[Chem. Pharm. Bull. 13(4) 473~482 (1965)] UDC 547.517.07

62. Hideo Nakao, Nobuo Soma, Yasunobu Sato, and Genshun Sunagawa : Studies on Seven-membered Ring Compounds. XVII.*1 Alkylation of Cycloheptimidazolone and Cyclohepta[*b*]pyrrolone.

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In the course of pharmacological screening test of cycloheptimidazole derivatives which have been synthesized in the previous paper,*1 1-alkylcycloheptimidazol-2(1*H*)-one has been found to be active analgesic and anti-inflammatory agent. In an effort to obtain more effective derivatives, alkylation of cycloheptimidazolone and its carbon analogue, cyclohepta[*b*]pyrrolone, was attempted. This paper will describe details of the results.

Murata, *et al.*[1,2] reported that the methylation of cycloheptimidazol-2(1*H*)-one with diazomethane or dimethyl sulfate afforded N- and O-methyl derivatives whereas with methyl iodide in the presence of potassium hydroxide afforded only N-methyl derivative. Therefore, cycloheptimidazol-2(1*H*)-one is considered to be present in the so-called lactim-lactam tautomers. Following the Murata's method, a number of 1-alkylcycloheptimidazol-2(1*H*)-one were prepared by the reaction of cycloheptimidazol-2(1*H*)-one with alkyl halide in the presence of alkali. Similarly, acylation with acylhalide afforded 1-acyl derivatives. The synthesized 1-substituted cycloheptimidazol-2(1*H*)-one derivatives are summarized in Table I.

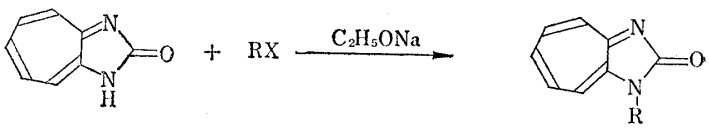
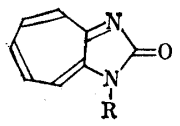


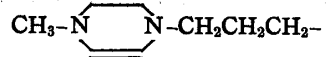
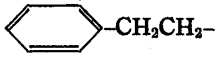
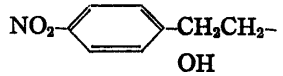
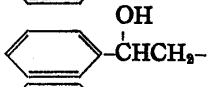
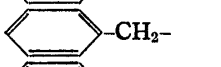
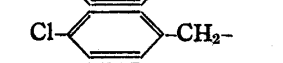
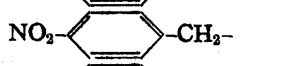
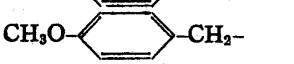
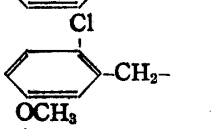
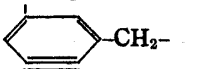
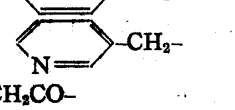
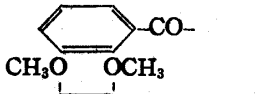
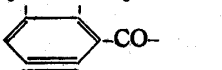
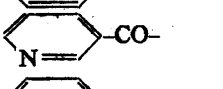
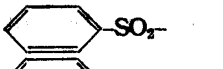
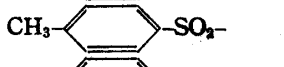
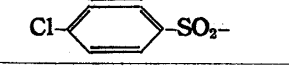
Chart 1.

Next, benzylation of 6-hydroxycycloheptimidazol-2(1*H*)-one (XXXI), which is considered to be present in the four tautomers, was attempted. The benzylation afforded di- and monobenzyl derivatives in approximately 10:1 ratio. The infrared spectrum of the former product exhibited absorption bands at 1710 and 1615 cm^{-1} for carbonyl groups of imidazolone and tropone, respectively, and the nuclear magnetic resonance spectrum showed a singlet band at 4.82 τ for four benzylic protons. From these spectral data, this compound was confirmed to be 1,3-dibenzylcycloheptimidazole-2,6-(1*H*,3*H*)-dione (XXXII). The monobenzyl derivative was assumed to be 1-benzylcycloheptimidazole-2,6(1*H*,3*H*)-dione (XXXIII) because its ultraviolet spectrum was similar to that of dibenzyl derivative. Similarly, benzylation of 4-hydroxycycloheptimidazol-2(1*H*)-one (XXXIV) afforded di- and monobenzyl derivatives. In accordance with the presence of two carbonyl groups in the infrared spectrum of the dibenzyl derivative, this compound was considered to be 1,3-dibenzylcycloheptimidazole-2,4(1*H*,3*H*)-dione (XXXV). On the other hand, the ultraviolet spectrum of the monobenzyl derivative was similar to that of the dibenzyl derivative, hence it was assumed to be either 1- or 3-benzyl derivative although further confirmation of this compound was not carried out. XXXIV was prepared by the acid hydrolysis of 2-amino-4-bromocycloheptimidazole (XXXVI), but the alkali hydrolysis of XXXVI afforded 2-amino-4-hydroxycycloheptimidazole (XXXVII). XXXIV was also obtained by the acid hydrolysis of XXXVII. Benzylation of XXXVII gave monobenzyl derivative which was assumed to be 2-amino-3-benzylcycloheptimidazol-

*1 Part XVI. Hideo Nakao, Genshun Sunagawa : This Bulletin, **13**, 465 (1965).
*2 Hiromachi, Shinagawa-ku, Tokyo (中尾英雄，相馬信夫，佐藤裕信，砂川玄俊).
1) T. Nozoe, T. Mukai, I. Murata : Proc. Japan Acad., **30**, 482 (1954).
2) I. Murata : Sci. Rep. R. I. Tohoku Univ., **12**, 271 (1960).

