Summary

Some 3β-acetoxy-5-ene steroids were reacted with sulfuryl chloride in pyridine and the corresponding 3β-acetoxy-5α,6β-dichloro steroids were obtained. Dehydroepiandrosterone acetate (VII) was transformed into 5α,6β,16,16-tetrachloro compound (VI) on treatment with sulfuryl chloride in chloroform. The reaction of androst-5-ene-3,17-dione (IX) with sulfuryl chloride in pyridine gave 6α-chloroandrost-4-ene-3,17-dione (X), whereas the same reaction on pregn-5-ene-3,20-dione (V) afforded the corresponding 5α,6β-dichloro compound (IIIa). Some transformations of compounds above-mentioned were also written.

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223. Genshun Sunagawa, Yasunobu Sato, and Mitsuo Watatani : Studies on Seven-membered Ring Compounds. VIII.*1 Syntheses of 5-Nitrosotropolone Derivatives.

(*Takamine Research Laboratory, Sankyo Co., Ltd.**2)

Anti-tumor activities of seven-membered ring compounds had been examined, owing to peculiar effects of colchicine on division cells of plants and animals.[1]

The authors also examined the anti-tumor activities of simple tropolone derivatives, and found that 5-nitrosotropolone (I) possesses remarkable anti-tumor activity on Ehrlich ascites carcinoma.[2] Recently, it was also demonstrated that nitrosoresorcine derivatives possess the anti-tumor activity on Ehrlich ascites carcinoma.[3] Accordingly, it seemed of interest to examine various 5-nitrosotropolones. The present paper describes the syntheses of some new compounds of this series.

First, an attempt was made to synthesize 3-substituted 5-nitrosotropolones by reacting 3-formylamino- (IIa),[4] 3-methoxy- (IIb),[5] 3-methylthio- (IIc)[6] and 3-phenylthiotropolone (IId)[6] with sodium nitrite in water or glacial acetic acid.

Nitrosation of IIa gave only the normal corresponding nitroso compound. Its structure was considered to be 3-formylamino-5-nitrosotropolone (IIIa), which was confirmed by the following reactions. Catalytic reduction of IIIa afforded an amino compound, which was identical with 5-amino-3-formylaminotropolone (Va) obtained from 3-amino-5-nitrotropolone (VI).[7] A similar nitrosation of IIb afforded only 3-methoxy-5-nitrosotropolone (IIIb).

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*1 Part VII. N. Soma : Yakugaku Zasshi, **82**, 898 (1962).

*2 Nishi-shinagawa, Shinagawa-ku, Tokyo (砂川玄俊, 佐藤裕信, 綿谷充雄).

1) S. Seto, S. Matsumura : Bull. Chem. Research Inst. Non-Aq. Soln., Tohoku Univ., **7**, 93 (1958).
2) This was presented at ths 19th and 21st General Meeting of Japanese Cancer Association (1960, 1962).
3) T. Ukita, *et al.*, presented at the 19th General Meeting of Japanese Cancer Association (1960).
4) Y. Kitahara : Sci. Repts. Tohoku Univ. I, **40**, 83 (1956).
5) *Idem* : *Ibid.*, I, **39**, 265 (1956).
6) T. Nozoe, M. Sato, K. Matsui : *Ibid.*, I, **37**, 211 (1953).
7) T. Nozoe, Y. Kitahara, K. Doi, M. Takahashi : Bull. Chem. Research Inst. Non-Aq. Soln., Tohoku Univ., **9**, 7 (1959).

However, nitrosation of IIc afforded 3-methylthio-5-nitrosotropolone (IIIc) and nearly an equal amount of orange needles, m.p. 191~192°, whose analytical values agreed with a composition of $C_8H_7O_4NS$. It had been reported that the nitrosation of hinokitiol gives 4-isopropyl-7-nitrotropolone, owing to steric hindrance of a isopropyl group in the 4-position.[8] On the other hand, the compound, m.p. 191~192° was identical with nitration product of IIc. It was therefore presumed to be 3-methylthio-5-nitrotropolone (IVa), owing to no steric hindrance of a methylthio group in the 3-position with 5-position, which was confirmed by conversion to 5-amino-3-methylthiotropolone (Vb). A similar nitrosation of IId afforded only the corresponding nitro compound, which was considered to be 5-nitro-3-phenylthiotropolone (IVb).

