimidazol-2(1*H*)-one Derivatives



Compound No.	R	mp (°C)	Method Material	Reagent	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
	H	245	II	HCl	$C_8H_6ON_2 \cdot \frac{1}{4}H_2O$	63.78	4.35	18.60	63.43	4.35	18.42
XXXV	4-Br	>290 (220 black)	VIII	HBr	$C_8H_5ON_2Br$	42.69	2.24	12.45	42.78	2.28	12.29
XXXVI	6-Br	>290	IX	HBr	$C_8H_5ON_2Br$	42.69	2.24	12.45	42.92	2.30	12.22
XXXVII	4-Cl	>290 (245 black)	VIII X	HCl HCl	$C_8H_5ON_2Cl$	53.20	2.79	15.51	52.70	2.78	15.18
XXXVIII	6-Cl	>290 (240 black)	IX XI	HCl HCl	$C_8H_5ON_2Cl$	53.20	2.79	15.51	53.15	2.86	15.61
XXXIX	4-$N(CH_3)_2$	240 (dec)	XXXI	HCl	$C_{10}H_{11}ON_3$	63.47	5.86	22.21	63.01	5.92	22.45
XL	6-$N(CH_3)_2$	295 (dec)	XXXII	HCl	$C_{10}H_{11}ON_3$	63.47	5.86	22.21	62.95	5.72	22.15
XLI	6-NO_2	>290	XII	HCl	$C_8H_5O_3N_3$	50.26	2.64	21.99	50.12	2.63	21.39
XLII	4-CN	>290	XIII	HCl	$C_9H_5ON_3$	63.16	2.94	24.55	62.67	3.08	24.83
XLIII	4-COOH	268 (dec)	XIII XIV	conc. HBr HCl	$C_9H_6O_3N_2$	56.84	3.18	14.73	56.82	3.19	14.81



VIII –XIV, XXXI , XXXII — XXXV–XLIII

XXXIII — XLIV — IX — XXXVI

Chart 5

of XLIV was proved by its identification with the alkaline hydrolysis product of IX. This preferential hydrolysis of the ethoxyl group at C-6 is probably due to the lower electron density on the seven-membered ring such as reported for 2,6-dichlorocycloheptimidazole by Nozoe, *et al.*[4]

Experimental[10]

2-Ethoxycycloheptimidazole (II)——i) To an EtOH solution of NaOEt, prepared from 0.27 g of Na and 20 ml of EtOH, 1.5 g of O-ethylisourea hydrochloride and then an EtOH solution (20 ml) of 1.36 g of 2-methoxytropone (I) were added . The mixture was refluxed for 7 hr and the separated solid was filtered off. After removal of EtOH, the residue was dissolved in benzene and chromatographed on alumina with benzene. The benzene eluate, after recrystallization from cyclohexane, gave colorless needles, mp 101—102°. Yield, 0.85 g. *Anal.* Calcd. for $C_{10}H_{10}ON_2$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.84; H, 5.90; N, 15.90. UV λ_{max}^{EtOH} mμ (log ε): 224 (4.23), 253 (4.63), 328 (4.10). The picrate was recrystallized from EtOH and melted at 182—183°. *Anal.* Calcd. for $C_{16}H_{13}O_8N_5$: C, 47.65; H, 3.25; N, 17.37. Found: C, 47.53; H, 3.24; N, 16.92.

ii) To an EtOH solution of NaOEt, prepared from 70 mg of Na and 50 ml of EtOH, 450 mg of 2-chlorocycloheptimidazole (IV) was added and the mixture was refluxed for 1 hr. The reaction mixture was treated as described in i) giving 460 mg of colorless needles, mp 101—102°. *Anal.* Calcd. for $C_{10}H_{10}ON_2$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.73; H, 5.72; N, 15.97. This product was identified with the product obtained in i) by mixed melting point determination.

