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Studies on Psychotropic Agents. I. Synthesis of 3,8-Disubstituted-1-oxa-3,8-diazaspiro[4,5]decan-2,4-dione Derivatives[1]

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A series of 3,8-disubstituted-1-oxa-3,8-diazaspiro[4,5]decan-2,4-diones (XI) were synthesized for pharmacological testing.

3-Substituted-8-benzyl compounds (IIIb—h), the intermediates of XI, were prepared by the following three methods: 1) condensation of methyl 1-benzyl-4-hydroxyisonipecotate (II) with urea, followed by alkylation, 2) treatment of II with isocyanates and 3) reaction of 1-benzyl-4-cyano-4-piperidinol (I) with isocyanates followed by hydrolysis. The last method was inferior to the other two methods. Reductive debenzylation of III followed by condensation with appropriate halides afforded XI.

Among the compounds (XI) synthesized, 8-[3-(2-chlorophenothiazin-10-yl)propyl]-3-methyl compound (XIa) had excellent central nervous system depressing activities.

A number of 4,4-disubstituted piperidine derivatives which have (*p*-fluorobenzoyl)propyl or 2-substituted phenothiazin-10-yl propyl moiety in their 1-position have been reported[3] to possess psychotropic activity. Among them, spiroperidol[4] (A) and spiclomazine[5] (B) which have a spiro ring in the 4-position of piperidine have been evaluated clinically as major tranquilizers. On the other hand, some oxazolidine-2,4-dione derivatives[6] have been used as antiepileptic agents, so we intended to synthesize a group of 1-oxa-3,8-diazaspiro[4,5]decan-2,4-dione derivatives (C), which have oxazolidine-2,4-dione moiety as a spiro ring, and introduce (*p*-fluorobenzoyl)propyl or 2-substituted phenothiazin-10-yl propyl moiety in their 8-position.

Although many methods have been known for the synthesis of oxazolidine-2,4-dione derivatives in literature,[7] as the synthetic methods of 8-benzyl-1-oxa-3,8-diazaspiro[4,5]decan-2,4-diones (IIIa—h), the following three methods (method A, B and C) were studied.

As the first method (method A), 1-benzyl-4-cyano-4-piperidinol (I) was treated with hydrogen chloride in methanol followed by hydrolysis to afford α-hydroxy ester (II). The heating of II with urea in the presence of sodium ethylate in ethanol yielded oxazolidine-2,4-dione derivative (IIIa) in 82% yield. Some alkylated compounds (IIIb—f) were prepared by the reaction of IIIa with alkylating agents, such as dialkylsulfates and appropriate halides, in good yields.

1) Presented at the 24 th Annual Meeting of Kinki Branch, Pharmaceutical Society of Japan, Osaka, November 1974.
2) Location: *33–94, Enokicho, Suita, Osaka.*
3) P.A.J. Janssen, C. van de Westeringh, A.H.M. Jageneau, P.J.A. Demoen, B.K.F. Hermans, G. van Daele, K.H.L. Schellekens, C. van der Eycken and C.J.E. Niemegeers, *J. Med. Chem.*, **1**, 281 (1959); C. van de Westeringh, P. van Dael, B. Hermans, C. van der Eycken, J. Boy and P.A.J. Janssen, *J. Med. Chem.*, **7**, 619 (1964); M. Nakanishi, C. Tashiro, T. Munakata, K. Araki, T. Tsumagari and H. Imamura, *J. Med. Chem.*, **13**, 644 (1970).
4) P.A.J. Janssen, U.S. Patent 3161644 (1962) [*C.A.*, **63**, 9952 (1965)]; K. Yamatsu, T. Ohgo and K. Otsu, *Nippon Yakurigaku Zasshi*, **63**, 16 (1967).
5) M. Nakanishi, K. Arimura, T. Tsumagari and M. Shiraki, Japan Patent 23091 (1969) [*C.A.*, **72**, 17253 (1970)]; M. Nakanishi, T. Okada and T. Tsumagari, *Yakugaku Zasshi*, **90**, 800 (1970).
6) Trimetadione, paramethadione and propazone.
7) J.W. Clark-Lewis, *Chem. Rev.*, **58**, 63 (1958); K. Gulbins, M. Roth and K. Hamann, *Angew. Chem.*, **73**, 434 (1961).

