Chem. Pharm. Bull. 13(7) 819~828 (1965)

UDC 547.517.07

107. Nobuo Soma, Jun-ichi Nakazawa, Taiichiro Watanabe, Yoshio Sato, and Genshun Sunagawa: Studies on Seven-membered Ring Compounds. XIX.*1 Reactions of Troponeimine Derivatives. (1).*2

(*Research Laboratories, Sankyo Co., Ltd.**3)

Previous work in this series[1] has shown that the direct alkylation of 2-aminotropone derivatives with dialkyl sulfate resulted in O-alkylation yielding 2-alkoxytroponeimine derivatives. The present paper deals with some reactions of 2-alkoxytroponeimine derivatives.

The reaction of 2-methoxytroponeimine (I) with amines afforded 2-aminotroponeimine derivatives, including N-nonsubstituted (II) and N-substituted derivatives (III). The production of II and III was found to be dependent on three factors as described below. The first factor is the basicity of the utilized amines. When I was refluxed in ethanol with *p*-anisidine, 2-(*p*-anisidino)troponeimine (II, R=*p*-$CH_3OC_6H_4$) was obtained. Similar reactions with aniline, *p*-toluidine and 2-hydrazinotropone also gave the corresponding N-nonsubstituted derivatives. On the other hand, when I was allowed to react with the more basic benzylamine, substitution of both the imino as well as the methoxy group occurred even at room temperature yielding a mixture of 2-benzylaminotroponeimine (II, R=$CH_2C_6H_5$) and N-benzyl-2-benzylaminotroponeimine (III, R=$CH_2C_6H_5$). Reaction of I with methylamine similarly afforded both 2-methylaminotroponeimine (II, R=CH_3) and N-methyl-2-methylaminotroponeimine (III, R=CH_3). The second factor is the presence of proton which promotes the formation of N-substituted

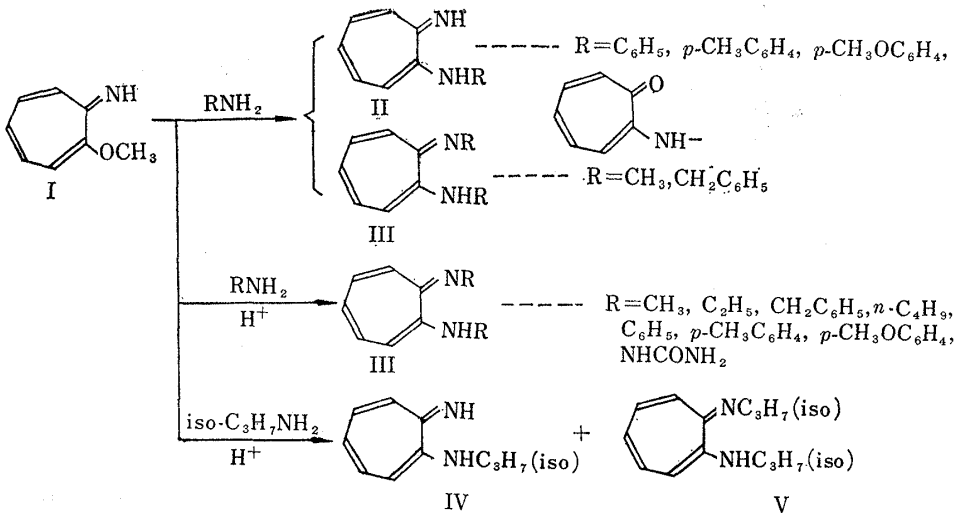

Chart 1.

derivatives (III). For instance, when the above-described reaction of I with *p*-anisidine was carried out in the presence of a small amount of acetic acid or hydrochloric acid, N-(*p*-methoxyphenyl)-2-(*p*-anisidino)troponeimine (III, R=*p*-$CH_3OC_6H_4$) was obtained, in

*1 Part XVIII: H. Nakao: This Bulletin, **13**, 810 (1965).

*2 Presented at the General Meeting of Tohoku District of the Chemical Society of Japan, Morioka, September, 1964.

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1) N. Soma, J. Nakazawa, T. Watanabe, Y. Sato, G. Sunagawa: This Bulletin, **13**, 457 (1965).

place of 2-(*p*-anisidino)troponeimine (II, R=*p*-$CH_3OC_6H_4$). Furthermore, the reactions of an apueous solution of the monomethyl sulfate of I with methylamine, ethylamine, butylamine, benzylamine, aniline, *p*-anisidine, *p*-toluidine, and semicarbazide gave respectively, the corresponding N-substituted-2-aminotroponeimine derivatives (III). The third factor is the steric effects which are exhibited by the bulky amines and cause the difficulty of the formation of N-substituted derivatives. For instance, when isopropylamine was allowed to react with I, in the presence of proton and under the same conditions which yielded no N-nonsubstituted derivatives with methylamine or butylamine, it afforded both 2-isopropylaminotroponeimine (IV) and N-isopropyl-2-isopropylaminotroponeimine (V) in about equal ratio.

Several substituted 2-alkoxytroponeimines were also allowed to react with amines in a similar procedures as described above to give the corresponding substituted

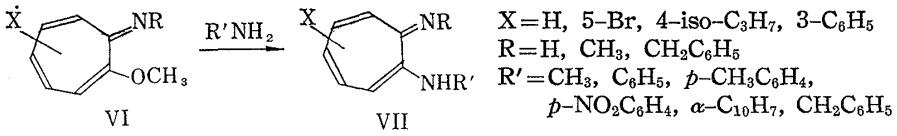


Chart 2.

2-aminotroponeimine derivatives. New 2-aminotroponeimine derivatives are listed in Table I.

While several 2-aminotroponeimines have been previously reported by Brasen[2] and Nakao,*[1] the majority of the work has dealt with the symmetrically substituted troponeimines. The present procedure for the preparation of troponeimine derivatives facilitate the preparation of N-nonsubstituted troponeimine derivatives. Therefore, the reactions of N-nonsubstituted troponeimines were examined as follows.