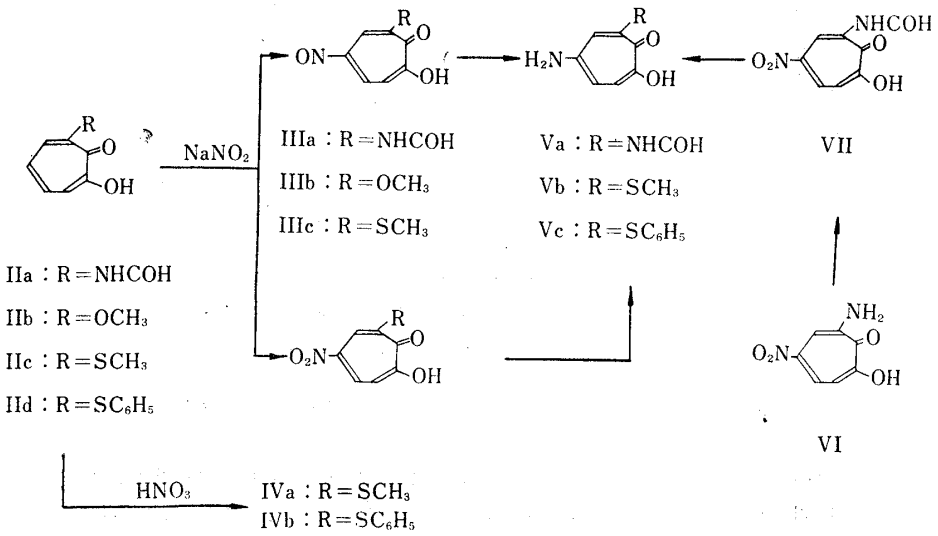


Chart 1.

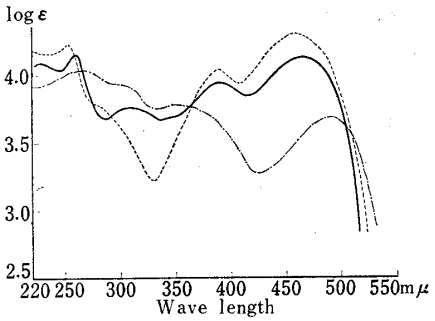


Fig. 1. Ultraviolet Spectra of 3-Substituted 5-Nitrosotropolones in Ethanol

——— IIIa
- - - - - - IIIb
— — — — IIIc

5-Nitrosotropolone (I) can be assumed to possess the configuration (I′) of 5-monoxime of unknown *p*-tropoquinone, exhibiting properties of *α*-diketone, because I undergoes condensation easily with ethylenediamine or *o*-phenylenediamine, as reported by Nozoe, *et al.* Therefore, syntheses of 7*H*-cyclohepta[*b*]pyrazin-7-one oximes (VIIIa, b), 8*H*-cyclohepta[*b*]quinoxalin-8-one oximes (IXa~c), and 9*H*-cyclohepta[*b*]naphtho[2,3-*e*]pyrazine-9-one oxime (X) were examined in accordance with Nozoe's report. It was interesting to note that dehydrogenation took place in the course of the condensation of I with ethylenediamine derivatives.[9,10]

8) T. Nozoe, S. Seto, M. Kunori, T. Sato: Proc. Japan Acad., **28**, 89 (1952).
9) T. Nozoe, S. Seto, H. Takeda, T. Sato: Sci. Repts. Tohoku Univ. I, **35**, 274 (1952).
10) S. Ito: *Ibid.*, I, **42**, 236, 247 (1958).

Thus, the condensation of I with 1,2-diamines afforded tropone oximes with the heterocyclic system, and further an attempt was made to react I with guanidine carbonate which gave reddish violet needles. Its ultraviolet spectrum was almost superimposable with 5-nitrosotropolone sodium salt,[9] as shown in Fig. 2, and its analytical values agreed with a composition of $C_8H_{10}O_3N_3$. Moreover, it was soluble in water and it regenerated I on treatment with dilute hydrochloric acid. From these results, this product was concluded to be different from an expected condensation heterocyclic compound, and was 5-nitrosotropolone guanidine adduct (XI).

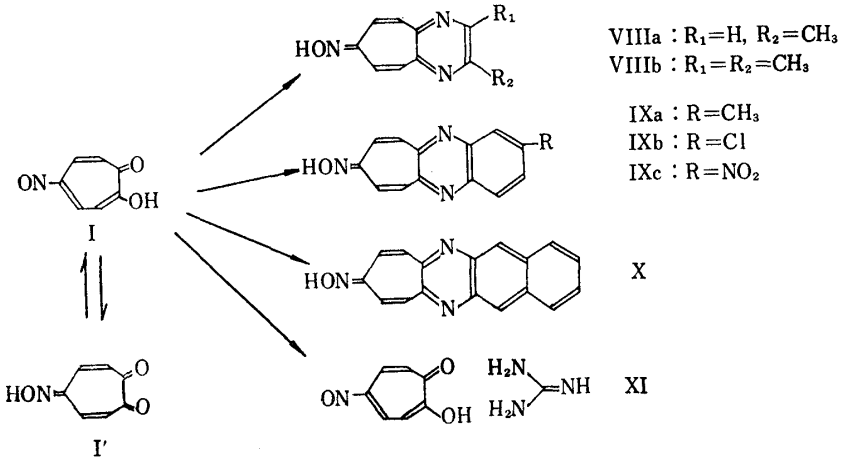


Chart 2.