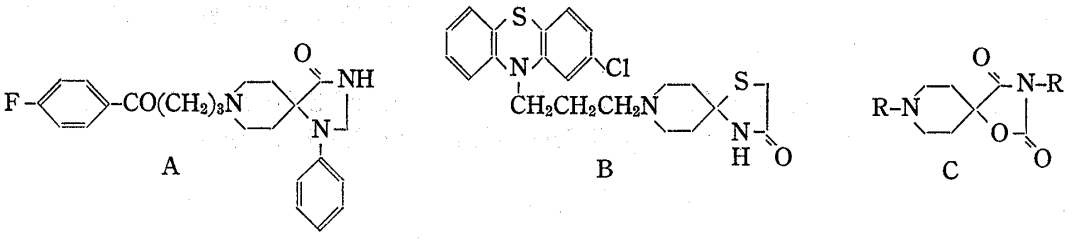


Chart 1

As the second method (method B), compound (II) was treated with phenyl isocyanate, benzyl isocyanate and methyl isocyanate in ether under heating for 3 hours to give IIIg, IIIf and IIIb in 90, 80 and 17% yields, respectively. With respect to IIIb, by extending of reaction time to 15 hours the yield was increased to 70%.

As the third method (method C), Patton's method[8] was studied. He reported that the reaction of 1-cyanocyclopentanol (D) with 2 moles of arylisocyanates in the presence of triethylamine in benzene gave 3-aryl-4-arylcarbamoylimino-1-oxa-3-azaspiro[4,4]nonan-2-ones (E) and treatment of D with alkyl isocyanates yielded 1,3-dialkyl-4-imino-2,5-imidazolidinediones (F), which arose from the reaction of alkylisocyanates with hydrogen cyanide formed by the dissociation of D. Treatment of I with 2 moles of phenylisocyanate and *p*-chlorophenylisocyanate according to Patton's procedure gave 8-benzyl-4-carbamoylimino-1-oxa-3,8-diazaspiro[4,5]decan-2-one derivatives (IVa, b) in high yields and 4-imino-2,5-imidazolidinedione derivatives (Va, b) in low yields. On the other hand, when I was allowed to react with 2 moles of methyl isocyanate and *n*-propyl isocyanate, 8-benzyl-4-imino-1-oxa-3,8-diazaspiro-[4,5]decan-2-one derivatives (VIa, b) together with imidazolidinedione derivatives (Vc, d) were isolated. In this case the yields of VI were low and those of Vc and Vd were high. Treatment of I with 2 moles of acetylisocyanate and benzoylisocyanate afforded 8-benzyl-3-acyl-4-imino-1-oxa-3,8-diazaspiro[4,5]decan-2-ones (VIIa, b) in excellent yields. These results are summarized in Table I and II.

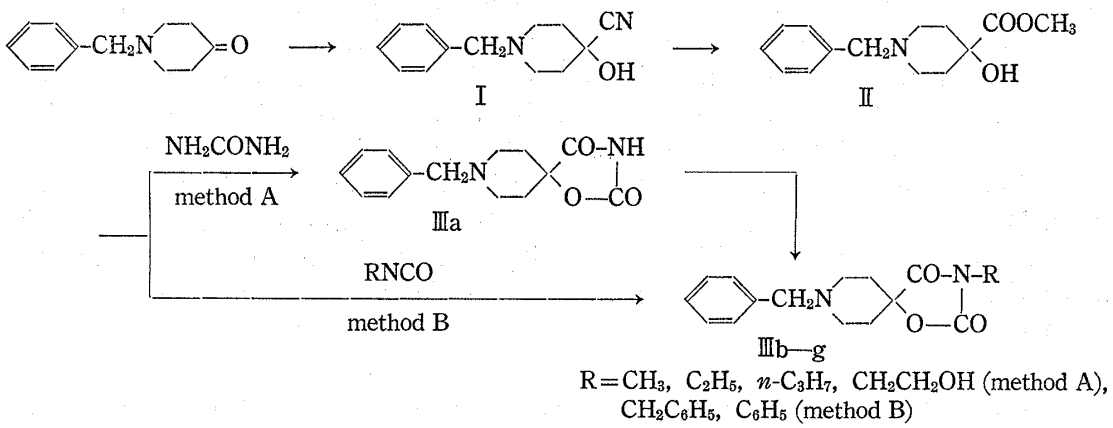


Chart 2

The structures of these products (IV, VI and VII) were confirmed by infrared (IR) spectra measurements and elemental analyses. No absorption bands of the nitrile groups were present and absorption maxima characteristic of the cyclic carbamate carbonyl and exocyclic C=N groups appeared as shown in Table I in their IR spectra.

The reactivity of alkyl isocyanates is so low that they reacted slowly with the tertiary hydroxyl group of I, so the yields of VI were low and one additional mole of alkyl isocyanates did not react with 4-imino group of VI. As to the acyl isocyanates the reactivity of 4-imino

8) T.L. Patton, *J. Org. Chem.*, 32, 383 (1967).