Table I. 1-Substituted Cycloheptimidazol-2(*H*)-one



Compound	R	m.p. (°C)	Formula	Analysis					
				Calcd.			Found		
				C	H	N	C	H	N
I	C_2H_5–	140	$C_{10}H_{10}ON_2$	68.95	5.79	16.08	68.50	5.57	16.21
II	C_3H_7–	126	$C_{11}H_{12}ON_2$	70.18	6.43	14.88	69.89	6.40	14.59
III	$(CH_3)_2CHCH_2$–	157	$C_{12}H_{14}ON_2$	71.26	6.98	13.85	71.16	6.92	13.95
IV	$CH_2=CHCH_2$–	212[a]	$C_{11}H_{11}ON_2Cl$	59.33	4.98	12.58	58.89	4.91	12.63
V	$CH\equiv CCH_2$–	166	$C_{11}H_8ON_2$	71.72	4.38	15.21	71.63	4.56	15.03
VI	$C_2H_5OOCCH_2$–	141	$C_{12}H_{12}O_3N_2$	62.06	5.21	12.06	61.90	4.71	12.30
VII	$HOCH_2CH_2$–	201	$C_{10}H_{10}O_2N_2$	63.15	5.30	14.73	62.92	5.27	14.70
VIII	$NCCH_2CH_2CH_2$–	226[a]	$C_{12}H_{12}ON_3Cl$	57.71	4.85	16.83	57.62	4.90	16.77
IX	$(CH_3)_2NCH_2CH_2$–	134	$C_{12}H_{15}ON_3$	66.34	6.96	19.34	66.65	6.84	19.03
X	$(C_2H_5)_2NCH_2CH_2$–	235[a]	$C_{14}H_{20}ON_3Cl$	52.83	6.65	13.20	52.81	6.45	12.93
XI	$(CH_3)_2N-CH_2-CH(CH_3)$–	125	$C_{13}H_{17}ON_3$	67.50	7.41	18.17	67.05	7.38	18.35
XII	$(CH_3)_2NCH_2CH_2CH_2$–	261[a]	$C_{13}H_{18}ON_3Cl$	51.32	6.29	13.81	51.65	6.65	14.04
XIII		125	$C_{16}H_{22}ON_4$	67.10	7.74	19.57	66.80	7.74	19.48
XIV		173	$C_{16}H_{14}ON_2$	76.78	5.64	11.19	76.95	5.79	11.21
XV		225	$C_{16}H_{13}O_3N_3$	65.08	4.44	14.23	64.90	4.32	14.39
XVI		246[a]	$C_{16}H_{15}O_2N_2Cl$	63.47	4.99	9.25	63.44	5.24	8.95
XVII		181	$C_{15}H_{12}ON_2$	76.25	5.12	11.86	76.14	4.96	11.98
XVIII		173	$C_{15}H_{11}ON_2Cl$	66.54	4.10	10.35	66.71	4.13	10.10
XIX		260	$C_{15}H_{11}O_3N_3$	64.54	3.94	14.94	64.47	4.06	14.73
XX		193	$C_{16}H_{14}O_2N_2$	72.16	5.30	10.52	72.14	5.27	10.35
XXI		223	$C_{15}H_{11}ON_2Cl$	66.54	4.10	10.35	66.35	4.02	10.41
XXII		154	$C_{16}H_{14}O_2N_2$	72.16	5.30	10.52	72.18	5.20	10.34
XXIII		173	$C_{14}H_{11}ON_3$	70.87	4.67	17.71	71.02	4.61	17.56
XXIV	CH_3CH_2CO–	159	$C_{11}H_{10}O_2N_2$	65.33	4.98	—	65.40	4.86	—
XXV		199	$C_{15}H_{10}O_2N_2$	71.99	4.03	11.20	72.01	3.92	11.03
XXVI		173	$C_{17}H_{14}O_4N_2$	65.80	4.55	9.03	65.86	4.57	9.18
XXVII		184	$C_{14}H_9O_2N_3$	66.92	3.61	16.73	66.58	3.71	16.58
XXVIII		150	$C_{14}H_{10}O_3N_2S$	58.73	3.52	9.79	58.52	3.43	9.86
XXIX		199	$C_{15}H_{12}O_3N_2S$	59.99	4.03	9.33	59.86	4.03	9.42
XXX		193	$C_{14}H_9O_3N_2ClS$	52.42	2.83	8.74	52.03	2.82	8.82

a) Hydrochloride

4(3*H*)-one (XXXVIII) on the basis of ultraviolet and infrared spectra. Thus, alkylation and acylation of cycloheptimidazolone yielded N-substituted derivative. This fact indicates that cycloheptimidazolone exists in lactam rather than lactim structure.