The N-nonsubstituted 2-aminotroponeimine derivatives (II) were converted into the N-substituted 2-aminotroponeimines (III) by reactions with amines under the appropriate conditions as follows : 2-*p*-anisidinotroponeimine (II, R=*p*-$CH_3OC_6H_4$) was converted into N-(*p*-methoxyphenyl)-2-*p*-anisidinotroponeimine (III, R=*p*-$CH_3OC_6H_4$) by refluxing in ethanol with *p*-anisidine in the presence of a small amount of acetic acid; whereas 2-methylaminotroponeimine (II, R=CH_3) and 2-benzylaminotroponeimine (II, R=$CH_2C_6H_5$) were converted into the corresponding N-substituted troponeimines by standing in ethanol at room temperature with large excess of methylamine and benzylamine,

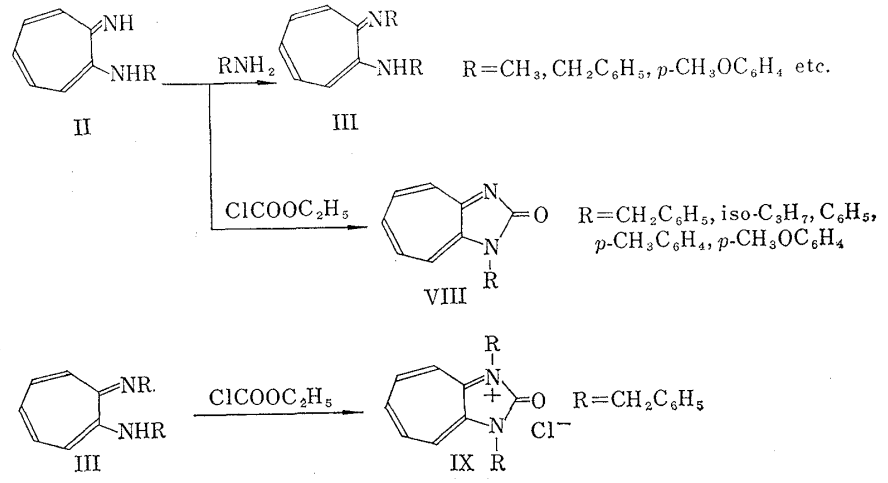
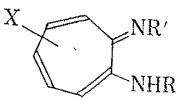
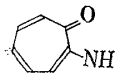


Chart 3.

2) W. R. Brasen, H. E. Holmquist, R. E. Benson : J. Am. Chem. Soc., 83, 3125 (1961).

TABLE I.



No.	X	R	R'	m.p. (°C) [b.p. (°C/mm. Hg)]	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	H	CH_3	H	64	$C_8H_{10}N_2$	71.61	7.51	20.88	71.41	7.55	20.81
				picrate 220	$C_{14}H_{13}O_7N_5$	46.28	3.61	19.28	46.62	3.99	19.30
2	〃	iso-C_3H_7	〃	[106/0.35]	$C_{10}H_{14}N_2$	74.03	8.70	17.27	73.64	8.64	17.00
				picrate 131	$C_{16}H_{17}O_7N_5$	49.10	4.38	17.90	49.09	4.42	18.05
3	〃	$CH_2C_6H_5$	〃	80	$C_{14}H_{14}N_2$	79.96	6.71	13.32	79.91	6.85	13.22
4	〃	C_6H_5	〃	92.5	$C_{13}H_{12}N_2$	79.56	6.16	14.28	79.79	6.30	14.38
5	〃	$C_6H_4CH_3(p)$	〃	87	$C_{14}H_{14}N_2$	79.96	6.71	13.32	79.69	6.76	13.49
6	〃	$C_6H_4OCH_3(p)$	〃	100	$C_{14}H_{14}ON_2$	74.31	6.24	12.38	74.30	6.20	12.44
7	〃		〃	169	$C_{14}H_{13}ON_3$	70.27	5.48	17.56	70.57	5.44	17.65
8	〃	C_2H_5	C_2H_5	[110/0.5]	$C_{11}H_{16}N_2$	74.95	9.15	15.90	74.90	9.24	16.06
				picrate 180	$C_{17}H_{19}O_7N_5$	50.37	4.72	17.28	50.23	4.80	17.19
9	〃	iso-C_3H_7	iso-C_3H_7	62	$C_{13}H_{20}N_2$	76.42	9.87	13.71	76.59	9.87	13.81
				picrate 171	$C_{19}H_{23}O_7N_5$	52.65	5.35	16.16	52.75	5.38	16.25
10	〃	n-C_4H_9	n-C_4H_9	[150/0.7]	$C_{15}H_{24}N_2$	77.53	10.41	12.06	77.31	10.41	11.96
				picrate 149	$C_{21}H_{27}O_7N_5$	54.65	5.90	15.18	54.64	6.09	15.44
11	〃	$-NHCONH_2$	$-NHCONH_2$	222 (decomp.)	$C_9H_{12}O_2N_6$	45.76	5.12	35.58	45.57	5.22	35.64
12	5-Br	$CH_2C_6H_5$	$CH_2C_6H_5$	126	$C_{21}H_{19}N_2Br$	66.49	5.09	7.39	66.67	5.03	7.57
13	4-iso-C_3H_7	CH_3	CH_3	picrate 198	$C_{18}H_{21}O_7N_5$	51.55	5.05	16.70	51.41	5.15	17.09
14	3-C_6H_5	〃	〃	〃 159	$C_{21}H_{19}O_7N_5$	55.63	4.22	15.45	55.40	4.30	15.34
15	H	C_6H_5	〃	115	$C_{14}H_{14}N_2$	79.96	6.71	13.32	79.94	6.77	13.32
16	〃	$C_6H_4 \cdot CH_3(p)$	〃	98	$C_{15}H_{16}N_2$	80.32	7.19	12.49	80.22	7.12	12.56
17	〃	$C_6H_4 \cdot NO_2(p)$	〃	165	$C_{14}H_{13}O_2N_3$	65.87	5.13	16.46	65.54	5.24	16.40
18	〃	$C_{10}H_7(\alpha)$	〃	picrate 182	$C_{24}H_{19}O_7N_5$	58.89	3.91	14.31	58.76	3.89	14.40

respectively. The reactions of II with ethyl chloroformate afforded 1-substituted cycloheptimidazol-2(1*H*)-ones (VIII): 1-benzyl-(VIII, R=$CH_2C_6H_5$), 1-isopropyl-(VIII, R=iso-C_3H_7), 1-phenyl-(VIII, R=C_6H_5), 1-*p*-methoxyphenyl-(VIII, R=*p*-$CH_3OC_6H_4$), and 1-*p*-tolyl-(VIII, R=*p*-$CH_3C_6H_4$)-cycloheptimidazol-2(1*H*)-one were obtained from the corresponding 2-aminotroponeimine derivatives. The similar reaction of N-benzyl-2-benzylaminotroponeimine (III, R=$CH_2C_6H_5$) with ethyl chloroformate gave 2-oxo-1,3-dibenzylcycloheptimidazolinium chloride (IX, R=$CH_2C_6H_5$).