Reaction of 2-Methoxytroponeimine (V) with O-ethylisourea——In 60 ml of EtOH, 2.5 g of metallic Na was dissolved. To this solution, were added 13.6 g O-ethylisourea hydrochloride and an EtOH solution of V, prepared from 12.1 g of 2-aminotropone according to the directions of Soma, *et al.*[11] The mixture was allowed to stand overnight. After filtration, the filtrate was evaporated to dryness, and the residue was treated with benzene and filtered. The crystals obtained were recrystallized from EtOH to 1.3 g of yellow prisms, mp 295° (decomp.), which were identical with an authentic sample of 2-aminocycloheptimidazole (VI) by mixed mp determination and comparison of their UV and infrared (IR) spectra.

The benzene filtrate was evaporated to dryness and the residue was submitted to chromatography on alumina with benzene. The initial eluate was evaporated to dryness and the residue was recrystallized from AcOEt to 0.68 g of yellow needles, mp 158—159°, which were identified with an authentic sample of 2-phenylcycloheptimidazole (VII) by mixed mp determination and comparison of their UV and IR spectra.

The later eluate was evaporated to dryness and the residue was recrystallized from cyclohexane to 1.2 g of white crystals, mp 101—102°, which were identified with II obtained from IV and NaOEt by mixed mp determination and comparison of their UV and IR spectra.

Substituted 2-Ethoxycycloheptimidazoles (VIII, X to XIV)——Substituted 2-methoxytropones were allowed to react with O-ethylisourea as described for the preparation of II from I. Substituted 2-ethoxycycloheptimidazoles thus obtained are listed in Table I.

Reaction of 5-Bromo-2-methoxytropone (XV) with O-Ethylisourea——Fourty grams of XV was reacted with O-ethylisourea hydrochloride as described for the preparation of II from I. The resulting inorganic salt was filtered off, the filtrate was concentrated and filtered to give a crude product of 6-bromo-2-ethoxycycloheptimidazole (IX). The mother liquor was evaporated to dryness and the residue was chromatographed on alumina with benzene and then with AcOEt. The crystals obtained from the benzene eluate were combined with the above-mentioned crude product and recrystallized from water to 11.2 g of IX as colorless scales, mp 141°. The analytical data are shown in Table I. UV λ_{max}^{EtOH} mμ (log ε): 224 (4.12), 259 (4.61), 343 (4.32).

The AcOEt eluate was evaporated to dryness and the residue was recrystallized from benzene to O-ethyl-N-(2-ethoxytropon-5-yl)isourea (XVI) as pale yellow crystals, mp 191—192°. Yield, 0.61 g. *Anal.* Calcd. for $C_{12}H_{16}O_3N_2$: C, 61.00; H, 6.83; N, 11.86; OC_2H_5, 38.14. Found: C, 60.86; H, 6.69; N, 12.02; OC_2H_5, 37.70. UV λ_{max}^{EtOH} mμ (log ε): 232 (4.335), 350 (4.185). IR ν_{max}^{Nujol} cm^{-1}: 3356, 3185, 1661, 1631. NMR (in $CDCl_3$) τ: 8.67 (3H, triplet, J=7 cps), 8.52 (3H, triplet, J=7 cps), 5.97 (2H, quartet, J=7 cps), 5.74 (2H, quartet, J=7 cps).

Acid Hydrolysis of XVI——A solution of 150 mg of XVI in 3 ml of 10% HCl was heated on a water bath for 3 hr. The reaction mixture was neutralized with aqueous NaOH and the separated crystals were collected to 76 mg of pale yellow crystals, mp 210° (decomp.), which colored with $FeCl_3$ solution. *Anal.* Calcd. for $C_8H_7O_4N$[5-tropolonylcarbamic acid (XVIII)]: C, 53.04; H, 3.90; N, 7.73. Found: C, 53.65; H, 4.32; N, 8.31. UV λ_{max}^{EtOH}: 231, 343 mμ. IR ν_{max}^{Nujol} cm^{-1}: 3205 (broad), 1730, 1650.

The filtrate was extracted with $CHCl_3$, the extracted was dried over Na_2SO_4 and evaporated to 34 mg of yellow crystals, mp 169—172°, which were identical with an authentic sample of 5-aminotropolone (XVII) by mixed mp determination and comparison of their IR spectra.