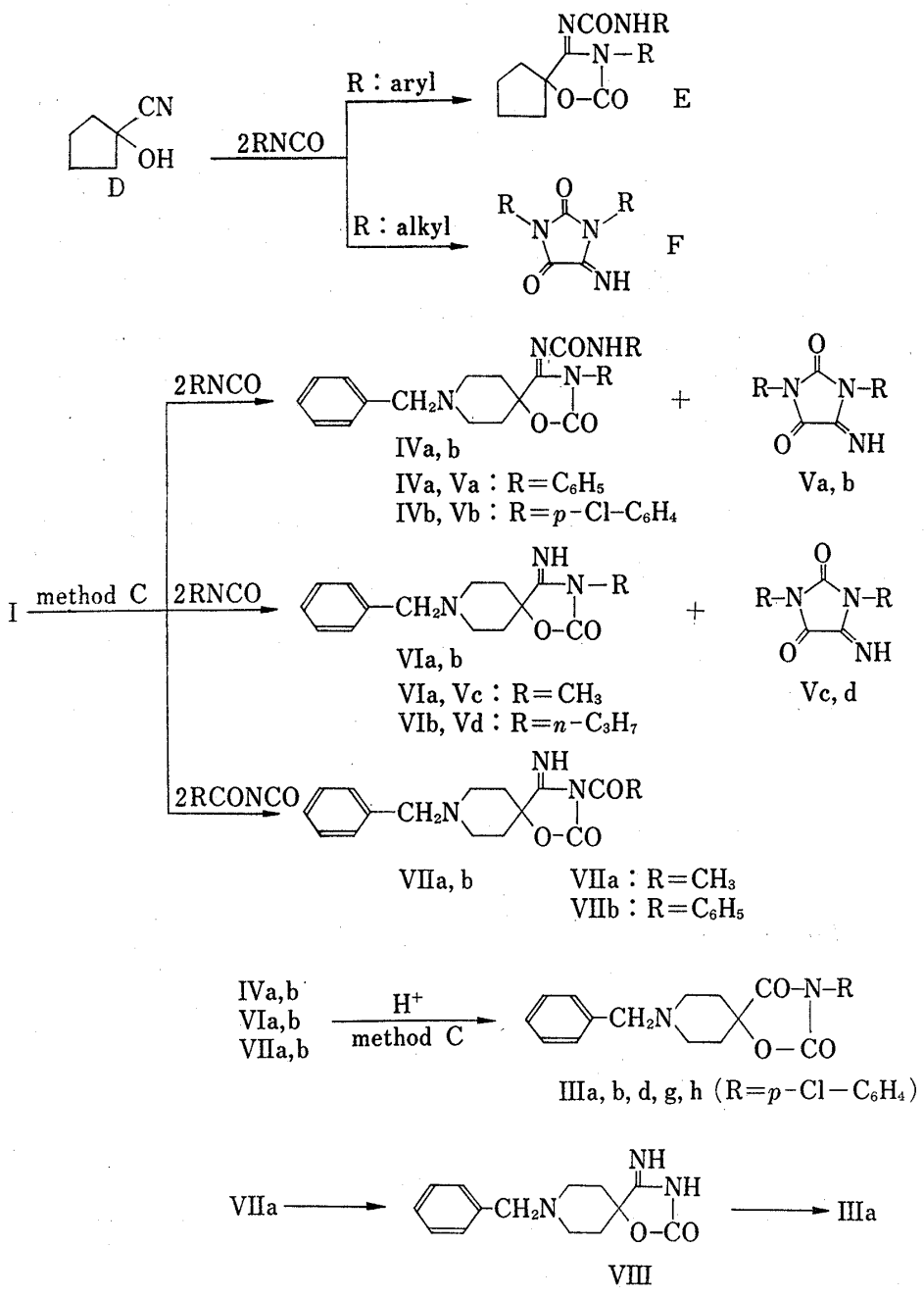


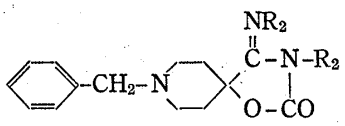
Chart 3

group of VII may be very low under the influence of 3-acyl group so that 1 additional mole of acyl isocyanate cannot react with that group, and the reactivity of acyl isocyanates is so high that they reacted readily with the tertiary hydroxyl group of I, so the dissociation of I to liberate hydrogen cyanide would hardly proceed.