The reaction of I with benzamidine afforded 2-phenylcycloheptimidazole (X, R=C_6H_5). Since the formation of X (R=C_6H_5) by simple heating of I has been previously reported,[1] a doubt may raise about the role of benzamidine in this reaction. However, this doubt was dismissed by the significant increase in the yield of X (R=C_6H_5) in presence of benzamidine, and the formation of 2-(*p*-tolyl)cycloheptimidazole (X, R=*p*-$CH_3C_6H_4$) by the similar reaction of I with *p*-methylbenzamidine.

When I was allowed to react with either cyanamide or with guanidine in ethanol, 2-aminocycloheptimidazole (XI, R=H) was obtained. When this procedure was modified

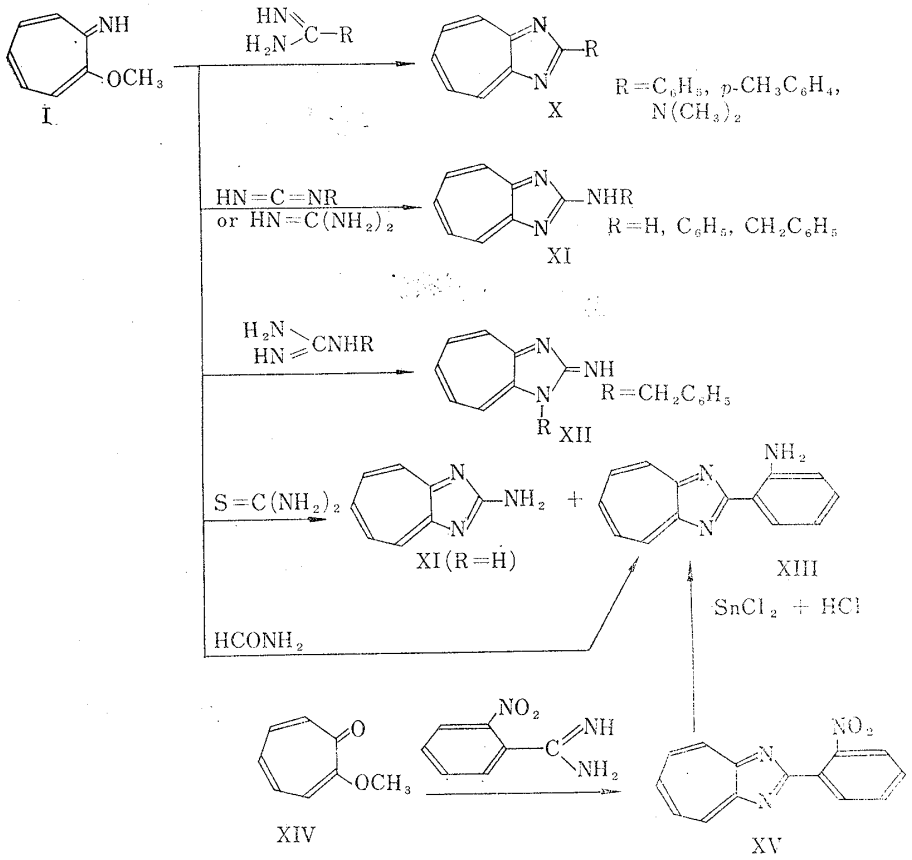


Chart 4.

by using calcium cyanamide in aqueous solution, the results were satisfactory. Furthermore, the reactions with substituted cyanimide and with substituted guanidines were examined. In this respect, the possibility of the formation of 2-substituted cycloheptimidazole and 1-substituted 2-imino-1,2-dihydrocycloheptimidazole from the reactions of I with the monosubstituted derivatives was evidenced from the production of 2-benzylaminocycloheptimidazole (XI, R=$CH_2C_6H_5$) and 1-benzyl-2-imino-1,2-dihydrocycloheptimidazole (XII, R=$CH_2C_6H_5$) respectively, from the reaction with benzylcyanamide and with benzylguanidine. The reaction of I with N,N-dimethylguanidine afforded 2-dimethylaminocycloheptimidazole (X, R=$N(CH_3)_2$).

When I was refluxed in ethanol with thiourea, 2-aminocycloheptimidazole (XI, R=H) and 2-(*o*-aminophenyl)cycloheptimidazole (XIII) were obtained. The similar reaction of I with formamide also gave XIII. The structure of XIII was proved by identification with the reduction product of 2-(*o*-nitrophenyl)cycloheptimidazole (XV) which was obtained by the condensation of 2-methoxytropone (XIV) with *o*-nitrobenzamidine. The formation of XIII from I, probably, proceeds through the course shown in Chart 1, in which the attack on C-3 of the nucleus, ring contraction and dehydrogenation are involved.*4 The attack on the C-3 of tropone ring by the base and the successive ring contraction have been previously reported by Kitahara for 2,7-dihalogenotropone.[3]

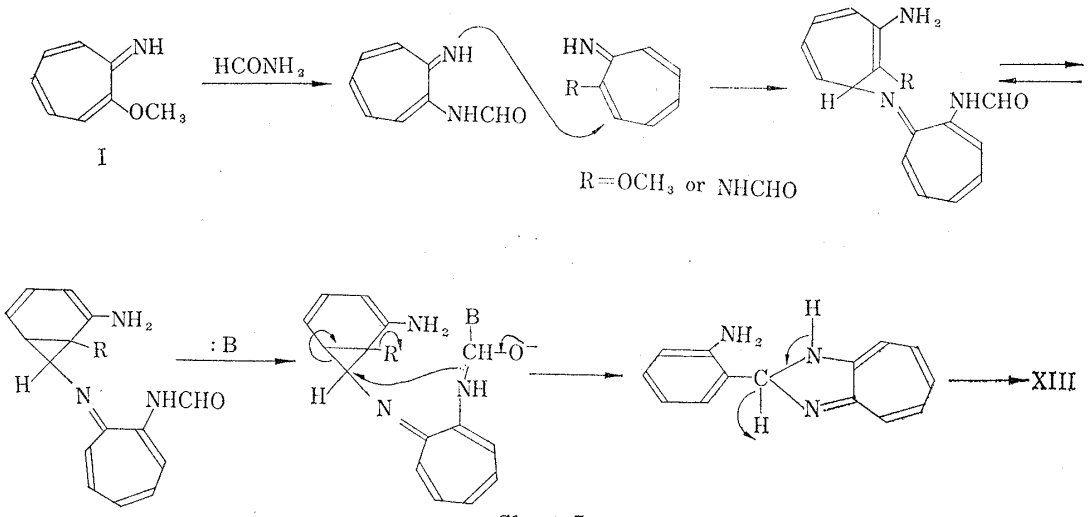


Chart 5.