Hydrolysis of XVI with Alkali——To an EtOH solution (5 ml) of 150 mg of XVI, 5 ml of aqueous NaOH was added and the solution was heated on a water bath for 5 hr. After removal of EtOH, the residue was dissolved in water and neutralized with dil. HCl. The separated crystals (67 mg) were collected and recrystallized from EtOH to 5-cyanaminotropolone (XIX) as yellow crystals, which gradually changed to black

10) All melting points are uncorrected.

11) N. Soma, J. Nakazawa, T. Watanabe, Y. Sato, and G. Sunagawa, *Chem. Pharm. Bull.* (Tokyo), **13**, 457 (1965).

from around 195° and did not melt at 290°. *Anal.* Calcd. for $C_8H_6O_2N_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.12; H, 4.01; N, 17.54. UV λ_{max}^{EtOH} mμ (log ε): 232.5 (4.33), 343 (4.04), 381 (4.10), 398 (4.09). IR ν_{max}^{Nujol} cm^{-1}: 3226, 2700 (broad), 2222, 1623.

Transetherification of II——i) To BuOH solution of BuONa, prepared from 0.76 g of Na and 50 ml of BuOH, 5.2 g of II was added and the mixture was refluxed for 1 hr. After removal of BuOH, the residue was dissolved in benzene and chromatographed on alumina with benzene. Evaporation of the eluate gave 4.16 g of a colorless oil, which was characterized as a picrate. The picrate was recrystallized from BuOH to yellow crystals, mp 172—173°. *Anal.* Calcd. for $C_{18}H_7O_8N_5$[picrate of 2-buthoxycycloheptimidazole (XXIV)]: C, 50.12; H, 3.97; N, 16.24. Found : C, 50.03; H, 4.00; N, 16.38.

ii) To a solution of 14 mg of metallic Na dissolved in 5 ml of EtOH, 0.1 g of XXIX obtained as in i) was added and the mixture was refluxed for 20 min. After removal of EtOH, the residue was chromatographed on alumina with benzene and then ether. The benzene eluate gave 17 mg of unchanged XXIX. The ether eluate was evaporated to dryness and the residue was recrystallized from cyclohexane to 46 mg of colorless crystals, mp 101—102°, undepressed on admixture with II obtained from IV and NaOEt.

Reaction of II with Amines——i) Reaction with ammonia: A mixture of 70 mg of II and 50 ml of EtOH saturated with NH_3 was heated in a sealed tube for 3 hr at 100—110°. After removal of EtOH and excess NH_3, the residue was recrystallized from EtOH to 60 mg of yellow crystals, mp 295° (decomp.), which were identified with an authentic sample of 2-aminocycloheptimidazole (VI) by mixed mp determination and from their UV and IR spectra.

ii) Reaction with dimethylamine: By the same procedure as for the reaction of II with NH_3, 30 mg of II was allowed to react with dimethylamine to give 40 mg of yellow crystals, mp 133.5—134°, which were identical with an authentic sample of 2-dimethylaminocycloheptimidazole (XXX) by mixed mp determination and comparison of their UV and IR spectra.

4-Dimethylamino-2-ethoxycycloheptimidazole (XXXI)——To a solution of 0.2 g of Na in 50 ml of EtOH, 0.7 g of dimethylamine hydrochloride and then 2.0 g of 4-bromo-2-ethoxycycloheptimidazole (VIII) were added. The mixture was heated in a sealed tube for 3 hr at 100°. After filtration, the filtrate was passed through a column of ion-exchange resin (Amberlite IRA-410). The eluate was evaporated to dryness and the residue was submitted to chromatography on alumina with AcOEt. The eluate was evaporated to dryness and the residue was recrystallized from AcOEt to 1.51 g of yellow needles, mp 92—93°. *Anal.* Calcd. for $C_{12}H_{15}ON_3$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.24; H, 6.92; N, 19.19.

6-Dimethylamino-2-ethoxycycloheptimidazole (XXXII)——By the same procedure as described for XXXI, 6-bromo-2-ethoxycycloheptimidazole (IX) was allowed to react with dimethylamine to give XXXII as yellow crystals, mp 159—160°, in 88% yield. *Anal.* Calcd. for $C_{12}H_{15}ON_3$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.40; H, 6.98; N, 19.15.