The acid hydrolysis of the 4-imino compounds (IV and VI) gave the corresponding 4-oxo compounds (IIIb, IIId, IIIg and IIIh) in quantitative yields, respectively. The same treatment of VII yielded IIIa with removal of 3-acyl groups. By treatment of VIIa with diethylamine in boiling ethanol 8-benzyl-4-imino-1-oxa-3,8-diazaspiro[4,5]decan-2-one (VIII) could be isolated, which was readily hydrolyzed in the presence of acid to afford IIIa.

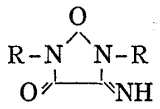
From the above mentioned facts, method A and B were superior to method C, as the method for the preparation of III, which was accompanied with the by-product (V) or required an expensive reagent, acylisocyanate.

Table I. 8-Benzyl-4-imino-1-oxa-3,8-diazaspiro[4,5]decan-2-ones



Compd. No.	R_1	R_2	IR ν_{max}^{KBr} cm^{-1} C=O	IR exo-cyclic C=N	mp (°C)	Yield (%)	Recryst. solvent	Formula	Analysis (%) Calcd. (Found) C	H	N	Cl
IVa	C_6H_5	C_6H_5-NHCO	1803 1705	1655	200—202 (decomp.)	68	benzene	$C_{27}H_{26}O_3N_4$	71.34 (71.23)	5.77 (5.94)	12.33 (12.24)	
IVb	*p*-Cl-C_6H_4	*p*-Cl-C_6H_4NHCO	1803 1700	1665	222—223 (decomp.)	75	dioxane	$C_{27}H_{24}O_3N_4Cl_2$	61.95 (61.94)	4.62 (4.66)	10.71 (10.44)	13.55 (13.34)
VIa	CH_3	H	1770	1675	45— 47	15	ether	$C_{15}H_{19}O_2N_3$	65.91 (66.03)	7.01 (7.05)	15.37 (15.66)	
VIb	*n*-C_3H_7	H	1765	1665	89— 91	7	ether	$C_{17}H_{23}O_2N_3$	67.75 (67.52)	7.69 (7.53)	13.94 (14.01)	
VIIa	CH_3CO	H	1780 1738	1607	185—187	82	EtOH	$C_{16}H_{19}O_3N_3$	63.77 (63.75)	6.36 (6.35)	13.95 (13.84)	
VIIb	C_6H_5CO	H	1803 1658	1615	173—175	84	benzene +petr. ether	$C_{21}H_{21}O_3N_3$	69.40 (69.08)	5.83 (5.73)	11.56 (11.67)	
VIII	H	H	1765	1685	281—283	96	pyridine +petr. ether	$C_{14}H_{17}O_2N_3$	64.84 (64.76)	6.61 (6.55)	16.21 (16.00)	

Table II. 1,3-Disubstituted-4-imino-1,3-imidazolidine-2,5-diones



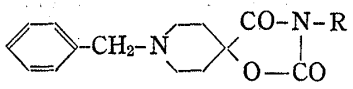
Compd. No.	R	mp (°C) (bp °C/mmHg)	Yield (%)	Recryst. solvent	Formula	Analysis (%) Calcd. (Found) C	H	N	Cl
Va	C_6H_5	153—156	14	EtOH	$C_{15}H_{11}O_2N_3$	67.91 (67.84)	4.18 (4.29)	15.84 (16.05)	
Vb	*p*-Cl-C_6H_4	220—222	10	AcOEt	$C_{15}H_9O_2N_3Cl_2$	53.91 (53.79)	2.71 (2.89)	12.58 (12.34)	21.22 (21.00)
Vc[6]	CH_3	117—119 (122—8/4)	78	benzene					
Vd	*n*-C_3H_7	(133—8/4)	61		$C_9H_{15}O_2N_3$	54.80 (54.49)	7.67 (7.89)	21.31 (21.04)	

The catalytic hydrogenation of 3-substituted-8-benzyl-1-oxa-3,8-diazaspiro[4,5]decan-2,4-diones (IIIb—h) on palladium-carbon afforded 8-debenzylated compounds (IX), which were allowed to react with the reactive derivatives of tricyclic compounds represented by formula X or (*p*-fluorobenzoyl)propyl chloride to yield 3,8-disubstituted compounds (XI).

Among the products (XI), 8-[3-(2-chlorophenothiazin-10-yl)propyl]-3-methyl-1-oxa-3,8-diazaspiro[4,5]decan-2,4-dione (XIa) had the most significant central nervous system depressing activities. So the synthesis of 10-(3-chloropropyl)-2-chlorophenothiazine (Xa), the intermediate of the preparation of XIa, was studied for a large scale preparation of XIa. 2-Chlorophenothiazine was treated with 2 moles of bromochloropropane in the presence of 1.5 mole of sodium hydride in dimethylformamide at 40° for 3 hours to give crude Xa. It was found from the gas chromatography analysis that the crude product consisted of Xa (32.1%),

10-(3-bromopropyl)-2-chlorophenothiazine (43.4%) and 10-allyl analogue (9.6%). This crude oily mixture could be used for the preparation of XIa. Although many methods[9] for the preparation of Xa from the same starting materials have been known, those methods also gave a mixture of Xa and a small amount of 10-(3-bromopropyl) analogue by our reexaminations.