The reaction of 2-methoxytroponeimine with hydrogen sulfide and with ethyl mercaptan afforded, respectively, 2-aminotroponethione (XVI, R=X=H) and 2-ethylthiotroponeimine (XVII, R=X=H). Substituted 2-methoxytroponeimines were also allowed to react with hydrogen sulfide to give the corresponding 2-aminotroponethione derivatives (XVI).

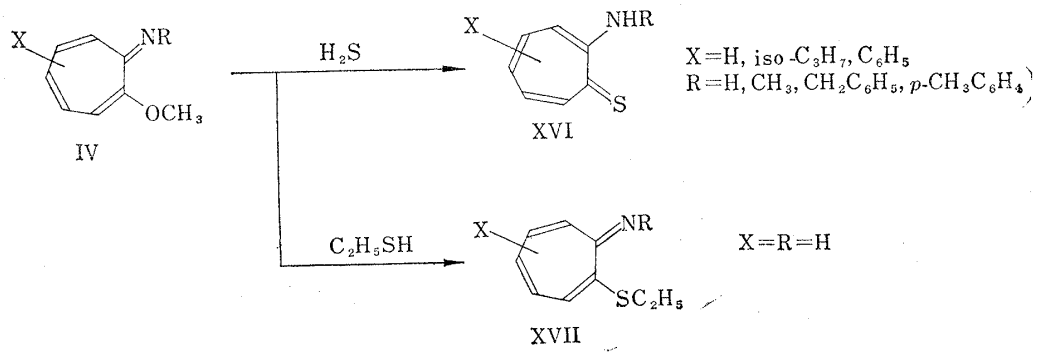


Chart 6.

Further work is now in progress on the reactions of 2-alkoxytroponeimines and will be reported in the proceeding report.

*4 The authors are grateful to Prof. Y. Kitahara and Dr. T. Asao of Tohoku University for the discussions about this reaction mechanism.

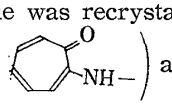
3) Y. Kitahara : Sci. Repts. Tohoku Univ., **I**, **39**, 250 (1956).

Experimental

Reactions of 2-Methoxytroponeimine (I) with Amines——i) Reactions with aniline, *p*-toludine and *p*-anisidine. (a) In the absence of proton : An example is cited for the reaction with *p*-toluidine as follows. To an EtOH solution (10 ml.) of I prepared from 1.8 g. of 2-aminotropone, was added 3.0 g. of *p*-toluidine, and the mixture was allowed to stand overnight and then refluxed for 2 hr. Ethanol was removed under reduced pressure, and the residue was acidified with 10% HCl and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with aqueous Na_2CO_3 and dried over Na_2SO_4. After removal of $CHCl_3$, the residue was chromatographed on alumina with benzene as solvent and recrystallized from cyclohexane giving 1.1 g. of 2-(*p*-toluidino)troponeimine (II, R=*p*-$CH_3C_6H_4$), m.p. 87°. The analytical data are shown in Table I. The reactions of I with aniline and with *p*-anisidine were carried out in the same manner as described above to give 2-anilinotroponeimine (II, R=C_6H_5) and 2-(*p*-anisidino)troponeimine (II, R=*p*-$CH_3OC_6H_4$), respectively. The analytical data of these products are shown in Table I. (b) In the presence of proton : To an EtOH solution (25 ml.) of I prepared from 2.0 g. of 2-aminotropone, were added 5.0 g. of *p*-anisidine and 0.5 ml. of AcOH, and the mixture was refluxed for 2 hr. The reaction mixture was treated as described in (a), and the product was recrystallized from EtOH to give 2.8 g. of N-(*p*-methoxyphenyl)-2-(*p*-anisidino)-troponeimine (III, R=*p*-$CH_3OC_6H_4$) as red prisms, m.p. 113°. *Anal.* Calcd. for $C_{21}H_{20}O_2N_2$: C, 75.88; H, 6.07; N, 8.43. Found : C, 75.69; H, 6.19; N, 8.57.

ii) Reactions with methylamine, ethylamine, butylamine and benzylamine : An example is cited for the reaction with benzylamine as follows. (a) In the absence of proton : To an EtOH solution (20 ml.) of I prepared from 3.0 g. of 2-aminotropone, was added 4.0 g. of benzylamine, and the mixture was allowed to stand at room temperature for 3 days. The resulted mixture was treated in the same manner as described for the reaction with *p*-toluidine in (i) (a), except that benzene and then $CHCl_3$ were used as the solvent for the chromatography. The benzene eluate gave 1.6 g. of N-benzyl-2-benzylaminotroponeimine (III, R=$CH_2C_6H_5$), m.p. 82°, which was identified with the authentic sample by mixed melting point determination; the $CHCl_3$ eluate gave 1.7 g. of 2-benzylaminotroponeimine (II, R=$CH_2C_6H_5$), m.p. 64°, the analytical data of which are shown in Table I. In another experiment, the reaction was carried out under reflux for 2 hr. and the reaction mixture was treated as described above to give 1.2 g. of III (R=$CH_2C_6H_5$) and 0.8 g. of II (R=$CH_2C_6H_5$). Similarly, the reaction of I with methylamine was carried out as described above to give N-methyl-2-methylaminotroponeimine (III, R=CH_3), m.p. 67°, and 2-methylaminotroponeimine (II, R=CH_3), m.p. 64°. The analytical data are shown in Table I. (b) In the presence of proton : To an aqueous solution (30 ml.) of the monomethyl sulfate of I prepared from 3.0 g. of 2-aminotropone, there was added a solution of 15 g. of benzylamine in 15 ml. of EtOH, and the mixture was allowed to stand overnight. The separated crystals were filtered and recrystallized from EtOH to give 6.9 g. of N-benzyl-2-benzylaminotroponeimine (III, R=$CH_2C_6H_5$), m.p. 82°, which was identified with the authentic sample by mixed melting point determination. In a similar procedure the reaction of the monomethyl sulfate of I with methylamine gave N-methyl-2-methylaminotroponeimine (III, R=CH_3), m.p. 67°, which was identified with the authentic sample by mixed melting point determination. The reactions of the monomethyl sulfate of I with ethylamine and with butylamine were carried out as described above, except that the products were purified by distillation to give N-ethyl-2-ethylaminotroponeimine (III, R=C_2H_5), b.$p_{0.5}$ 110°, and N-butyl-2-butylaminotroponeimine (III, R=*n*-C_4H_9), b.$p_{0.7}$ 150°, respectively. The analytical data are shown in Table I.