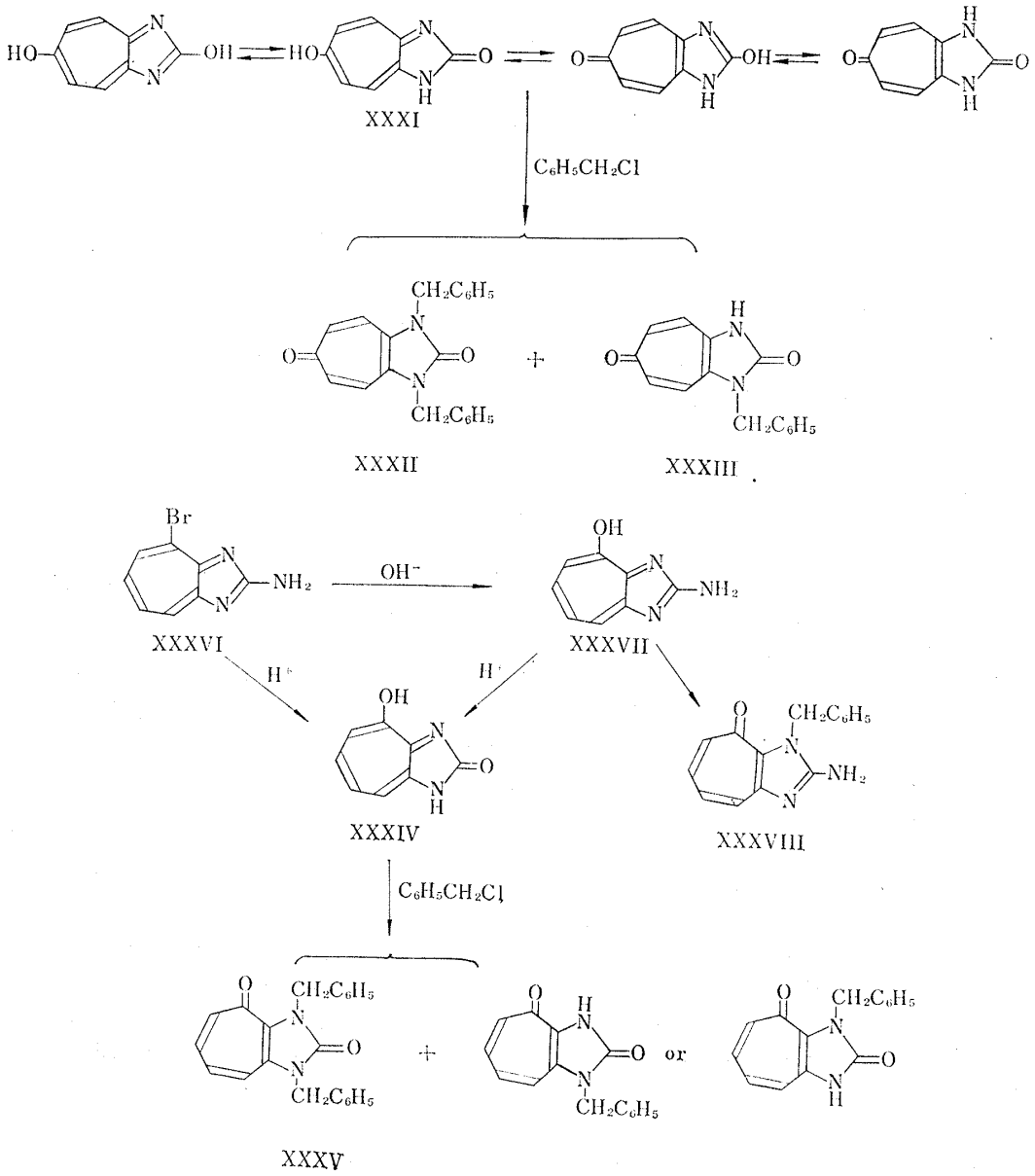


Chart 2.

Furthermore, benzylation of cyclohepta[*b*]pyrrol-2(1*H*)-one (XXXIX), which is assumed to have lactam-lactim tautomers like cycloheptimidazol-2(1*H*)-one, was attempted. Reaction of equimolar amounts of benzyl chloride and XXXIX in the presence of sodium ethoxide afforded two kinds of monobenzyl derivatives, m.p. 133° and 209°, in approximately 1:1 ratio. In the infrared spectrum of the former, no band showed at around 3000 cm^{-1} for NH or OH group but in contrast, a band at 1670 cm^{-1} for C=O group was present. Therefore, this compound was assumed to be 1-benzylcyclohepta[*b*]pyrrol-2(1*H*)-one (XL). The structure of XL was proved by its identity with an authentic sample synthesized by the successive hydrolysis and decarboxylation of 1-benzyl-3-cyanocyclohepta[*b*]pyrrol-2(1*H*)-one (XLI), which was prepared by the reaction of 2-methoxytropone with N-benzyl-2-cyanoacetamide. On the other hand, the compound of

m.p. 209°, showed a broad band at around 3000 cm^{-1} for a hydrogen bonded NH or OH group and a sharp band at 1650 cm^{-1} for C=O group. This spectrum suggested that the position of the benzyl group is neither at 1 nor 2. Since the 3-position of cyclohepta[*b*]pyrrol-2(1*H*)-one is generally attacked by cationoid reagents *e.g.* bromocation,[3] it is evident to assume that the compound of m.p. 209° is 3-benzylcyclohepta[*b*]pyrrol-2(1*H*)-one (XLII).

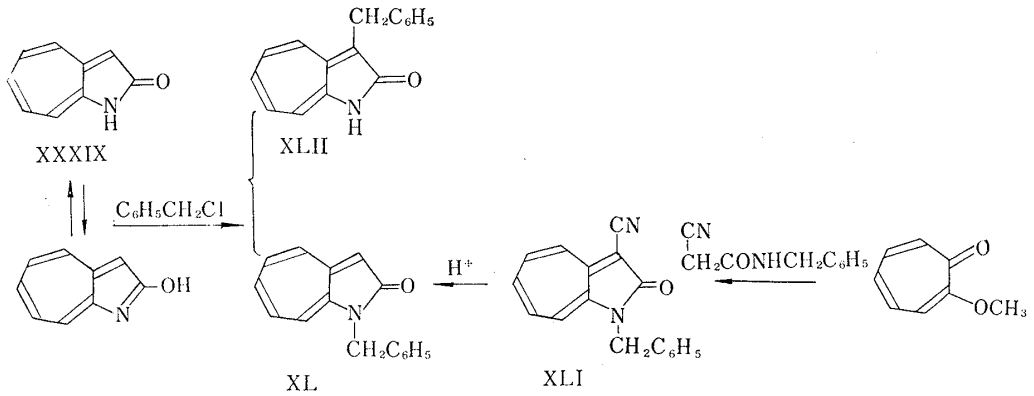


Chart 3.

Moreover, benzylation of cyclohepta[*b*]pyrrole-2,8(1*H*,3*H*)-dione (XLIII), which has been previously synthesized by Soma, *et al.*,[4] was attempted. As XLIII is assumed to have many tautomers, it was anticipated that many benzyl derivatives would be produced. Reaction of XLIII with one molar equivalent of benzyl chloride afforded mono- and dibenzyl derivatives, m.p. 223° (A) and 189° (B), respectively. The benzyl group in A was assumed to be located at either position 1 or 3, as evidenced from the above results of benzylation of cyclohepta[*b*]pyrrol-2(1*H*)-one (XXIX). This assumption has been verified by synthesizing the required 3-benzyl derivative (XLIV) by the reaction of 2-amino-3-bromotropone with diethyl benzylmalonate according to the reported Soma's method.[4] Reaction of XLII with two molar equivalents of benzylchloride afforded dibenzyl derivatives, m.p. 189° (B) and m.p. 183° (C) and tribenzyl derivatives, m.p. 162° (D) and m.p. 137° (E) in approximately 10:2:1:5 ratios. The use of three molar equivalents of benzylchloride for one mole of XLIII afforded also B, C, D, and E in approximately 2:1:20:1 ratios. Similary, benzylation of XLIV gave B, C, D, and E. Consequently, the following four structures can be proposed for the dibenzyl derivatives, B and C. The ultraviolet spectrum of B was diffierent from that of C, and

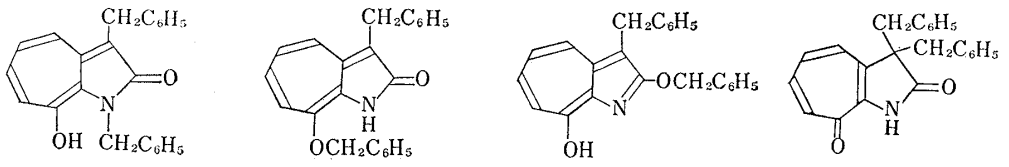


Chart 4.

similar to that of 2-acetaminotropone as shown in Figs. 1 and 2. Its infrared spectrum showed absorption bands at 3200 and 1725 cm^{-1} for NH and C=O groups, respectively. On the basis of these spectral data, B was assumed to be 3,3-dibenzyl derivative (XLV),

3) T. Nozoe, S. Seto, S. Matsumura, T. Terasawa : Chem. & Ind. (London), **1954**, 1356.
4) N. Soma, G. Sunagawa : Yakugaku Zasshi, **82**, 418 (1962).