TABLE III. 8-Benzyl-1-oxa-3,8-diazaspiro[4,5]decan-2,4-diones



Compd. No.	R	Method (yield %)	mp (°C)	Recryst. solvent	Formula (salt)	Analysis (%) Calcd. (Found) C	H	N	Cl
IIIa	H	A (81.5) C (79)	291—293 (decomp.)	dil. EtOH	$C_{14}H_{16}O_3N_2 \cdot HCl$	56.66 (56.73)	5.78 (5.63)	9.44 (9.54)	11.95 (12.04)
IIIb	CH_3	A[a] (70) B (70) C (14)	266—268 (decomp.)	MeOH	$C_{15}H_{18}O_3N_2 \cdot HCl$	57.97 (57.92)	6.16 (5.98)	9.02 (8.87)	11.41 (11.28)
IIIc	C_2H_5	A[a] (67)	103—105	dil. MeOH	$C_{16}H_{20}O_3N_2$	66.64 (66.57)	6.99 (6.91)	9.72 (9.63)	
IIId	n-C_3H_7	A[a] (64) C (11)	102—103	EtOH	$C_{17}H_{22}O_3N_2$	67.52 (67.40)	7.33 (7.26)	9.27 (9.49)	
IIIe	CH_2CH_2OH	A[a] (47)	127—128	dil. EtOH	$C_{16}H_{20}O_4N_2$	63.14 (63.21)	6.62 (6.59)	9.21 (9.09)	
IIIf	$C_6H_5CH_2$	A[a] (62) B (80)	113—115	dil. EtOH	$C_{21}H_{22}O_3N_2$	71.98 (71.72)	6.33 (6.25)	8.00 (8.03)	
IIIg	C_6H_5	B (90) C (55)	292—293 (decomp.)	AcOH	$C_{20}H_{20}O_3N_2 \cdot HCl$	64.42 (64.44)	5.68 (5.64)	7.52 (7.47)	9.51 (9.54)
IIIh	p-Cl-C_6H_4	C (70)	180—181	EtOH	$C_{20}H_{19}O_3N_2Cl$	64.77 (64.52)	5.16 (5.32)	7.56 (7.19)	9.56 (9.61)

a) followed by alkylation with corresponding alkyl halide or dialkylsulfate

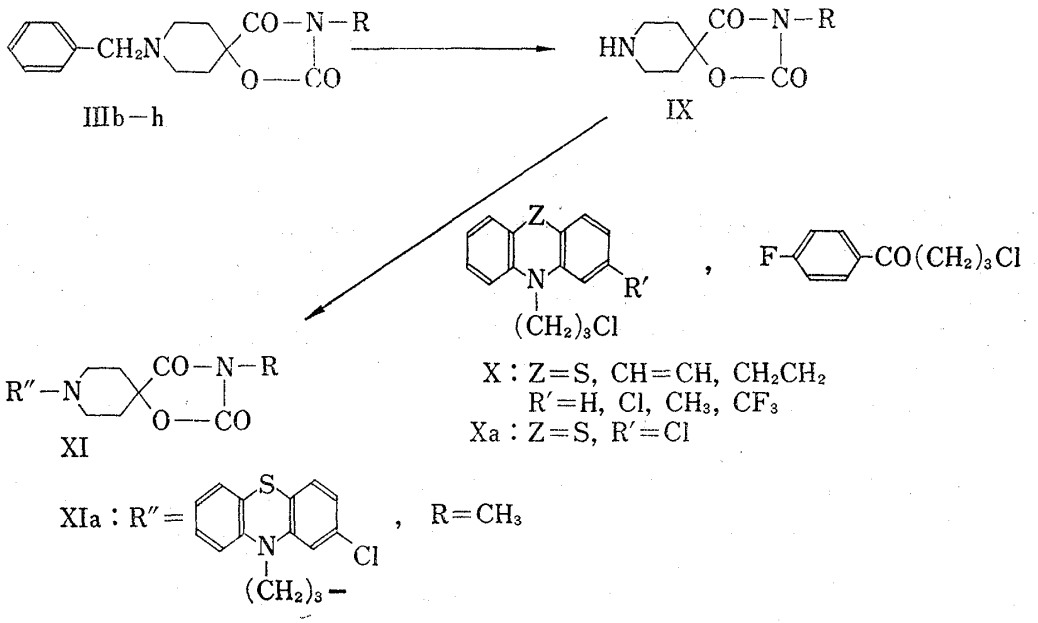
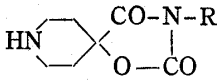