iii) Reaction with isopropylamine : To an aqueous solution (100 ml.) of the monomethyl sulfate of I prepared from 30 g. of 2-aminotropone, was added 38 g. of isopropylamine, and the mixture was allowed to stand at room temperature overnight. The reaction mixture was extracted with benzene, and the benzene extract, after being dried over Na_2SO_4, were concentrated and submitted to chromatography on alumina with benzene as solvent. The initial eluates, afer distillation at 112~114° under 0.6~0.7 mm. Hg, gave 7.0 g. of 2-isopropylaminotroponeimine (II, R=iso-C_3H_7), m.p. 62°, which was recrystallized from EtOH. The latter eluates gave 9.2 g. of N-isopropyl-2-isopropylaminotroponeimine (III, R=iso-C_3H_7) as yellow oil, b.$p_{0.35}$ 104~106°. Picrate, m.p. 131°. The analytical data of these products are shown in Table I.

iv) Reaction with 2-hydrazinotropone : To an EtOH solution (20 ml.) of I prepared from 2.0 g. of 2-aminotropone, was added 2.2 g. of 2-hydrazinotropone, and the mixture was allowed to stand at room temperatures for 2 days. After removal of EtOH under reduced pressure, the residue was dissolved in $CHCl_3$ and extracted with 10% HCl. The HCl solution was made alkaline with aqueous Na_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 and passed through a column of alumina. After removal of $CHCl_3$, the residue was recrystallized from benzene to give 0.8 g. of 1-(2-troponyl)-2-(2-troponeiminyl)hydrazine (II, R = ) as dark violet prisms melting at 169°. The analytical data are shown in Table I.

v) Reaction with semicarabzide: To an aqueous solution (20 ml.) of the monomethyl sulfate of I prepared from 2.5 g. of 2-aminotropone, was added 8.0 g. of semicarbazide hydrochloride and the mixture was adjusted to pH 10.0 by addition of aqueous NaOH and then allowed to stand for 2 days. The separated crytsals were filtered and recrystallized from water to give 1.5 g. of N-ureido-2-semicarbazidotroponeimine (III, R=NHCONH$_2$) as red needles, m.p. 225° (decomp.). The analytical data are shown in Table I.

Reactions of N-Methyl-2-methoxytroponeimine (VI, X=H, R=CH$_3$) with Amines——i) Reaction with methylamine: One gram of N-methyl-2-methoxytroponeimine (VI, X=H, R=CH$_3$) was added to 10 ml. of 40% aqueous solution of methylamine. The separated crystals were filtered and recrystallized from MeOH to give 0.75 g. of N-methyl-2-methylaminotroponeimine, m.p. 67°, which was identified with the authentic sample by mixed melting point determination.

ii) Reaction with *p*-toluidine: To a solution of 2.5 g. of N-methyl-2-methoytroponeimine (VI, X=H, R=CH$_3$) in 30 ml. of EtOH, was added 7.0 g. of *p*-toluidine and the mixture was allowed to stand for 2 days and then refiuxed for 3.0 hr. After removal of EtOH under reduced pressure, the residue was acidified with 10% HCl, and extracted with CHCl$_3$. The CHCl$_3$ extract was washed with aqueous Na$_2$CO$_3$ and then with water. After removal of CHCl$_3$, the residue was recrystallized from EtOH to give 2.5 g. of N-methyl-2-(*p*-toluidino)troponeimine (VII, X=H, R=CH$_3$, R'=*p*-CH$_6$C$_6$H$_4$) melting at 98°. The analytical data are shown in Table I.

iii) Reactions with aniline, *p*-nitroaniline and *α*-naphthylamine were carried out in a manner similar to that described in (ii), to give, respectively, N-methyl-2-anilinotroponeimine (VII, X=H, R=CH$_3$, R'=C$_6$H$_5$), m.p. 115°; N-methyl-2-(*p*-nitroanilino)troponeimine (VII, X=H, R=CH$_3$, R'=*p*-NO$_2$C$_6$H$_4$), m.p. 165°; N-methyl-2-(1-naphthylamino)troponeimine (VII, X=H, R=CH$_3$, R'=*α*-C$_{10}$H$_7$), m.p. of the picrate 182°. The analytical data of these products are shown in Table I.

Reaction of N-(*p*-Methylphenyl)-2-methoxytroponeimine (VI, X=H, R=*p*-CH$_3$C$_6$H$_4$) with *p*-toluidine——To an aqueous solution (20 ml.) of N-(*p*-methylphenyl)-2-methoxytroponeimine monomethyl sulfate prepared from 1.2 g. of 2-(*p*-toluidino)tropone, were added 20 ml. of EtOH and 2.0 g. of *p*-toluidine, and the mixture was allowed to stand at room temperature for 2 days. The separated crystals were filtered and recrystallized from EtOH to give orange leaflets melting at 141°, which were identified with the product obtained from the reaction of I and *p*-toluidine.

N-Methyl-2-methylamino-6-isopropyltroponeimine (VII, X=6-iso-C$_3$H$_7$, R=R'=CH$_3$)——To an aqueous solution (20 ml.) of 2-methoxy-6-isopropyltroponeimine monomethyl sulfate prepared from 2.5 g. of 2-amino-4-isopropyltropone, was added 10 ml. of 30% aqueous solution of methylamine, and the mixture was allowed to stand overnight. The reaction mixture was extracted with benzene, and the benzene extract, after concentration, was passed through a column of alumina. Benzene was evaporated to give 1.8 g. of yellow orange oil whose picrate was prepared by the usual method as yellow leaflets melting at 198°. The analytical data are shown in Table I.

N-Methyl-2-methylamino-3-phenyltroponeimine (VII, X=3-C$_6$H$_5$, R=R'=CH$_3$)——2-methoxy-3-phenyltroponeimine monomethyl sulfate was allowed to react with methylamine in the similar manner as described for the preparation of N-methyl-2-methylamino-6-isopropyltroponeimine. The picrate was obtained as yellow orange leaflets melting at 159°. The analytical data are shown in Table I.