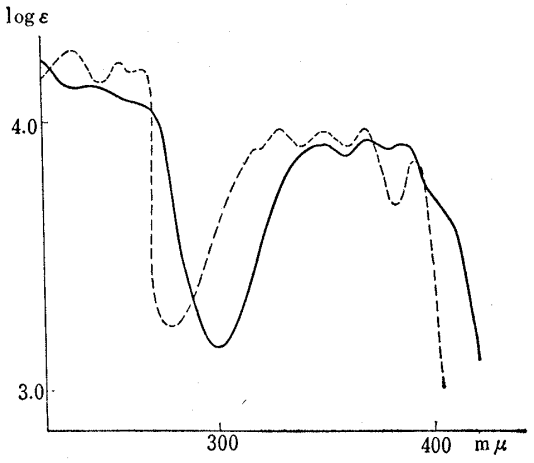


Fig. 1. Ultraviolet Spectra in Ethanol
——— B
– – – – – 2-Acetamidotropone

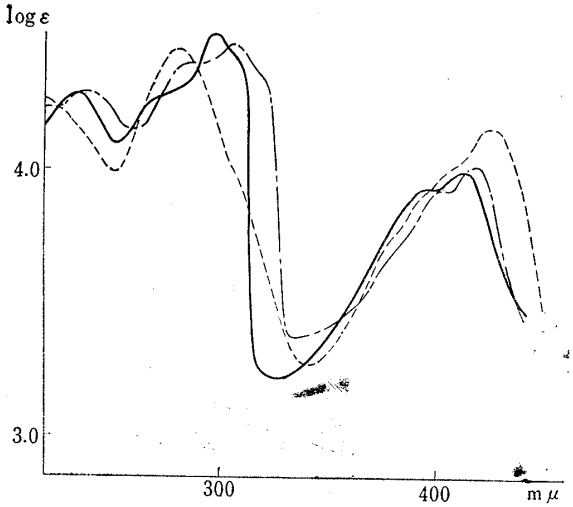


Fig. 2. Ultraviolet Spectra in Ethanol
——— C
– · – · – E
– – – – – 1-Benzyl-3-cyanocyclohepta-[*b*]pyrrol-2(1*H*)-one

which is represented as structure (iv). On the other hand, the ultraviolet spectrum of C was similar to that of 1-benzyl-3-cyanocyclohepta[*b*]pyrrol-2(1*H*)-one (Fig. 2) and its infrared spectrum showed absorption bands at 3030 and 1640 cm^{-1} for a weakly hydrogen bonded OH and C=O groups of 1-substituted-cyclohepta[*b*]pyrrol-2(1*H*)-one, respectively. Hence, C was assumed to be 1,3-dibenzyl derivative (XLVI) which is represented as structure (i).

For the tribenzyl derivatives (D) and (E), six structures can be proposed as Chart 5.

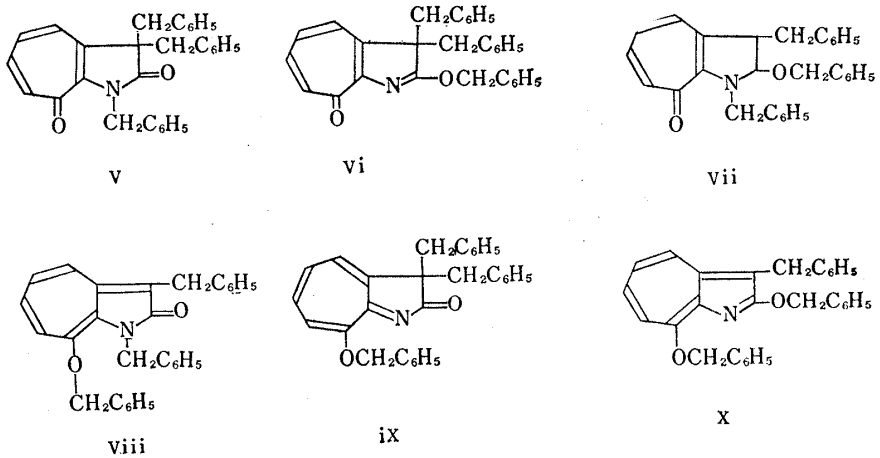


Chart 5.

The ultraviolet spectrum of D was similar to that of 3,3-dibenzyl berivative (XLV) and its infrared spectrum showed an absorption band at 1715 cm^{-1} for C=O group of γ-lactam. Consequently, D was assumed to be 1,3,3-tribenzyl derivative (XLVII), which is represented as structure (v). On the other hand, the ultraviolet spectrum of E was similar to that of 1,3-dibenzyl derivative (XLVI) (Fig. 2), and its infrared spectrum showed an absorption band at 1640 cm^{-1} as same as that of C. Therefore, E was assumed to be 8-benzyloxy-1,3-dibenzyl derivative (XLVIII), which is represented as structure (viii).

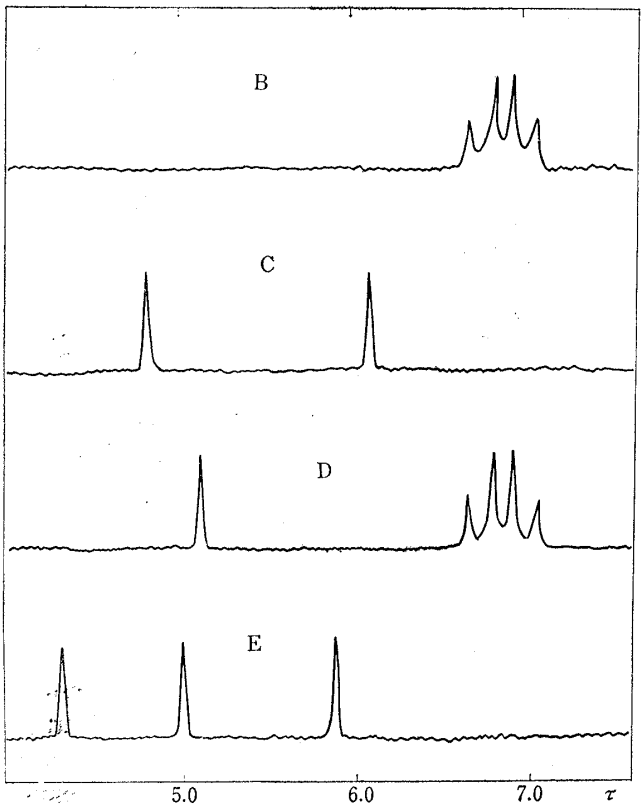
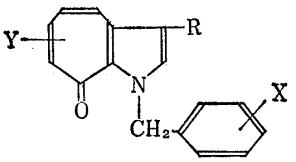