Chart 4

9) S.V. Zhravlev and Z.I. Ermakova, *Zh. Prikl. Khim.*, **38**, 1174 (1965) [*C.A.*, **63**, 8348 (1965)]; Scherico Ltd., Brit. Patent 833473 (1960) [*C.A.*, **54**, 21143 (1960)]; G, Cignarella, E. Occelli, G. Maffii and E. Testa. *J Med. Chem.*, **12**, 836 (1969); Z. Johannes, Ger. (East) Patent 77491 (1970 [*C.A.*, **75**, 98583 (1971)].

Table IV. 3-Substituted-1-oxa-3,8-diazaspiro[4,5]decan-2,4-diones



Compd. No.	R	mp (°C)	Recryst. solvent	Formula (salt)	Analysis (%) Calcd. (Found) C	H	N	Cl
IXa	CH_3	113—114	benzene	$C_8H_{12}O_3N_2$	52.16 (52.17)	6.57 (6.45)	15.21 (15.13)	
IXb	C_2H_5	75— 76	hexane +benzene	$C_9H_{14}O_3N_2$	54.53 (54.60)	7.12 (7.03)	14.14 (13.91)	
IXc	n-C_3H_7	155—157	EtOH +ether	$C_{10}H_{16}O_3N_2 \cdot HCl$	48.29 (48.59)	6.89 (6.88)	11.26 (11.21)	14.26 (13.95)
IXd	CH_2CH_2OH	206—207	EtOH	$C_9H_{14}O_4N_2 \cdot HCl$	43.12 (42.82)	6.03 (6.11)	11.18 (10.86)	14.14 (14.06)
IXe	$C_6H_5CH_2$	202—204	MeOH	$C_{14}H_{16}O_3N_2 \cdot HCl \cdot 1/2H_2O$	54.99 (55.32)	5.93 (5.77)	9.16 (9.25)	11.60 (12.04)
IXf	C_6H_5	158—159	EtOH	$C_{13}H_{14}O_3N_2$	63.40 (63.28)	5.73 (5.74)	11.38 (11.09)	
IXg	p-Cl-C_6H_4	>280	EtOH +ether	$C_{13}H_{13}O_3N_2Cl \cdot HCl \cdot 1/2C_2H_5OH$	49.42 (49.78)	5.04 (4.68)	8.24 (8.68)	20.84 (20.45)

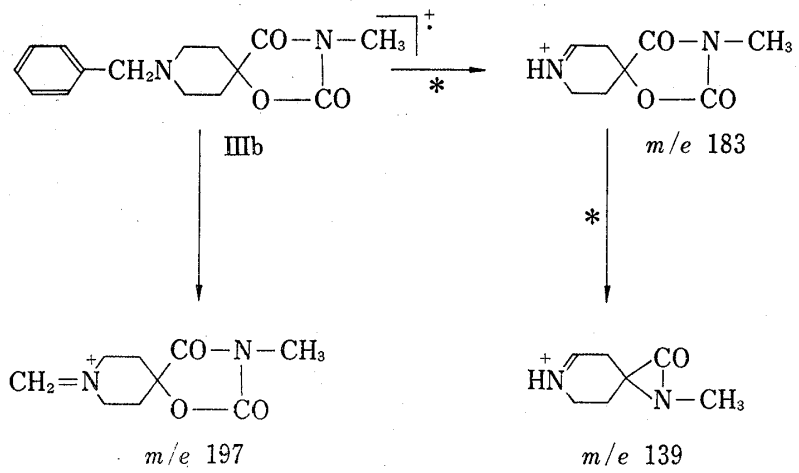


Chart 5

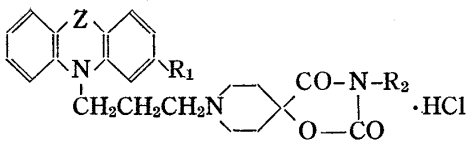
R.A. Locock and his co-worker reported[10] that mass spectra of trimethadione and paramethadione, oxazolidine-2,4-dione derivatives, showed abundant peaks due to loss of the neutral fragment $(CO)_2NMe$ or peaks ascribed to the fragment ions formed *via* the intermediate ions, which were yielded due to the loss of $(CO)_2NMe$. Contrary to our expectation, the mass spectrum of IIIb did not show the above mentioned fragmentation pathways. The plausible fragmentation processes are depicted in Chart 5.[11]