N-Benzyl-2-benzylamino-5-bromotroponeimine (VII, X=5-Br, R=R'=CH$_2$C$_6$H$_5$)——To an aqueous solution (15 ml.) of 2-methoxy-5-bromotroponeimine monomethyl sulfate prepared from 1.0 g. of 2-amino-5-bromotropone, was added 3.0 g. of benzylamine, and the mixture was allowed to stand overnight. The separated oil was extracted with benzene, and the benzene extract was chromatographed on alumina with benzene as solvent to give 0.5 g. of yellow needles, m.p. 126°, which were recrystallized from cyclohexane. The analytical data are shown in Table I.

Reaction of 2-Methylaminotroponeimine (II, R=CH$_3$) with Methyl Amine——To a solution of 150 mg. of II (R=CH$_3$) in 1.0 ml. of EtOH, was added 4 ml. of 25% EtOH solution of methylamiene, and the mixture was allowed to stand at room temperatures for 4 days. After removal of EtOH and excess methylamine, the residue was chromatographed on alumina with benzene and recrystallized from MeOH to give 70 mg. of N-methyl-2-methylaminotroponeimine, m.p. 66°, which was identified with the authentic sample by mixed melting point determination.

Reaction of 2-(*p*-Anisidino)troponeimine (II, R=*p*-CH$_3$OC$_6$H$_4$) with *p*-Anisidine——A mixture of 0.3 g. of II (R=*p*-CH$_3$OC$_6$H$_4$), 1.0 g. of *p*-anisidine and 0.1 g. of AcOH in 10 ml. of EtOH was refluxed for 3.5 hr. After removal of EtOH, the residue was dissolved in CHCl$_3$, and the resulted solution was washed with 10% HCl, 5% Na$_2$CO$_3$, and then with water. Chloroform was evaporated to dryness, and the residue was recrystallized from EtOH to give 0.33 g. of N-(*p*-methoxyphenyl)-2-*p*-anisidinotroponeimine, m.p. 113°, which was identified with the product obtained by the reaction of I and *p*-anisidine.

1-Substituted Cycloheptimidazol-2(1*H*)-ones (VIII)——An example is cited for the 1-benzylcycloheptimidazol-2(1*H*)-one (VIII, R=CH$_2$C$_6$H$_5$). To a solution of 5.6 g. of 2-benzylaminotroponeimine (II, R=CH$_2$C$_6$H$_5$) and 3.3 g. of triethylamine in 50 ml. of benzene, there was added dropwise a solution of 3.5 g. of ethyl chloroformate in 15 ml. of benzene at 5~7°. The mixture was stirred at room temperature for 3 hr., and extracted with 10% HCl. The HCl solution, after washing with CHCl$_3$, was made alkaline with 40%

aqueous NaOH. The separated crystals were filtered, washed with water and recrystallized from MeOH to give 4.8 g. of pale yellow needles melting at 181°, which were identified with the authentic sample by mixed melting point determination.

The following products were obtained from corresponding 2-aminotroponeimines by similar procedures as described above.

1-isopropylcycloheptimidazol-2(1*H*)-one (Ⅷ, R=iso-C_3H_7) : yellow oil; picrate m.p. 222°, *Anal.* Calcd. for $C_{17}H_{15}O_8N_5$: C, 48.92; H, 3.62; N, 16.78. Found : C, 48.92; H, 3.80; N, 16.27.

1-phenylcycloheptimidazol-2(1*H*)-one (Ⅷ, R=C_6H_5) : m.p. 158°; *Anal.* Calcd. for $C_{14}H_{10}ON_2$: C, 75.65; H. 4.54; N, 12.61. Found : C, 75.31; H, 4.56; N, 12.60.

1-(*p*-tolyl)cycloheptimidazol-2(1*H*)-one (Ⅷ, R=*p*-$CH_3C_6H_4$) : m.p. 192°; *Anal.* Calcd. for $C_{15}H_{12}ON_2$: C, 76.25; H, 5.12; N, 11.86. Found : C, 76.08, H, 5.15; N, 12.03.

1-(*p*-methoxyphenyl)cycloheptimidazol-2(1*H*)-one (Ⅷ, R=*p*-$CH_3OC_6H_4$) : m.p. 213°; *Anal.* Calcd. for $C_{15}H_{12}O_2N_2$: C, 71.41; H, 4.80; N, 11.11. Found : C, 71.31; H, 4.88; N, 11.24.

2-Oxo-1,3-dibenzylcycloheptimidazolinium Chloride (IX, R=$CH_2C_6H_5$)——A mixture of 2.0 g. of N-benzyl-2-benzylaminotroponeimine (Ⅲ, R=$CH_2C_6H_5$) and 10.0 g. of ethyl chloroformate in 40 ml. of benzene was stirred at room temperatures for 2 days. The produced solid products were filtered and recrystallized from water containing a small amount of dilute HCl to give 1.1 g. of white needles, m.p. 237° (decomp.), which were identified with the authentic sample by mixed melting point determination.

2-Phenylcycloheptimidazole (X, R=C_6H_5)——To an EtOH solution (30 ml.) of I prepared from 2.5 g. of 2-aminotropone, was added a mixture of 4.1 g. of benzamidine hydrochloride and NaOEt prepared from 0.57 g. of Na in 20 ml. of EtOH. The mixture was refluxed for 7 hr. and the resulted white solid was filtered off. The filtrate was concentrated under reduced pressure, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was extracted with 5% HCl. The HCl solution, after washing with $CHCl_3$, was made alkaline with aqueous NaOH. The separated crystals were filtered and recrystallized from benzene-cyclohexane to give 2.5 g. of white needles melting at 160°, which were identified with the authentic sample by mixed melting point determination.

2-(*p*-Tolyl)cycloheptimidazole (X, R=*p*-$CH_3C_6H_4$)——In 20 ml. of EtOH, was dissolved 0.57 g. of metallic Na. To this solution, were added 4.2 g. of *p*-methylbenzamidine and an EtOH solution of I prepared from 2.5 g. of 2-aminotropone. The mixture was refluxed for 15 hr. and treated as described for the prepation of 2-phenylcycloheptimidazole (X, R=C_6H_5) giving 2.2 g. of yellow prisms melting at 182°, which showed no melting point depression on admixture with the authentic sample.