Fig. 3. Nuclear Magnetic Resonance Spectra of B (XLV), C (XLVI), D (XLVII) and E (XLVIII), at 60 Mc.p.s. (in $CDCl_3$)

Additional support for the structures of these di- and tribenzyl derivatives was given by their nuclear magnetic resonance spectra. The spectrum of B (Fig. 3) showed four-line spectra of the methylene groups at around 6.8 τ. The exact analysis of the spectra yielded chemical shifts of 6.66 and 6.93 τ (J=13 c.p.s.). Therefore, B has presumably *gem*-C-benzyl groups in which the protons of each methylene group are nonequivalent. The spectrum of C indicated the presence of C- and N-benzylic protons, represented by two singlets with equal intensity at 6.1 and 4.8 τ. The spectrum of D showed four-line spectra at around 6.8 τ as same as that of B and a singlet band with an intensity of two protons at 5.1 τ. Therefore, D was suggested to have *gem*-C-benzyl and N-benzyl groups. The spectrum of E showed three singlets of equal intensity at 5.9, 5.0, and 4.3 τ. This confirms that E has presumably C-, N-, and O-benzyl groups. From this

Table II. 1-Benzylcyclohepta[*b*]pyrrol-8(1*H*)-one Derivatives



Compound	R	X	Y	m.p. (°C)	Formula	Analysis					
						Calcd.			Found		
						C	H	N	C	H	N
L	CH_3	H	H	91	$C_{17}H_{15}ON$	81.90	6.06	5.62	82.08	6.22	5.54
LI	〃	*p*-Cl	〃	98	$C_{17}H_{14}ONCl$	71.95	4.97	4.94	71.67	4.67	5.09
LII	〃	*p*-NO_2	〃	162	$C_{17}H_{14}O_3N_2$	69.37	4.80	9.52	69.11	4.85	9.47
LIII	〃	H	7-Br	162	$C_{17}H_{14}ONBr$	62.21	4.30	4.27	62.11	4.33	4.44
LIV	〃	*p*-Cl	〃	131	$C_{17}H_{13}ONBrCl$	56.30	3.61	3.86	56.89	3.83	3.99
LV	〃	H	5-Cl	110	$C_{17}H_{14}ONCl$	71.96	4.97	4.94	71.88	5.02	4.69
LVI	〃	*m*-OCH_3	H	174[a]	$C_{24}H_{20}O_9N_4$	56.69	3.97	11.02	56.39	4.26	10.88
LVII	C_2H_5	H	〃	103	$C_{18}H_{17}ON$	82.10	6.51	5.32	81.83	6.44	5.29
LVIII	〃	*p*-Cl	〃	136[a]	$C_{24}H_{19}O_8N_4Cl$	54.71	3.63	10.63	54.99	3.48	10.86
LIX	〃	*p*-NO_2	〃	131	$C_{18}H_{16}O_3N_2$	70.11	5.23	9.09	70.23	5.39	9.46
LX	C_6H_5	H	〃	101	$C_{22}H_{17}ON$	84.86	5.50	4.50	84.96	5.51	4.85
LXI	〃	*p*-Cl	〃	116	$C_{22}H_{16}ONCl$	76.40	4.66	4.05	76.27	4.70	4.21
LXII	〃	*p*-NO_2	〃	203	$C_{22}H_{16}O_3N_2$	74.14	4.53	7.86	74.14	4.67	7.96
LXIII	〃	*o*-Cl	〃	144	$C_{22}H_{16}ONCl$	76.40	4.66	4.05	76.52	4.81	3.85
LXIV	〃	*m*-OCH_3	〃	222[a]	$C_{29}H_{22}N_4O_9$	61.05	3.89	9.82	60.86	3.78	9.90

a) Picrate

series of experiments, it became clear that benzylation of cyclohepta[*b*]pyrrol-2(1*H*)-one derivatives easily occurs at the 1- and 3-positions.

Finally, benzylation of 3-methylcyclohepta[*b*]pyrrol-8(1*H*)-one (XLIX) afforded 1-benzyl-3-methylcyclohepta[*b*]pyrrol-8(1*H*)-one (L). In addition, various 1-benzyl derivatives were synthesized. The products are listed in Table II.

Among the cycloheptimidazol-2(1*H*)-one and cyclohepta[*b*]pyrrolone derivatives obtained in this series, 1-benzylcycloheptimidazol-2(1*H*)-one has been found to be the most active analgesic and anti-inflammatory agent.