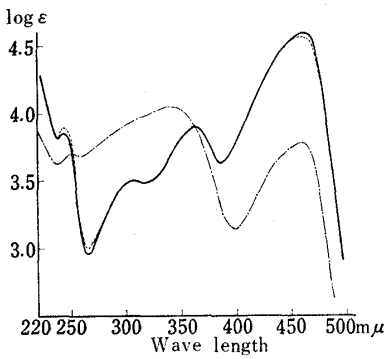


Fig. 2. Ultraviolet Spectra in Ethanol

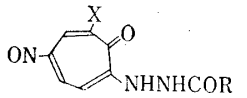
——— XI
- - - - - - 5-Nitrosotropolone sodium salt
– – – – – I

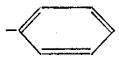
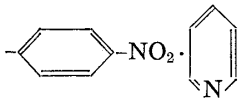
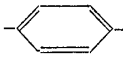
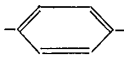
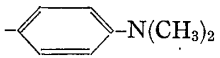
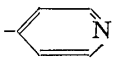
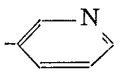
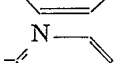
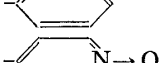
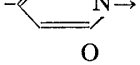
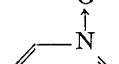
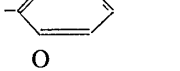
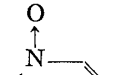
Next, the authors attempted to condense I with hydrazine derivatives. Reaction of I with hydrazine hydrate gave a resinous material and a desired material was not obtained. However, the condensation reaction of I with acetic acid hydrazide afforded yellow needles, m.p. 185° (decomp.), whose analytical values agreed with a composition of $C_9H_9O_3N_3$. The condensation product was considered to be 2-(2-acetylhydrazino)-5-nitrosotropone (XII). However, it was presumed to exist in its tautomeric form, 2-acetylhydrazono-3,6-cycloheptadiene-1,5-dione 5-oxime (XII') in a solution, because it showed a similar type of ultraviolet absorption curve as that of its acetyl derivative, which was confirmed to be 2-acetylhydrazono-3,6-cycloheptadiene-1,5-dione 5-oxime acetate (XIII). The infrared spectrum of XIII showed strong absorption bands at 1812 and 1168 cm^{-1}, which corresponded to absorption bands of I' O-acetate at 1789 and 1100 cm^{-1}, and 7*H*-cyclohepta[*b*]pyrazin-7-one oxime (VIII, $R_1=R_2=H$) O-acetate at 1764 and 1187 cm^{-1}.

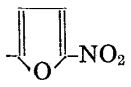
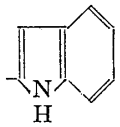
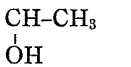
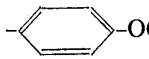
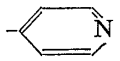
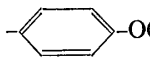
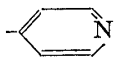
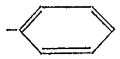
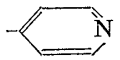
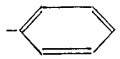
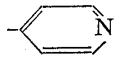
Furthermore, various 2-(2-acylhydrazino)-5-nitrosotropones were synthesized. The products prepared are listed in Table I. Similarly, the condensation reaction of I with 2-hydrazinotropone afforded 2-(2-troponylhydrazino)-5-nitrosotropone (XIV) easily.

TABLE I. 2-(2-Acylhydrazino)-5-nitrosotropones

General Formula



X (3 or 7)	R	m.p. (°C) (decomp.)	Appearance	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H		192～193	orange yellow needles	62.45	4.12	15.61	62.04	4.25	15.66
〃		199～200	orange yellow microcrystals	58.01	3.84	17.87	58.10 58.11	3.87 4.12	17.63
〃		219～220	orange needles	63.69	4.63	14.83	63.69	4.64	14.97
〃		230～231	orange yellow microcrystals	60.19	4.38	14.04	60.54	4.24	13.91
〃		221～222	reddish violet needles	60.63	5.16	17.94	60.24	5.47	17.27
〃		242～243	orange microcrystals	57.77	3.73	20.73	58.05	3.57	20.87
〃		230～231	〃	57.77	3.73	20.73	57.78	3.95	20.60
〃		225	yellow needles	57.77	3.73	20.73	57.77	3.53	20.81
〃		220	orange yellow microcrystals	54.55	3.52	19.58	54.91	3.73	19.60
〃		236	reddish orange microcrystals	54.55	3.52	19.58	54.18	3.59	19.20
〃		237～238	orange microcrystals	54.55	3.52	19.58	54.06	3.72	19.52
〃		189～190	yellow microcrystals	48.42	3.77	20.17	48.13	3.87	19.86
〃		255	〃	53.14	3.34	25.82	53.42	3.50	25.94