Reaction of I with Cyanamide——i) To an EtOH solution (30 ml.) of I which was prepared from 3.6 g. of 2-aminotropone, was added dropwise a solution of 1.8 g. of cyanamide in 10 ml. of EtOH, under cooling with ice-water and the mixture was allowed to stand overnight at room temperature. The separated crystals were filtered to give 2.9 g. of yellow crystals, m.p. 295° (decomp.), undepressed on admixture with an authentic sample of 2-aminocycloheptimidazole (XI, R=H).

ii) A suspension of 10 g. of calcium cyanamide in 60 ml. of water was warmed at 50° for 30 min. and filtered. To this filtrate, was added an aqueous solution (50 ml.) of the monomethyl sulfate of I prepared from 5.0 g. of 2-aminotropone. The mixture was adjusted to pH 11 with aqueous NaOH, and warmed at 50° for 1 hr. The separated crystals were filteted and recrystallized from MeOH to give 3.5 g. of yellow prisms, m.p. 295° (decomp.), undepressed on admixture with an authentic saple of XI (R=H).

Reaction of I with Guanidine——One gram of metallic Na was dissolved in 40 ml. of EtOH. To this solution, were added 4.0 g. of guanidine hydrochloride and an EtOH solution (60 ml.) of I prepared from 5.0 g. of 2-aminotropone, and the mixture was refluxed for 7 hr. Ethanol was removed under reduced pressure, and water was added to the residue. The separated crystalline mass was filtered and washed with 10 ml. of hot EtOH. Recrystallization from MeOH gave 2.3 g. of yellow prisms, m.p. 295° (decomp.), undepressed on admixture with an authentic sample of XI (R=H).

Reaction of I with Benzylguanidine——To an EtOH solution of NaOEt which was prepared from 0.3 g. of Na and 10 ml. of EtOH, there were added 2.65 g. of benzylguanidine sulfate and an EtOH solution (10 ml.) of I prepared from 1.5 g. of 2-aminotropone. The mixture was refluxed for 2 hr. and the resulted solid product was filtered off. Ethenol was removed under reduced pressure, water was added to the residue, and the mixture was extracted with benzene. Benzene was evaporated to dryness, and the residue, after treatment with a small amount of ether, was recrystallized from EtOH, to give 0.3 g. of yellow prisms, m.p. 203° (decomp.), which were identified with an authentic sample of 1-benzyl-2-imino-1,2-dihydrocycloheptimidazole (XII, R=$CH_2C_6H_5$) by mixed melting point determination and comparison of IR spectra.

Reaction of I with Benzylcyanamide——To an EtOH solution (50 ml.) of I which was prepared from 5.0 g. of 2-aminotropone, was added 7.0 g. of benzylcyanamide and the mixture was allowed to stand at room temperatures for 3 days. Ethanol was removed, and the residue was extracted with 10% HCl. The HCl solution was made alkaline with aqueous NaOH and extracted with $CHCl_3$. The $CHCl_3$ was removed and the residue was dissolved in benzene and chromatographed on alumina. The $CHCl_3$ eluate gave, after recrystallization from EtOH, 0.3 g. of yellow needles melting at 174°, which were identified

with the authentic sample of 2-benzylaminocycloheptimidazole (XI, R=$CH_2C_6H_5$) by mixed melting point determination.

Reaction of I with Phenylcyanamide——To an EtOH solution (30 ml.) of I prepared from 2.9 g. of 2-aminotropone, was added 3.4 g. of phenylcyanamide, and the mixture was allowed to stand overnight. Ethanol was removed, and the residue, after extraction with benzene, was chromatographed on alumina. The $CHCl_3$ eluate, after recrystallization from EtOH, gave yellow scales melting at 240°, which was identified with an authentic sample of 2-anilinocycloheptimidazole (XI, R=C_6H_5).

Reaction of I with N,N-Dimethylguanidine——In 20 ml. of EtOH, 0.35 g. of metallic Na was dissolved. To this solution, were added 2.0 g. of N,N-dimethylguanidine and an EtOH solution (30 ml.) of I prepared from 2.5 g. of 2-aminotropone, and the mixture was refluxed 4 hr. Ethanol was removed under reduced pressure, water was added, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ was evaporated to dryness, and the residue was chromatographed on alumina with benzene as solvent to give, after recrystallization from cyclohexane, yellow prisms melting at 134°, which were identified with an authentic sample of 2-dimethylaminocycloheptimidazole (X, R=$N(CH_3)_2$) by mixed melting point determination.

Reaction of I with Formamide——To an EtOH solution (35 ml.) of I prepared from 3.5 g. of 2-aminotropone, was added 8.0 g. of formamide, and the mixture was refluxed for 4 hr. After removal of EtOH, the residue was extracted with hot benzene. Benzene was evaporated to dryness, and the residue was recrystallized from EtOH to give 0.35 g. of red needles, m.p. 190°, undepressed on admixture with an authentic sample of 2-(*o*-aminophenyl)cycloheptimidazole (XIII) which is produced by the reduction of XV.

Reaction of I with Thiourea——To an EtOH solntion (60 ml.) of I prepared from 3.6 g. of 2-aminotropone, was added 2.3 g. of thiourea, and the mixture was reffluxed for 8 hr. Ethanol was removed under reduced pressure, and the residne was treated with hot benzene. The benzene soluble portion, after removal of the solvent and recrystallization of the residue, gave 0.1 g. of red needles, m.p. 190°, undepressed on admixture with an authentic sample of 2-(*o*-aminophenyl)cycloheptimidazole (XIII) which is produced by the reduction of XV. The benzene insoluble solid portion was extracted with 5% HCl and the HCl solution was made alkaline with aqueous NaOH. The separated crystals were filtered and recrystallized from MeOH to give 0.4 g. of pale yellow prisms, m.p. 295° (decomp.), which were identified with an authentic sample of 2-aminocycloheptimidazole by mixed melting point determination and comparison of their IR spectra.

2-(*o*-Nitrophenyl)cycloheptimidazole (XV)——In 20 ml. of EtOH, was dissolved 277 mg. of metallic Na. To this solntion, were added 3.9 g. of *o*-nitrobenzamidine benzenesulonate and 1.65 g. of 2-methoxytropone, and the mixture was refluxed for 2 hr. Ethanol was removed under reduced pressure, and water was added to the residue. The separated crystls were filtered and recrystallized from EtOH to give 0.7 g. of yellow scales melting af 200°. *Anal.* Calcd. for $C_{14}H_9O_2N_3$: C, 66.92; H, 3.61; N, 16.73. Found: C, 66.69; H, 3.59; N, 17.03.