Pharmacology

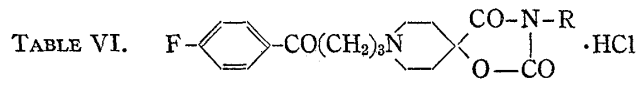
Compounds (XI) were examined in detail pharmacologically. Compound (XIa) showed the most excellent central nervous system depressing activities which were comparable to those of chlorpromazine (CPZ). Some of the activities of XIa and CPZ together with their LD_{50} were summarized in Table VII. Further pharmacological studies with XIa would be published elsewhere. The toxicity of XIa was very low in comparison with that of CPZ, so XIa was selected for clinical trials.

10) R.A. Locock and R.T. Coutts, *Org. Mass Spectrom.*, 3, 735 (1970).
11) Metastable transitions detected are shown by asterisks.

TABLE V.



Compd. No.	Z	R_1	R_2	mp (°C)	Yield (%)	Recryst. solvent	Formula (salt)	Analysis (%) Calcd. (Found) C	H	N	S	Cl
XIa	S	Cl	CH_3	262—263 (decomp.)	85	dioxane+H_2O	$C_{23}H_{24}O_3N_3SCl\cdot HCl$	55.86 (55.80)	5.10 (5.01)	8.50 (8.28)	14.35 (14.70)	6.48 (6.50)
XIb	S	Cl	C_2H_5	249—250	65	MeOH	$C_{24}H_{26}O_3N_3SCl\cdot HCl$	56.69 (56.57)	5.35 (5.36)	8.26 (8.29)	13.95 (13.75)	6.31 (6.35)
XIc	S	Cl	n-C_3H_7	198—200	60	EtOH	$C_{25}H_{28}O_3N_3SCl\cdot HCl$	57.47 (57.16)	5.59 (5.79)	8.04 (7.84)	13.57 (13.50)	6.14 (5.99)
XId	S	Cl	CH_2CH_2OH	270—272	54	MeOH	$C_{24}H_{26}O_4N_3SCl\cdot HCl$	54.96 (54.74)	5.19 (5.20)	8.01 (7.84)	13.52 (13.21)	6.11 (6.29)
XIe	S	Cl	$C_6H_5CH_2$	155 (decomp.)	48	EtOH+ether	$C_{29}H_{28}O_3N_3SCl\cdot HCl$	61.05 (61.30)	5.12 (5.28)	7.37 (7.32)	12.43 (12.38)	5.62 (5.66)
XIf	S	Cl	C_6H_5	253—255 (decomp.)	32	MeOH	$C_{28}H_{26}O_3N_3SCl\cdot HCl$	60.43 (60.20)	4.87 (4.73)	7.55 (7.33)	12.74 (12.65)	5.76 (5.88)
XIg	S	CH_3O	CH_3	231—232	30	MeOH	$C_{24}H_{27}O_4N_3S\cdot HCl$	58.82 (58.71)	5.76 (5.91)	8.58 (8.70)	6.54 (6.62)	7.24 (7.16)
XIh	S	CF_3	CH_3	239—241 (decomp.)	61	EtOH	$C_{24}H_{24}O_3N_3SF_3\cdot HCl$	54.60 (54.41)	4.77 (5.01)	7.96 (7.75)	6.71 (6.61)	6.07 (6.32)
XIi	S	H	CH_3	258—259	45	MeOH	$C_{23}H_{25}O_3N_3S\cdot HCl$	60.05 (60.05)	5.70 (5.98)	9.13 (8.73)	7.71 (8.16)	6.97 (6.70)
XIj	CH_2CH_2	H	CH_3	255—257 (decomp.)	40	MeOH	$C_{25}H_{29}O_3N_3\cdot HCl$	65.85 (65.81)	6.63 (6.63)	9.22 (9.27)	7.78 (7.85)	
XIk	CH=CH	H	CH_3	218—219 (decomp.)	42	iso-PrOH	$C_{25}H_{27}O_3N_3\cdot HCl$	66.14 (65.90)	6.22 (6.39)	9.26 (8.96)	7.81 (7.99)	

Table VI. 