2,6-Diethoxycycloheptimidazole (XXXIII)——i) To an EtOH solution of NaOEt, prepared from 0.1 g of Na and 20 ml of EtOH, 1 g of IX was added and the mixture was refluxed for 3 hr. After removal of EtOH, the residue was washed with water, recrystallized from water, and dried at 40—50° under reduced pressure to give 0.74 g of white crystals, mp 119—120°. *Anal.* Calcd. for $C_{12}H_{14}O_2N_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 65.95; H, 6.45; N, 13.34.

ii) To an EtOH solution of NaOEt, prepared from 0.105 g of Na and 20 ml of EtOH, 1 g of 2-ethoxy-6-nitrocycloheptimidazole (XII) was added and the mixture was stirred for 3 hr at room temperature. The reaction product was obtained by the same treatment as described in i). mp 119—120°. Yield, 0.88 g. This product was identical with the product obtained in i) by mixed mp determination and comparison of their IR spectra.

6-Bromo-4-(*p*-dimethylamino)phenyl-2-ethoxycycloheptimidazole (XXXIV)——To a mixture of 0.22 g of metallic Li and 45 ml of dehyd. ether, ether solution (5 ml) of 3.16 g of *p*-(dimethylamino)bromobenzene was added and the mixture was refluxed for 1 hr. A suspension of 2 g of IX in 10 ml of dehyd. ether was added and the mixture was refluxed for 15 min. Water was added and the resultant mixture was extracted with $CHCl_3$. The extract was dried over Na_2SO_4, $CHCl_3$ was evaporated, and the residue was chromatographed on alumina with ether as developer. Removal of ether from the eluate and recrystallization of the residue from cyclohexane gave 0.53 g of red needles, mp 183—185°. *Anal.* Calcd. for $C_{18}H_{18}ON_3Br$: C, 58.07; H, 4.87; N, 11.29. Found: C, 58.51; H, 5.10; N, 10.89. UV λ_{max}^{EtOH} mμ (log ε): 260.5 (4.61), 295 (shoulder), 341(4.29), 340 (shoulder), 465 (4.16).

Cycloheptimidazol-2(1*H*)-ones (XXXV to XLIII)——An example is cited for 4-bromocycloheptimidazol-2(1*H*)-one (XXXV). A mixture of 300 mg of VIII and 5 ml of 5% HBr solution was heated on a water bath for 30 min. The solution was neutralized with aq. NaOH and cooled in an ice bath. The separated crystals were collected and recrystallized from MeOH to 200 mg of pale yellow crystals, which changed to black from around 220° but did not melt up to 290°. The analytical data are shown in Table II.

Cycloheptimidazol-2(1*H*)-one and other substituted derivatives (XXXVI to XLIII) were obtained by the similar procedure as above (Table II).

2-Ethoxycycloheptimidazol-6(1*H*)-one (XLIV)——i) A solution of 0.2 g of XXXIII in 5% AcOH solution was heated at 40° for 30 min and then neutralized with aq. $NaHCO_3$. The separated crystals were collected

and recrystallized from water to 0.13 g of colorless crystals, mp 226—227°. *Anal.* Calcd. for $C_{10}H_{10}O_2N_2 \cdot \frac{1}{2}H_2O$: C, 60.29; H, 5.57; N, 14.06. Found: C, 60.48; H, 5.45; N, 13.94. UV λ_{max}^{EtOH} mμ (log ε): 246 (4.37), 350 (4.37).

ii) A mixture of 0.3 g of IX and 9 ml of 10% NaOH solution was heated on a water bath for 1 hr. The reaction mixture was neutralized with dil. HCl and filtered. The separated crystals were dissolved in 10% HBr solution. The solution was adjusted to pH 1.6—1.8 and filtered. The separated crystals were recrystallized from water to 0.06 g of XLIV as colorless crystals, mp 226—227°, which were identical with the product obtained in i) by mixed mp determination and comparison of their UV and IR spectra. The filtrate, on adjusting to pH 2.4—2.8, gave 0.06 g of 6-bromocycloheptimidazol-2(1*H*)-one (XXXVI), which was identical with the product of hydrolysis of LX with dil. HBr by comparison of their UV and IR spectra.