No.										
11	〃		243～244	orange needles	47.37	2.65	18.42	47.36	2.67	18.26
	〃		234～235	reddish orange microcrystals	62.33	3.92	18.18	62.67	4.06	17.89
	〃	H	210	yellowish brown needles	49.74	3.65	21.76	49.87	3.71	21.70
	〃	CH_3	185	yellow needles	52.17	4.38	20.28	51.93	4.45	20.72
	〃	$CH_2CH_2CH_3$	155	〃	56.16	5.57	17.86	56.67	5.75	17.69
	〃	$CH_2CH(CH_3)_2$	167～168	yellowish brown needles	57.82	6.07	16.86	57.77	6.01	16.99
	〃	$(CH_2)_6CH_3$	143～144	yellow scales	61.84	7.27	14.42	62.10	7.59	14.95
	〃	$(CH_2)_7CH_3$	115	greenish yellow microcrystals	62.93	7.59	13.76	62.85	7.56	13.70
	〃	$CH_2 \cdot OC_6H_5$	205～206	yellow silky needles	60.19	4.38	14.04	60.05	4.45	14.11
	〃		212	yellow scales	54.88	3.68	17.07	54.81	3.74	16.81
	〃		183	yellow microcrystals	50.63	4.67	17.72	50.53	4.88	17.98
	OC_6H_5		182	orange microcrystals	64.44	4.38	10.74	64.32	4.58	10.49
	OCH_3		239	〃			18.66			18.85
	Br		194～195	orange needles	47.64	3.20	11.11	47.83	3.47	11.21
	〃		232～233	orange microcrystals	44.72	2.60	16.05	45.08	2.91	15.98
	〃	CH_3	176～178	yellowish brown microcrystals	37.78	2.82	14.69	37.50	2.65	15.09
	CH_3		197	orange needles	63.59	4.63	14.83	63.70	4.72	14.77
	〃		223	orange microcrystals	59.15	4.26	19.71	59.24	4.26	19.53
	〃	$CH_2CH_2CH_3$	142～143	yellow needles	57.82	6.07	16.86	57.84	6.07	16.76
	C_6H_6		221	orange needles	69.55	4.38	12.17	69.44	4.42	12.34
	〃	$CH_2CH(CH_3)_2$	170～171	orange microcrystals	66.44	5.89	12.92	66.06	5.38	12.85
	〃		226～227	〃	65.89	4.07	16.18	65.90	4.19	15.79

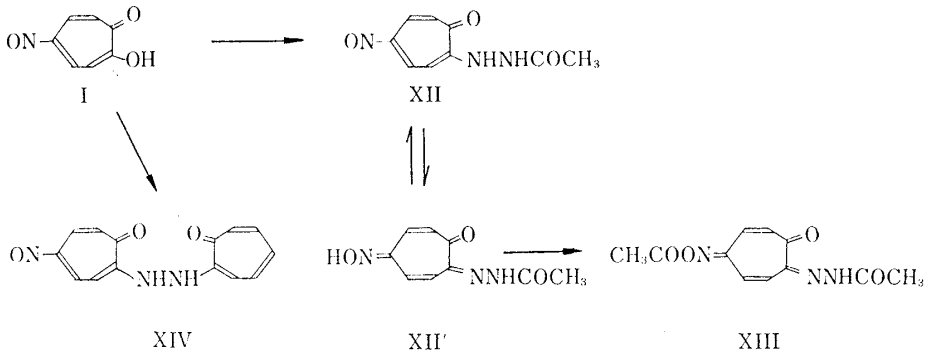


Chart 3.

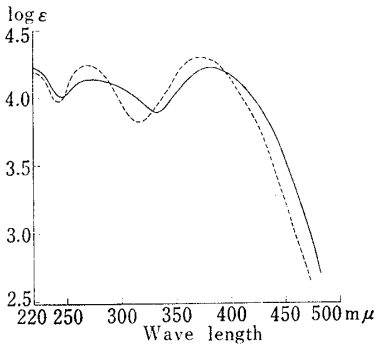


Fig. 3. Ultraviolet Spectra in Ethanol

——— XII
····· XIII

5-Nitrosotropolone derivatives synthesized showed anti-tumor activities on ascitic and solid forms of Ehrlich tumor and Sarcoma 180. Of this series, 2-(2-isonicotinoylhydrazino)-5-nitrostropone and its N-oxide showed remarkable increase in the activities as compared with I. The detailed account of the activities will be given elsewhere.