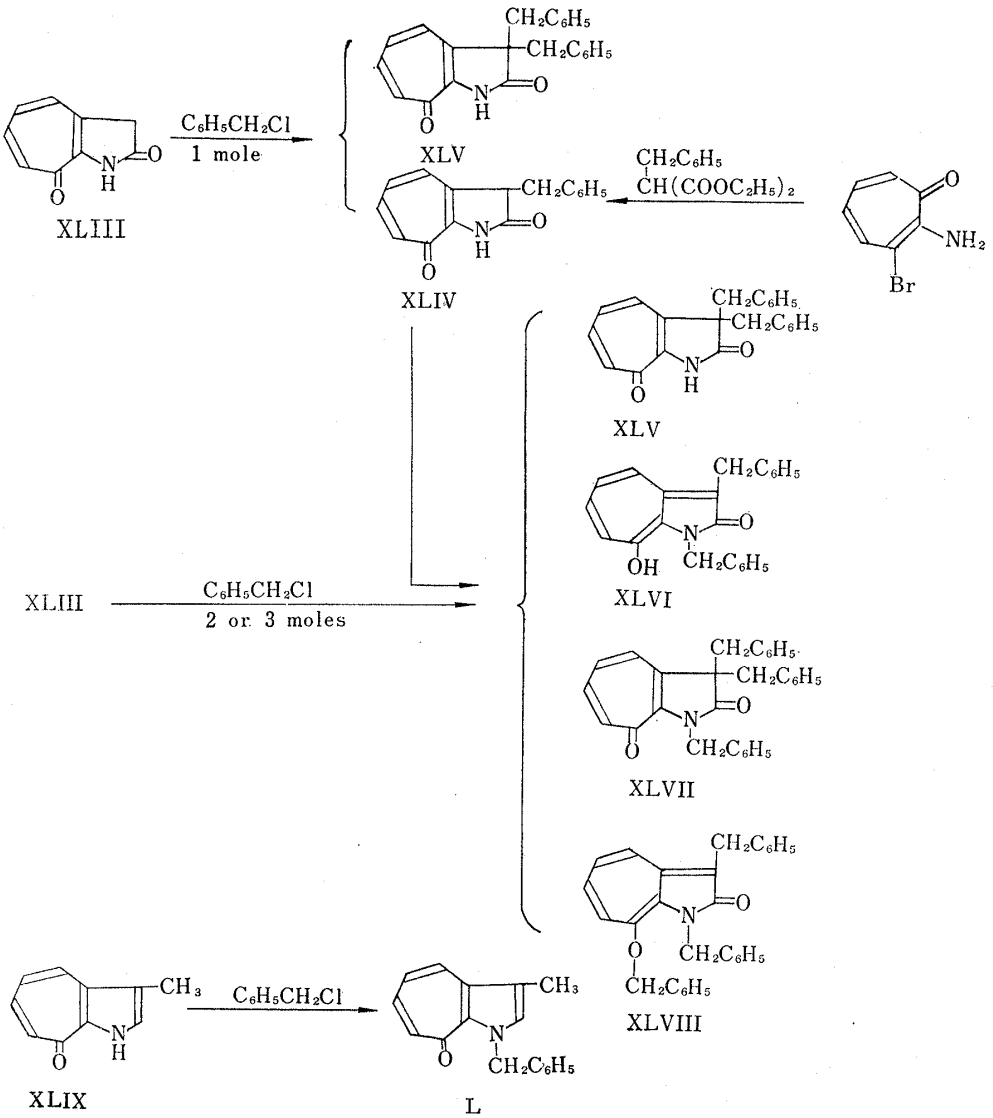


Chart 6.

Experimental

General Procedure for the Synthesis of 1-Alkylcycloheptimidazol-2(1*H*)-one——A solution of 14.6 g. of cycloheptimidazol-2(1*H*)-one in 80 ml. of 5% NaOH was concentrated to dryness giving sodium salt of cycloheptimidazol-2(1*H*)-one. Yield, 16 g. To a suspension of this sodium salt (0.01 mole) in 20 ml. of EtOH was added 0.01 mole of alkyl halide. The mixture was stirred under reflx for 5 hr. After removal of EtOH under reduced pressure, the residue was extracted with $CHCl_3$. The extract was washed with water and concentrated to dryness to give crude product. Recrystallization from EtOH or benzene gave 1-alkylcycloheptimidazol-2(1*H*)-one. Yield, 30~80%.

General Procedure for the Synthesis of 1-Acylcycloheptimidazol-2(1*H*)-one——To a suspension of sodium salt (0.01 mole) of cycloheptimidazol-2(1*H*)-one in 130 ml. of dry benzene was added 0.01 mole of acylhalide. The mixture was stirred under reflux for 2 hr. and then filtered off to remove the inorganic product. After cooling the filtrate, the separated crystals were collected and recrystallized from benzene to give 1-acylcycloheptimidazol-2(1*H*)-one. Yield, 30~70%.

Benzylation of 6-Hydroxycycloheptimidazol-2(1*H*)-one (XXXI)——To a solution of 1 g. of XXXI in 10 ml. of 5% NaOH was added 10 ml. of EtOH followed by 1.16 g. of benzylchloride. The mixture was stirred under reflux for 6 hr. After cooling, 5 ml. of 5% NaOH and 25 ml. of water were added. The separated crystals were collected by filtration and recrystallized from 70% aqueous MeOH to give 500 mg. of 1,3-dibenzylcycloheptimidazole-2,6(1*H*,3*H*)-dione, m.p. 221°. *Anal.* Calcd. for $C_{22}H_{18}O_2N_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 76.85; H, 5.32; N, 7.84. UV λ_{max}^{EtOH} mμ (log ε): 256 (4.32), 360 (4.31). IR ν_{max}^{Nujol} cm^{-1}: 1710, 1615.

The filtrate was adjusted to pH 4.5 with 10% HCl and the separated crystals were collected and recrystallized from EtOH to give 30 mg. of 1-benzylcycloheptimidazole-2,6(1*H*,3*H*)-dione, m.p. above 290°. *Anal.* Calcd. for $C_{15}H_{12}O_2N_2$: C, 71.41; H, 4.80; N, 11.11. Found: C, 71.33; H, 4.92; N, 10.80. UV λ_{max}^{EtOH} mμ (log ε): 251 (4.31), 364 (4.31). IR ν_{max}^{Nujol} cm^{-1}: 3050~3250, 1720.

Benzylation of 4-Hydroxycycloheptimidazol-2(1*H*)-one (XXXIV)——To a solution of 1 g. of XXXIV in 10 ml. of 2.5% NaOH was added 10 ml. of EtOH followed by 580 mg. of benzyl chloride. The mixture was stirred under reflux for 6 hr. After cooling, 5 ml. of 5% NaOH and 30 ml. of water were added and the mixture was extracted with $CHCl_3$. The extract was concentrated and the residue was purified by alumina chromatography followed by recrystallization from benzene-cyclohexane to give 100 mg. of 1,3-dibenzylcycloheptimidazole-2,4(1*H*,3*H*)-dione, m.p. 163°. *Anal.* Calcd. for $C_{22}H_{18}O_2N_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.17; H, 5.20; N, 7.82. UV λ_{max}^{EtOH} mμ (log ε): 231 (4.33), 261 (4.36), 271 (4.33), 325 (3.93), 380 (3.79). IR ν_{max}^{Nujol} cm^{-1}: 1720, 1620.

The alkaline mother solution was adjusted to pH 4.5 with 10% HCl, then extracted with $CHCl_3$. The insoluble solid in both $CHCl_3$ and water was identified as the starting material. The extract was concentrated and the resulted residual solid was recrystallized from EtOH to give 106 mg. of monobenzyl derivative, m.p. 234°. *Anal.* Calcd. for $C_{15}H_{12}O_2N_2$: C, 71.41; H, 4.80; N, 11.11. Found: C, 71.18; H, 4.72; N, 11.03.

2-Amino-4-hydroxycycloheptimidazole (XXXVII)——A mixture of 3 g. of 2-amino-4-bromocycloheptimidazole and 30 ml. of 20% NaOH was refluxed for 8 hr. After cooling, the mixture was filtered off to remove the insoluble material. The filtrate was neutralized with 10% HCl and the separated crystals were recrystallized from water to give 1 g. of pale yellow needles, m.p. above 280°. *Anal.* Calcd. for $C_8H_7ON_3 \cdot \frac{1}{2}H_2O$: C, 56.46; H, 4.74; N, 24.70. Found: C, 56.74; H, 4.74; N, 24.49.