Methylation of 3-Tropolonecarboxylic Acid (XXI)——To a suspension of 3.9 g of XXI in 300 ml of ether, ether solution of excess CH_2N_2 was added and the mixture was allowed to stand overnight. After removal of ether, the residue was chromatographed on acid alumina with ether as a solvent. The eluate was evaporated and the residue was recrystallized from benzene-cyclohexane to 1.7 g of methyl 7-methoxy-2-troponecarboxylate (XX) as colorless needles, mp 81—82°. *Anal.* Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.94; H, 5.17. UV λ_{max}^{EtOH} mμ (log ε): 243 (4.29), 323 (3.91), 354 (3.87). IR ν_{max}^{Nujol} cm^{-1}: 1730.

Concentration of the mother liquor from the recrystallization of XX left a colorless liquid which on distillation gave methyl 2-methoxy-3-troponecarboxylate (XXII) as pale yellow oil, $bp_{0.001}$ 81—84°. *Anal.* Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.23; H, 5.35. UV λ_{max}^{EtOH} mμ(log ε): 230 (4.25), 323 (3.84). IR ν_{max}^{liq}: 1736 cm^{-1}.

7-Aminotropone-2-carbonitrile (XXV)——A mixture of 1 g of 7-methoxytropone-2-carbonitrile (XXIV) and 100 ml of EtOH saturated with NH_3 was allowed to stand overnight at room temperature. After removal of EtOH and excess NH_3, the residue was recrystallized from EtOH to 0.65 g of yellow needles, mp 213—215°. *Anal.* Calcd. for $C_8H_6ON_2$: C, 65.75; H, 4.14; N, 19.7. Found: C, 65.69; H, 4.11; N, 18.98.

7-Aminotropone-2-carboxamide (XXIII)——i) A solution of 1.83 g of XXV in 18 ml of conc. H_2SO_4 was allowed to stand at room temperatures overnight. The solution was poured on ice and neutralized with Na_2CO_3 solution. The aqueous solution was extracted with $CHCl_3$. The extract, dried over Na_2SO_4, was evaporated to dryness and the residue was recrystallized from EtOH to yellow needles, mp 199—200°. Yield, 0.81 g. *Anal.* Calcd. for $C_8H_8O_2N_2$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.68; H, 4.80; N, 16.73.

ii) A mixture of 0.5 g of XX and 20 ml of EtOH saturated with NH_3 was allowed to stand overnight at room temperature. After removal of EtOH and excess NH_3, recrystallization of the residue from EtOH gave 0.3 g of yellow needles, mp 199—200°, which were identified with the product obtained in i) by mixed mp determination and comparison of their UV and IR spectra.

2-Aminotropone-3-carbonitrile (XXVIII)——The preparation of XXVIII form 2-methoxytropone-3-carbonitrile (XXVII) and NH_3 was achieved in 88% yield in the same manner as described for XXV: Yellow needles, mp 155°. *Anal.* Calcd. for $C_8H_6ON_2$: C, 65.75; H, 4.17; N, 19.17. Found: C, 65.76; H, 4.13; N, 18.80.

2-Aminotropone-3-carboxamide (XXVI)——i) The preparation of XXVI from XXVIII by hydrolysis with conc. H_2SO_4 was achieved in 75% yield in the same manner as described for the preparation of XXIII from XXV by hydrolysis. Pale yellow scales, mp 241—242°. *Anal.* Calcd. for $C_8H_8O_2N_2$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.45; H, 4.91; N, 16.97.

ii) The reaction of 0.8 g of XXII with NH_3, in the same manner as described for the preparation of XXIII from XX and NH_3, gave 0.5 g of yellow crystals, which were identified with the product obtained in i) by mixed mp determination and comparison of their UV and IR spectra.

Acknowledgement The authors are grateful to Prof. S. Uyeo of Kyoto University, Prof. T. Nozoe and Prof. Y. Kitahara of Tohoku University, and Mr. M. Matsui, Research Adviser of this Laboratory, for guidance and encouragements throughout the course of this work. They are also indebted to Mr. Y. Sato for his technical assistance and to the members of the Analytical and Physico-chemical Measurement Sections of this Laboratory for elemental analyses and absorption spectra, respectively.