Experimental

3-Formylamino-5-nitrosotropolone (IIIa)——To a solution of 150 mg. of IIa in 6.5 ml. of AcOH, a solution of 200 mg. of $NaNO_2$ in 1 ml. of H_2O was added dropwise under cooling. The color of the solution changed to orange, and orange solid was separated out. After stirring the reaction mixture for 5 hr., the orange solid was collected by filtration. Yield, 60 mg. The solid was recrystallized from MeOH-EtOH to give orange microcrystals, m.p. 216~217°(decomp.). *Anal.* Calcd. for $C_8H_6O_4N_2$: C, 49.47; H, 3.12; N, 14.43. Found: C, 49.66; H, 3.21; N, 14.18. UV λ_{max}^{EtOH} mμ (log ε): 228 (4.09), 260.5 (4.16), 308 (3.76), 388 (3.95), 462 (4.14).

3-Methoxy-5-nitrosotropolone (IIIb)——To a solution of 152 mg. of IIb and 400 mg. of NaOH in 10 ml. of H_2O, 345 mg. of $NaNO_2$, and then 2*N* H_2SO_4 was added at 0~5°, until the solution reached to pH 1.2. After stirring the mixture for 7 hr., crystals which formed were collected. Yield, 30 mg. The crystals were recrystallized from MeOH to give brown plates, m.p. 172~173°(decomp.). *Anal.* Calcd. for $C_8H_7O_4N$: C, 53.04; H, 3.90; N, 7.73. Found: C, 53.01; H, 3.74; N, 7.53. UV λ_{max}^{EtOH} mμ (log ε): 252 (4.23), 388 (4.06), 457 (4.30).

Reaction of 3-Methylthiotropolone (IIc) and $NaNO_2$——To a solution of 3 g. of IIc in 50 ml. of AcOH and 50 ml. of H_2O, a solution of 6 g. of $NaNO_2$ in 12 ml. of H_2O was added dropwise under cooling. After stirring the mixture for 4 hr., crystals separated were collected, and recrystallized from EtOH to give 300 mg. of 3-methylthio-5-nitrotropolone (IVa) as orange needles, m.p. 191~192°. *Anal.* Calcd. for $C_8H_7O_4NS$: C, 45.08; H, 3.31; N, 6.57. Found: C, 45.28; H, 3.49; N, 6.82. UV λ_{max}^{EtOH} mμ (log ε): 310 (4.26), 386 (3.97), 405 (3.91). No depression in melting point of this product was observed upon admixture with 3-methylthio-5-nitrotropolone obtained by nitration of IIc, and the IR spectrum of the former was identical with that of the latter.

The alcoholic filtrate from the recrystallization of IVa was evaporated and the residue was recrystallized from EtOH to give 276 mg. of 3-methylthio-5-nitrosotropolone (IIIc) as reddish brown microcrystals, m.p. 205~206°(decomp.). *Anal.* Calcd. for $C_8H_7O_3N_3$: C, 48.74; H, 3.58; N, 7.11. Found: C, 48.90; H, 3.80; N, 7.03. UV λ_{max}^{EtOH} mμ (log ε): 264 (4.05), 351 (3.78), 492 (3.69). Condensation reaction of IIIc with *o*-phenylenediamine afforded 6-methylthio-8*H*-cyclohepta[*b*]quinoxalin-8-one oxime, m.p.

235～236°(decomp.). *Anal.* Calcd. for $C_{14}H_{11}ON_3S$: C, 62.45; H, 4.12; N, 15.61. Found: C, 62.50; H, 4.31; N, 15.61. UV λ_{max}^{EtOH} mμ (log ε): 246 (4.42) (shoulder), 278 (4.68), 415 (4.16).

3-Methylthio-5-nitrotropolone (IVa)——To a solution of 1 g. of IIc in 30 ml. of AcOH, a solution of 400 mg. of 94% HNO_3 in 5 ml. of AcOH was added dropwise at 15°. After stirring the mixture for 5 hr., the mixture was diluted with H_2O and the crystals separated were collected by filtration. Yield, 397 mg. The crystals were recrystallized from EtOH to orange needles, m.p. 191～192°. *Anal.* Calcd. for $C_8H_7O_4NS$: C, 45.08; H, 3.31; N, 6.57. Found: C, 45.39; H, 3.49; N, 6.59.

5-Nitro-3-phenylthiotropolone (IVb). i) Reaction of 3-Phenylthiotropolone (IId) and $NaNO_2$——To a solution of 100 mg. of IId in 26 ml. of H_2O containing 6 drops of 2*N* NaOH, 200 mg. of $NaNO_2$, and then 2*N* H_2SO_4 was added at 0～5°, until the solution reached to pH ca. 1.5. After stirring the mixture, the solid separated was recrystallized from 80% EtOH to give 25 mg. of orange needles, m.p. 190～191°. *Anal.* Calcd. for $C_{13}H_9O_4N$: C, 56.71; H, 3.29; N, 5.09. Found: C, 56.69; H, 3.48; N, 5.17. UV λ_{max}^{EtOH} mμ (log ε): 309.5 (4.25), 390 (4.06).

ii) Nitration of 3-Phenylthiotropolone (IId)——Preparation of IId was carried out by the similar manner as in the case of IVa. The product was recrystallized from 80% EtOH to give orange needles, m.p. 190～191°, which showed no depression of melting point on admixture with IVb obtained in (i).