4-Hydroxycycloheptimidazol-2(1*H*)-one (XXXIV)——a) A mixture of 5 g. of 2-amino-4-bromocycloheptimidazole and 30 ml. of conc. HCl was heated at 200° for 24 hr. in a sealed tube. After cooling, the mixture was made alkaline with 5% NaOH and filtered off to remove the insoluble material. The filtrate was neutralized with 10% HCl and the separated crystals were recrystallized from water giving 2 g. of pale yellow needles, m.p. above 280°. *Anal.* Calcd. for $C_8H_6O_2N_2$: C, 59.26; H, 4.98; N, 12.58. Found: C, 58.89; H, 4.91; N, 12.63.

b) By the same procedure as described above, 1 g. of XXXVII gave 0.6 g. of XXXIV.

Benzylation of 2-Amino-4-hydroxycycloheptimidazole (XXXVII)——To a solution of Na (105 mg.) in EtOH (10 ml.) and H_2O (4 ml.) was added 740 mg. of XXXVII followed by 530 mg. of benzyl chloride. The mixture was stirred under reflux for 4 hr. After cooling, 50 ml. of H_2O was added and the mixture was made alkaline with 10% NaOH and extracted with $CHCl_3$. The extract was concentrated to 10 ml. and chromatographed on alumina. From the $CHCl_3$ eluate, a crude product was obtained. Recrystallization from benzene-EtOH gave 50 mg. of yellow prisms, m.p. 230°, which were assumed to be 1-benzyl-2-aminocycloheptimidazol-8(*H*)-one (XXXVIII). *Anal.* Calcd. for $C_{15}H_{13}ON_3$: C, 71.67; H, 5.21; N, 16.72. Found: C, 71.57; H, 5.05; N, 16.89.

Benzylation of Cyclohepta[*b*]pyrrol-2(1*H*)-one (XXXIX)——A mixture of 300 mg. of sodium salt of XXXIX, 300 mg. of benzyl chloride and 4 ml. of MeOH was refluxed for 5 hr. After removal of the solvent under reduced pressure, 5 ml. of water was added, and the mixture was extracted with $CHCl_3$. The extract was concentrated to small volume and chromatographed on alumina. A solid was obtained from the first colored eluate and gave on recrystallization from cyclohexane 100 mg. of 1-benzylcyclohepta[*b*]pyrrol-2(1*H*)-one, m.p. 130°. *Anal.* Calcd. for $C_{16}H_{13}ON$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.92; H, 5.64; N, 5.58.

The second colored eluate gave a solid which on recrystallization afforded 80 mg. of 3-benzylcyclohepta-[*b*]pyrrol-2(1*H*)-one, m.p. 209°. *Anal.* Calcd. for $C_{16}H_{13}ON$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.89; H, 5.69; N, 6.08.

Reaction of 2-Methoxytropone with N-Benzyl-2-cyanoacetamide——To a solution of Na (85 mg.) in 15 ml. of EtOH was added a solution of N-benzyl-2-cyanoacetamide (640 mg.) in 15 ml. of EtOH followed by 500 mg. of 2-methoxytropone. The mixture was allowed to stand overnight at room temperature. The

separated crystals were collected by filtration and recrystallized from AcOH giving 70 mg. of 1,3-bis-(benzylcarbamoyl)-2-aminoazulene, m.p. 249°. *Anal.* Calcd. for $C_{26}H_{23}O_2N_3$: C, 76.26; H, 5.66; N, 10.26. Found : C, 76.36; H, 5.77; N, 10.29. UV λ_{max}^{EtOH} mμ (log ε) : 252 (4.45), 322 (4.63), 390 (3.83).

The filtrate was left for one more day. The separated crystals were collected and recrystallized from EtOH giving 200 mg. of 1-benzyl-3-cyanocyclohepta[*b*]pyrrol-2(1*H*)-one, m.p. 196°. *Anal.* Calcd. for $C_{17}H_{12}ON_2$: C, 78.44; H, 4.65; N, 10.76. Found : C, 78.28; H, 4.64; N, 10.64. UV λ_{max}^{EtOH} mμ (log ε) : 279 (4.37), 425 (4.05). IR ν_{max}^{Nujol} cm^{-1} : 2200, 1675.

Hydrolysis of 1-Benzyl-3-cyanocyclohepta[*b*]pyrrol-2(1*H*)-one (XLI)——a) A mixture of 250 mg. of XLI and 4 ml. of conc. HBr was refluxed for 1 hr. After cooling, the separated crystals were collected, washed with water and recrystallized from EtOH giving 100 mg. of 1-benzyl-3-carbamoylcyclohepta[*b*]-pyrrol-2(*H*)-one as yellow prisms, m.p. 223°. *Anal.* Calcd. for $C_{17}H_{14}O_2N_2$: C, 73.36; H, 5.07; N, 10.07. Found : C, 73.17; H, 5.16; N, 9.54.

b) A mixture of 200 mg. of XLI and 3 ml. of 75% H_2SO_4 was heated at 165° for 15 min. After cooling, 10 ml. of H_2O was added and the mixture was extracted with $CHCl_3$. The extract was concentrated to small volume and purified by alumina chromatography giving 50 mg. of orange yellow crystals, m.p. 130°, which were proved to be identical with 1-benzylcyclohepta[*b*]pyrrol-2(1*H*)-one by a mixed melting point determination.

Benzylation of Cyclohepta[*b*]pyrrole-2,8(1*H*,3*H*)-dione (XLIII)——a) To a solution of 180 mg. of NaOH in 10 ml. of water were added 640 mg. of XLIII, 550 mg. of benzyl chloride and 5 ml. of EtOH. The mixture was stirred at 80° for 3 hr. During the reaction, the mixture was kept alkaline by the addition of aqueous NaOH. After cooling, the separated crystals were collected by filtration and purified by alumina chromatography followed by recrystallization from EtOH giving 300 mg. of pale yellow prisms, m.p. 189° (B), which were assumed to be 3,3-dibenzyl derivative (XLV). *Anal.* Calcd. for $C_{23}H_{19}O_2N$: C, 80.91; H, 5.61; N, 4.10. Found : C, 81.07; H, 5.67; N, 4.31. UV λ_{max}^{EtOH} mμ (log ε) : 235 (4.13), 264 (4.08), 345 (3.94), 370 (3.93), 386 (3.91), 405 (3.67).