Reduction of 2-(*o*-Nitrophenyl)cycloheptimidazole (XV)——To a solution of 0.4 g. of XV in 10 ml. of 10% HCl, was added 5 ml. of aqueous solution of 1.2 g. of stannous chloride. The separated brown solid mass was filtered, suspended in water, and warmed. The resulted red aqueous solution was made alkaline with aqueous NaOH, and extracted with $CHCl_3$. After removal of $CHCl_3$, the residue was recrystallized from EtOH to give 0.25 g. of red needles melting at 190°. This product is 2-(*o*-aminophenyl)cycloheptimidazole (XIII). *Anal.* Calcd. for $C_{14}H_{11}N_3$: C, 75.99; H, 5.01; N, 18.99. Found: C, 76.14; H, 5.11; N, 18.57.

2-Aminotroponethiones (XVI)——Examples are given for 2-aminotroponethione (XVI, R=X=H). (i) An EtOH solution (10 ml.) of I which was prepared from 3.0 g. 2-aminotropone was saturated with H_2S and allowed to stand at room temperature for 2 days. The separated crystals were filtered and recrystallized from MeOH to give 1.5 g. of orange needles melting at 137°. *Anal.* Calcd. for C_7H_7NS: C, 61.27; H, 5.15; N, 10.21. Found: C, 61.57; H, 5.18; N, 10.28. (ii) To 40 ml. of aqueous solution of the monomethyl sulfate of I which was prepared from 4.0 g. of 2-aminotropone, were added 10 g. of sodium sulfide and 15 ml. of EtOH. After standing overnight, the separated crystals were filtered and recrystallized from MeOH to yield 2.8 g. of orange needles melting at 137°, which were identified with the product obtained in (i) by mixed melting point determination.

The following products were obtained from corresponding 2-methoxytroponeimines by the similar procedure as described above.

2-Amino-4-isopropyltroponethione (XVI, X=4-iso-C_3H_7, R=H): orange oil; Cu-salt: m.p. 229°, *Anal.* Calcd. for $C_{20}H_{24}N_2S_2Cu$: C, 57.18; H, 5.76; N, 6.67. Found: C, 57.37; H, 5.72; N, 6.79.

2-Amino-5-phenyltroponethione (XVI, X=5-C_6H_5, R=H): m.p. 165°; *Anal.* Calcd. for $C_{13}H_{11}NS$: C, 73.20; H, 5.20; N, 6.57. Found: C, 72.89; H, 4.94; N, 6.75.

2-Methylaminotroponethione (XVI, X=H, R=CH_3): m.p. 68°, undepressed on admixture with an authentic sample.[4] *Anal.* Calcd. for C_8H_9NS: C, 63.55; H, 6.00; N, 9.26. Found: C, 63.29; H, 5.89; N, 8.93.

4) W. R. Brasen, R. E. Benson: J. Am. Chem. Soc., 83, 3135 (1961).

2-Benzylaminotroponethione (XVI, X=H, R=$CH_2C_6H_5$) : m.p. 138°; *Anal.* Calcd. for $C_{14}H_{13}NS$: C, 73.96; H, 5.76; N, 6.16. Found : C, 73.61; H, 5.70; N, 6.11.

2-*p*-Toluidinotroponethione (XVI, X=H, R=*p*-$CH_3C_6H_4$) : m.p. 100°; *Anal.* Calcd. for $C_{14}H_{13}NS$: C, 73.96; H, 5.76; N, 6.16. Found : C, 73.69; H, 5.70; N, 6.18.

2-Ethylthiotroponeimine (XVII, R=X=H)——To an EtOH solution (50 ml.) of I prepared from 5.0 g. of 2-aminotropone, was added 10 g. of ethyl mercaptan. The pH of the mixture was adjusted to 10, and then the mixture was allowed to stand overnight. Ethanol and excess ethylmercaptan were removed under reduced pressure, and the residue was extracted with benzene, washed with water, dried over Na_2SO_4. Removal of benzene gave 1.1 g. of yellow oil. The picrate prepared by the usual method melted at 174°. *Anal.* Calcd. for $C_{15}H_{14}O_7N_4S$: C, 45.68; H, 3.58; N, 14.21; S, 8.13. Found : C, 45.34; H, 3.86; N, 14.21; S, 8.39.

The authors are indebted to Prof. T. Nozoe and Prof. Y. Kitahara of Tohoku University, Prof. S. Ueo of Kyoto University, and Mr. M. Matsui, Director of this Laboratory for guidance and encouragement. The authors are also indebted to the members of the Analytical and Physico-chemical Measurement Sections of this Laboratory for elemental analyses and absorption spectra, respectively.

Summary

Reactions of 2-methoxytroponeimines were examined. Reactions with amines afforded 2-aminotroponeimine derivatives, including N-nonsubstituted and N-substituted derivatives. The reactions of the former products with ethyl chloroformate gave 1-substituted cycloheptimidazol-2(1*H*)-ones (Ⅷ), whereas similar reaction on a latter gave 2-oxocycloheptimidazolium derivative (Ⅸ). Reactions of benzamidine, cyanamide, guanidine and their derivatives with 2-methoxytroponeimines afforded cycloheptimidazole derivatives (X～XIII). Reactions of 2-methoxytroponeimines with hydrogen sulfide afforded 2-aminotroponethiones (XVI) and the reaction with ethyl mercaptane afforded 2-ethylthiotroponeimine (XVII).

(Received December 26, 1964)

[Chem. Pharm. Bull. 13(7) 828～837 (1965)]

UDC 547.517.07

108. Hideo Nakao, Nobuo Soma, and Genshun Sunagawa : Studies on Seven-membered Ring Compounds. XX.[*1] Reactions of Troponeimine Derivatives. (2).

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In the previous paper of this series, Soma, *et al.*[*1] reported that the reaction of 2-methoxytroponeimine (I) with amines afforded 2-aminotroponeimine derivatives. The present paper deals with the reactions of I with active methylene compounds.

It has been previously reported[1～4] that 2-chlorotropone or 2-methoxytropone reacts with active methylene compounds in the presence of sodium ethoxide to yield azulene, 1-azaazulene or 1-oxaazulene derivatives. According to these reactions, the reactions of I with active methylene compounds were carried out.

[*1] Part XIX : This Bulletin, **13**, 819 (1965).

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