5-Amino-3-formylaminotropolone (Va). i) Catalytic Reduction of 3-Formylamino-5-nitrosotropolone (IIIa)——Eight hundred and thirty-three milligrams of IIIa was catalytically reduced in 50 ml. of MeOH over 20 mg. of PtO_2. After 182 ml. of H_2 was absorbed, 40 ml. of MeOH was added and the reaction mixture was heated on water bath and filtered while hot. The filtrate was concentrated under reduced pressure and the residue was recrystallized from 80% EtOH to give yellowish brown needles, m.p. 192～193°(decomp.). *Anal.* Calcd. for $C_8H_8O_3N_2$: C, 53.33; H, 4.48; N, 15.55. Found: C, 53.47; H, 4.76; N, 15.65. UV λ_{max}^{EtOH} mμ (log ε): 281 (4.29), 370 (4.16), 390 (4.12) (shoulder).

ii) Catalytic Reduction of 3-Formylamino-5-nitrotropolone (VII)——Sixty-three milligrams of VII was catalytically reduced in 10 ml. of MeOH over 5 mg. of PtO_2. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was recrystallized from 80% EtOH to give yellowish brown needles, m.p. 192～193°, which showed no depression of melting point on admixture with Va obtained in (i).

3-Formylamino-5-nitrotropolone (VII)——A mixture of 270 mg. of VI and 2 ml. of 98% HCO_2H was refluxed for 3 hr. After cooling the mixture, H_2O was added to produce precipitate. The precipitate was recrystallized from H_2O-EtOH to give 100 mg. of reddish orange needles, m.p. 220°(decomp.). *Anal.* Calcd. for $C_8H_6O_5N_2$: C, 45.72; H, 2.88; N, 13.33. Found: C, 45.96; H, 3.03; N, 13.10. UV λ_{max}^{EtOH} mμ (log ε): 258 (4.23), 384 (4.15), 378 (4.12), 445 (3.98).

5-Amino-3-methylthiotropolone (Vb). i) Catalytic Reduction of 3-Methylthio-5-nitrosotropolone (IIIc)——Fifty milligrams of IIIc was catalytically reduced in 20 ml. of MeOH over 35 mg. of 10% Pd-C. After completion of the reduction, MeOH was distilled off and the residue (20 mg.) was recrystallized from EtOH to give yellowish brown needles, m.p. 285°(decomp.). *Anal.* Calcd. for $C_8H_9O_2NS$: C, 52.46; H, 4.95; N, 7.65. Found: C, 52.70; H, 5.21; N, 7.86. UV λ_{max}^{EtOH} mμ (log ε): 295 (4.34), 367 (4.10), 393 (4.04).

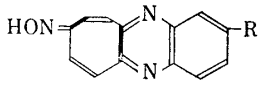
ii) Catalytic Reduction of 3-Methylthio-5-nitrotropolone (IVa)——Two hundred and thirty-three milligrams of IVa was catalytically reduced in 15 ml. of MeOH over 24 mg. of PtO_2. The reaction mixture was treated in the same way as described above, giving Vb as yellowish brown needles, m.p. 285° (decomp.). The IR spectrum of this product was identical with that of Vb obtained in (i).

5-Amino-3-phenylthiotropolone (Vc)——The reduction of IVb was carried out by the similar manner as in the case of Vb. The product was recrystallized from 50% MeOH to give yellowish brown needles, m.p. 187～188°(decomp.). *Anal.* Calcd. for $C_{13}H_{11}O_2NS$: C, 63.65; H, 4.52; N, 5.71. Found: C, 63.90; H, 4.77; N, 5.57. UV λ_{max}^{EtOH} mμ (log ε): 295 (4.22), 369 (4.11).

2-Methyl-7*H*-cyclohepta[*b*]pyrazin-7-one Oxime (VIIIa)——To a hot solution of 600 mg. of I in 60 ml. of EtOH, 350 mg. of 1,2-propylenediamine was added. The resulting mixture was refluxed for 10 min. The mixture was concentrated under reduced pressure and the residue was recrystallized from H_2O-EtOH to give yellowish brown needles, m.p. 176～177°(decomp.). *Anal.* Calcd. for $C_{10}H_9ON_3$: C, 64.16; H, 4.88; N, 22.45. Found: C, 64.35; H, 4.90; N, 22.45. UV λ_{max}^{EtOH} mμ (log ε): 232 (4.42), 280 (3.84), 353 (4.14).