The filtrate was adjusted to pH 2.5 with 10% HCl and the separated crystals were recrystallized from EtOH giving 400 mg. of orange yellow leaflets, m.p. 223°, which were identical with an authentic sample of 3-benzylcyclohepta[*b*]pyrrole-2,8(1*H*,3*H*)-dione (XLIV), obtained by the reaction of 2-amion-3-bromotropone with diethyl benzyl malonate.

b) To a solution of 420 mg. of NaOH in 20 ml. of 50% EtOH were added 800 mg. of XLIII and 1.3 g. of benzyl chloride. The mixture was stirred at 80° for 3.5 hr. During the reaction, the mixture kept alkaline by the addition of aqueous NaOH. After removal of EtOH under reduced pressure, the residual solution was extracted with $CHCl_3$. The extract was concentrated to small volume and chromatographed on alumina. From the first eluate, a solid was obtained. Recrystallization from EtOH gave 230 mg. of pale yellow prisms, m.p. 162° (E), which were assumed to be 1,3,3-tribenzylcyclohepta[*b*]pyrrole-2,8(1*H*,3*H*)-dione (XLVII). *Anal.* Calcd. for $C_{30}H_{25}O_2N$: C, 83.50; H, 5.84; N, 3.25. Found : C, 83.34; H, 5.82; N, 3.50. UV λ_{max}^{EtOH} mμ (log ε) : 234 (4.20), 268 (3.93), 347 (3.95), 378 (3.90), 397 (3.71).

To the residue, obtained by concentration of the second eluate was added a small amount of benzene, and the insoluble crystals were collected by filtration and recrystallized from EtOH giving 450 mg. of pale yellow prisms, m.p. 189°, which were identical with B obtained from method a).

The filtrate, benzene solution, was chromatographed on alumina. The first benzene eluate gave a solid. Recrystallization from EtOH yielded 40 mg. of red prisms, m.p. 137° (D), which were assumed to be 1,3-dibenzyl-8-benzyloxycyclohepta[*b*]pyrrol-2(1*H*)-one (XLVIII). *Anal.* Calcd. for $C_{30}H_{25}O_2N$: C, 83.50; H, 5.84; N, 3.25. Found : C, 83.24; H, 5.60; N, 3.42. UV λ_{max}^{EtOH} mμ (log ε) : 238 (4.28), 285 (4.41), 306 (4.47), 395 (3.87), 418 (3.96). The second $CHCl_3$ eluate gave a solid. Recrystallization from EtOH yielded 85 mg. of orange leaflets, m.p. 183° (C), which were assumed to be 8-hydroxy-1,3-dibenzylcyclohepta[*b*]pyrrol-2(1*H*)-one (XLVI). *Anal.* Calcd. for $C_{23}H_{19}O_2N$: C, 80.91; H, 5.61; N, 4.10. Found : C, 80.83; H, 5.71; N, 4.33. UV λ_{max}^{EtOH} mμ (log ε) : 233 (4.29), 278 (4.33), 297 (4.50), 369 (3.69), 391 (3.92), 413 (4.01).

c) By the same procedure as method b), benzylation of 2 g. of XLIII with 5 g. of benzyl chloride afforded 1.9 g. of XLVII, 0.2 g. of XLV, 90 mg. of XLVIII and 90 mg. of XLVI,

3-Benzylcyclohepta[*b*]pyrrole-2,8(1*H*,3*H*)-dione (XLIV)——To a solution of K (0.4 g.) in 10 ml. of *tert*-BuOH were added 2.5 g. of diethyl benzylmalonate and 1.2 g. of 2-amino-3-bromotropone. The mixture was refluxed for 3 hr. After cooling, the mixture was filtered off and 5% NaOH was added to the filtrate. The mixture was washed with ether and then adjusted to pH 3.0 with 10% HCl. The separated crystals were collected and recrystallized from EtOH giving 200 mg. of crystals, m.p. 223°. *Anal.* Calcd. for $C_{16}H_{13}O_2N$: C, 76.47; H, 5.22; N, 5.57. Found : C, 76.38; H, 5.37; N, 5.67.

Benzylation of XLIV——To a solution of 100 mg. of NaOH in 10 ml. of 50% NaOH were added 450 mg. of XLIV and 250 mg. of benzyl chloride. The mixture was refluxed for 5.5 hr. During the reaction, the mixture was kept alkaline by addition of aqueous NaOH. The reaction mixture was worked up as described in b) for benzylation of XLIII, when 150 mg. of XLVII, 110 mg. of XLV, 10 mg. of XLVI and 5 mg. of XLVIII were obtained.

General Procedure for the Benzylation of 3-Substituted Cyclohepta[*b*]pyrrol-8(1*H*)-one——A suspension of 3-substituted cyclohepta[*b*]pyrrol-8(1*H*)-one and one molar equivalent of *K* in dry toluene was refluxed for 4 hr. to give the corresponding potassium salt. To that mixture was added a slight excess of benzyl chloride. After stirring under reflux for 7～10 hr., the reaction mixture was poured into water. The separated organic layer was concentrated under reduced pressure and the residue was recrystallized from EtOH. Results are shown in Table II.

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Summary

In an effort to obtain active analgesic and anti-inflammatory agents, alkylation of cycloheptimidazolone and cyclohepta[*b*]pyrrolone was carried out. Benzylation of 4- and 6-hydroxycycloheptimidazol-2(1*H*)-one afforded 1-benzyl and 1,3-dibenzyl derivatives. Benzylation of cyclohepta[*b*]pyrrol-2(1*H*)-one afforded 1- and 3-benzyl derivatives. Benzylation of cyclohepta[*b*]pyrrole-2,8(1*H*,3*H*)-dione which is considered to be present in many tautomers afforded 3-benzyl, 3,3- and 1,3-dibenzyl, 1,3,3-tribenzyl and 1,3-dibenzyl-8-benzyloxy derivatives. By the alkylation of cycloheptimidazol-2(1*H*)-one and 3-substituted cyclohepta[*b*]pyrrol-8(1*H*)-one, a number of 1-alkyl derivatives were prepared. Among these products, 1-benzylcycloheptimidazol-2(1*H*)-one has been found to be the most active analgesic and anti-inflammatory agent.

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63. Shigenobu Okuda,*1 Isamu Murakoshi,*2 Hiromitsu Kamata,*1 Yoshihiko Kashida,*3 Joju Haginiwa,*2 and Kyosuke Tsuda*1 : Studies on Lupin Alkaloids. I. The Minor Alkaloids of Japanese *Sophora flavescens*.

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In 1889, Nagai and his coworker[1] isolated an alkaloid named matrine (I), m.p. 78°, $[\alpha]_D$ +39.1° (H_2O), from a chinese drug "Kushin (a dry root of *Sophora flavescens*)." Until recently very little was known regarding the minor alkaloids of this plant and only oxymatine (matrine N-oxide) (II) had been characterized.[1,2]

In 1958, Bohlmann[3] reported the isolation of (+)-matrine (I), (+)-oxymatrine (II), (+)-sophoranol (III), (−)-anagyrine (IV), (−)-methylcytisine (V) and (−)-baptifoline (VI) from

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3) F. Bohlmann, D. Rahtz, C. Arndt : Ber., **91**, 2189 (1958).