2,3-Dimethyl-7*H*-cyclohepta[*b*]pyrazin-7-one Oxime (VIIIb)——Preparation of VIIIb was carried out by the similar manner as in the case of VIIIa. The product was recrystallized from 75% EtOH to give yellow needles, m.p. 247～248°(decomp.). *Anal.* Calcd. for $C_{11}H_{11}ON_3$: C, 65.67; H, 5.51; N, 20.88. Found: C, 65.74; H, 5.59; N, 20.93. UV λ_{max}^{EtOH} mμ (log ε): 233 (4.45), 284 (3.83), 354 (4.19).

8*H*-Cyclohepta[*b*]quinoxalin-8-one Oximes (IXa～c)——To a hot solution of 0.004 mole of I in 60 ml. of EtOH, a solution of 0.004 mole of *p*-substituted *o*-phenylenediamine in EtOH was added. The resulting mixture was refluxed for 15 min. After cooling the reaction mixture, the solid separated was recrystallized from a suitable solvent. (Table II).

TABLE II. General formula 

R	m.p. (°C) (decomp.)	Recryst. solvent	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	245~246	EtOH	$C_{14}H_{11}ON_3$	70.87	4.67	17.71	70.62	4.86	17.76
Cl	252~253	pyridine-H_2O	$C_{13}H_8ON_3Cl$	60.59	3.13	16.31	60.34	3.22	16.63
NO_2	300	〃	$C_{13}H_8O_3N_4$	58.21	3.01	20.89	58.28	3.13	21.02

9*H*-Cyclohepta[*b*]naphtho[2,3-*e*]pyrazin-9-one Oxime (X)——Condenesation of with 2,3-diaminonaphthalene was carried out by the similar manner as in the case of IXa. The product was recrystallized from pyridine to give orange needles, m.p. 294~295°(decomp.). *Anal.* Calcd. for $C_{17}H_{11}ON_3$: C, 74.71; H, 4.06; N, 15.38. Found: C, 74.68; H, 4.22; N, 15.26.

5-Nitrosotropolone Guanidine Adduct (XI)——To a hot solution of 600 mg. of I in 60 ml. of EtOH, a solution of 540 mg. of guanidine carbonate in aq. EtOH was added, and the mixture was refluxed for 15 min. After cooling the reaction mixture, the solid separated was recrystallized from MeOH to gived Nark reddish violet needles, m.p. 195~196°(decomp.). *Anal.* Calcd. for $C_8H_{10}O_3N_4$: C, 45.71; H, 4.80; N, 26.66. Found: C, 45.78; H, 4.74; N, 26.41. UV λ_{max}^{EtOH} mμ (log ε): 244.5 (3.88), 304 (3.51) (shoulder), 362 (3.91), 462 (4.60). This material gave positive $FeCl_3$ reaction. On acidifying a solution of XI in H_2O, the crystals of I were separated, which on condensation with *o*-phenylenediamine afforded 8*H*-cyclohepta[*b*]quinoxalin-8-one oxime, m.p. 249~250°(decomp.).

2-(2-Acylhydrazino)-5-nitrosotropones (XII and its Analogues)——To a hot solution of 1 mole of I in EtOH, a solution of 1 mole of carboxylic acid hydrazide in EtOH was added. The resulting mixture was refluxed for 5~15 min. and treated by the following manner. The products are listed in Table I. As an example, the preparation of 2-(2-acetylhydrazine)-5-nitrosotropolone (XII) is described. To a hot solution of 600 mg. of I in 60 ml. of EtOH, a solution of 340 mg. of acetic acid hydrazide in 10 ml. of EtOH was added, and the mixture was refluxed for 15 min., and concentrated under reduced pressure. The solid separated was recrystallized from 50% EtOH to give 212 mg. of yellow needles, m.p. 185° (decomp.). UV λ_{max}^{EtOH} mμ (log ε): 275 (4.13), 384 (4.22). IR: ν_{max}^{Nujol} 1678 cm^{-1}(amide C=O). Analytical data are given in Table I.

Isonicotinic Acid Hydrazide N-Methylnitrate——A solution of 6.1 g. of $AgNO_3$ in water was added to 10 g. of methyl isonicotinate methiodide and AgI was removed by filtration. To the filtrate, 10% HCl was added to remove the Ag^+ and the precipitate was removed by filtration. The filtrate was concentrated under reduced pressure and the oily residue was reacted with 2 cc. of 90% $NH_2NH_2H_2O$ in 5 ml. of EtOH for 1.5 hr. under reflux. The solid which deposited was recrystallized from 96% EtOH to give yellow needles, m.p. 180~180.5°. *Anal.* Calcd. for $C_7H_{10}O_4N_4$: C, 39.25; H, 4.71; N, 26.16. Found: C, 39.14; H, 4.61; N, 25.87.

2-Acetylhydrazono-3,6-cycloheptadiene-1,5-dione 5-Oxime Acetate (XIII)——A mixture of 500 mg. of I and 100 mg. of AcONa in 5 ml. of Ac_2O was heated on water bath for 15 min. After cooling the mixture, the crystals were collected and recrystallized from 50% EtOH to give 200 mg. of yellow needles, m.p. 128~129°. *Anal.* Calcd. for $C_{11}H_{11}O_4N_3$: C, 53.01; H, 4.45; N, 16.86. Found: C, 52.94; H, 4.53; N, 16.94. UV λ_{max}^{EtOH} mμ (log ε): 271 (4.24), 372 (4.29). IR ν_{max}^{Nujol} cm^{-1}: 1812, 1168 (O-acetate C=O), 1730 (amide C=O), 1639, 1623, 1608 (tropone C=O, C=C).

2-(2-Troponylhydrazino)-5-nitrosotropone (XIV)——Nitrosotropone XIV was prepared from I and 2-hydrazinotropone by the similar manner as in the case of XII. The product was recrystallized from dimethylformamide-water to give reddish violet needles, m.p. 245°(decomp.). *Anal.* Calcd. for $C_{14}H_{11}O_3N_3$: C, 62.45; H, 4.12; N, 15.61. Found: C, 62.62; H, 4.19; N, 15.64. UV ν_{max}^{EtOH} mμ (log ε): 252 (4.25), 500 (4.57).

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Summary

3-Substituted 5-nitrosotropolone (IIIa～c), 7*H*-cyclohepta[*b*]pyrazin-7-one oxime (VIIIa,b), 8*H*-cyclohepta[*b*]quinoxalin-8-one oxime (IXa～c), 9*H*-cyclohepta[*b*]naphtho[2,3-*e*]pyrazin-9-one oxime (X), 5-nitrosotropolone guanidine adduct (XI), 2-(2-acetylhydrazino)-5-nitrosotropone (XII and its analogues) and 2-(2-troponylhydrazino)-5-nitrosotropone (XIV) were synthesized according to the schemes shown in Chart 1, 2, and 3. In addition, some reactions related to IIIa and IIIc were described. Among these derivatives, 2-(2-isonicotinoylhydrazino)-5-nitrosotropone and its N-oxide showed remarkable anti-tumor activities on ascitic and solid forms of Ehrlich tumor and Sarcoma 180.

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224. Yasunobu Sato: Studies on Seven-membered Ring Compounds. X.*1 Nitration of 5-Hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one Derivatives and their Rearrangement Reaction to Indole Derivatives.

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In the preceding paper,[1] the author reported the syntheses of 5-hydroxycyclohepta-[*b*]pyrrol-6-(1*H*)-one derivatives from 5-tropolonylhydrazone derivatives which were obtained from 5-aminotropolone (I) in single step by the application of Japp-Klingemann method. The present work was carried out to examine the chemical reactivities of 5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one derivatives and to investigate the rearrangement reactions of their nitro-derivatives to indole derivatives. 3-Aryl-5-hydroxycyclohepta-[*b*]pyrrol-6(1*H*)-ones were also synthesized in a similar manner as described earlier.

The application of the Japp-Klingemann reaction of I with ethyl 2-benzylacetate afforded ethyl phenylpyruvate 5-tropolonylhydrazone (IIa), which on methylation with diazomethane gave ethyl phenylpyruvate 2-methoxy-5-troponylhydrazone (IIc). Cyclization of IIa with concentrated sulfuric acid in ethylene glycol afforded 2-(2-hydroxyethoxy)carbonyl-3-phenyl-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one (IIIa) whose analytical values corresponded to the composition of $C_{18}H_{15}O_5N$. The hydrolysis of ester (IIIa) with 2*N* ethanolic potassium hydroxide furnished 2-carboxy-3-phenyl-5-hydroxycyclohepta-[*b*]pyrrol-6(1*H*)-one (IVa), whose esterification with absolute ethanol afforded 2-ethoxycarbonyl-3-phenyl-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one (Va). In a similar manner, Japp-Klingemann reaction of I with ethyl 2-(*p*-chlorobenzyl)acetoacetate afforded ethyl 2-(*p*-chlorophenyl)pyruvate 5-tropolonylhydrazone (IIb), from which could by obtained 2-(2-hydroxyethoxy)carbonyl- (IIIb), 2-carboxy- (IVb) and 2-ethoxycarbonyl-3-(*p*-chlorophenyl)-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one (Vb).

An attempted decarboxylation of IVa with hydrobromic acid failed to give desired compound, but with copper powder in quinoline afforded 3-phenyl-5-hydroxycyclohepta-[*b*]pyrrol-6(1*H*)-one (VIa). A similar decarboxylation of IVb afforded 3-(*p*-chlorophenyl)-5-hydroxycyclohepta[*b*]pyrrol-6(1*H*)-one (VIb).

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