Compd. No.	R	mp (°C) (decomp.)	Yield (%)	Recryst. solvent	Formula (salt)	Analysis (%) Calcd. (Found) C	H	N	Cl	F
XIe	CH_3	274—275	45	MeOH	$C_{18}H_{21}O_4N_2F\cdot HCl$	56.18 (5 .82)	5.76 (5.92)	7.28 (7.28)	4.94 (5.23)	9.21 (9.19)
XIm	n-C_3H_7	235—237	47	EtOH	$C_{20}H_{25}O_4N_2F\cdot HCl$	58.18 (58.06)	6.35 (6.52)	6.79 (6.65)	4.60 (4.70)	8.59 (8.58)
XIn	$C_6H_5CH_2$	250—251	42	EtOH	$C_{24}H_{25}O_4N_2F\cdot HCl$	62.53 (62.78)	5.69 (5.85)	6.09 (5.98)	4.12 (4.53)	7.69 (7.89)
XIo	C_6H_5	288—290	40	EtOH	$C_{23}H_{23}O_4N_2F\cdot HCl$	61.81 (62.11)	5.41 (5.64)	6.27 (6.25)	4.25 (4.18)	7.93 (8.20)
XIp	p-Cl-C_6H_4	273—275	42	MeOH	$C_{23}H_{22}O_4N_2ClF\cdot HCl$	57.39 (56.98)	4.82 (4.91)	5.82 (5.21)	3.95 (4.03)	14.73 (15.01)

Table VII. Comparative CNS Effects of XIa and CPZ

	Median effective dose, mg/kg *p.o.* Cataleptogenic activity[a] (mouse)	Prevention of methamphetamine induced hyperactivity[b] (mouse)	Inhibition of condition avoidance response[c] (rat)	Lethality (mouse)
XIa·HCl	17.0	2.6	9.8	2000
CPZ·HCl	41.0	17.0	2.1	135

a) S. Courvoisier, R. Ducrot and L. Julou, "Psychotropic drugs," Elsevier Publishing Company, Amsterdam, 1957, p. 373
b) S. Ueki, H. Sugano, N. Sato, J. Iwaki, H. Yonemaru, T. Fukuda, H. Yamada, S. Nurimoto, G. Hayashi and Y. Kowa, *Nippon Yakurigaku Zasshi*, **61**, 421 (1965)
c) R. Ader and D.W. Clink, *J. Pharmacol. Exptl. Therap.*, **121**, 144 (1957)

Experimental[12]

1-Benzyl-4-methoxycarbonyl-4-piperidinol (II)——To a solution of 50 g of 1-benzyl-4-cyano-4-piperidinol[13] (I) in a mixture of 50 ml of anhydrous MeOH and 100 ml of anhydrous ether dry HCl was introduced keeping the reaction temperature below 5° until the solution was saturated with dry HCl. After standing in icebox overnight, the reaction mixture was poured into 200 ml of ice-water under stirring. Aqueous layer was made to pH 8 with NaOH, the resulting precipitates were collected and recrystallized from dil. MeOH to give 45 g (90%) of II, mp 80—82°. *Anal.* Calcd for $C_{14}H_{19}NO_3$: C, 67.44; Y, 7.68; N, 5.62. Found: C, 67.43; H; 7.63; N, 5.91.

8-Benzyl-1-oxa-3,8-diazaspiro[4,5]decan-2,4-dione (IIIa)——A mixture of 25 g of II and 7 g of urea in 100 ml of anhydrous EtOH containing 9 g of sodium ethylate was heated under reflux for 10 hr and concentrated. After dil. HCl was added to the residue, resulting precipitates were collected and recrystallized from dil. EtOH yielding 24 g (81.5%) of IIIa·HCl, mp 291—293° (decomp.). This hydrochloride was dissolved in hot water and the solution was made basic with 28% NH_4OH to give IIIa, mp 185—187°. IR ν_{max}^{KBr} cm^{-1}: 1810, 1743 (C=O).

Alkylation of IIIa. 8-Benzyl-3-methyl (or ethyl)-1-oxa-3,8-diazaspiro[4,5]decan-2,4-dione (IIIb,c)——A mixture of IIIa (0.2 mole) and potassium carbonate (0.6 mole) in 200 ml of anhydrous acetone was stirred at room temperature for 2.5 hr. After the addition of dimethyl sulfate (or diethyl sulfate 0.2 mole) during 10 min, the reaction mixture was heated under reflux for 2 hr and then filtered. The filtrate was concentrated and the residue was recrystallized from suitable solvent. Results are summarized in Table III. IIIb, Mass Spectrum *m/e*: 274 (M^+, 10%), 197 (18%), 183 (38%), 139 (41%), 92 (18%), 91 (100%).

12) Melting points were uncorrected. IR spectra were determined on a Hitachi EPI-S_2 spectrometer and mass spectra on a Hitachi RMU-6L.
13) Science Union, Neth. Appl. Patent 6504602 (1965)[*C.A.*, **64**, 12679 (1966)].

8-Benzyl-3-propyl (hydroxyethyl or benzyl)-1-oxa-3,8-diazaspiro[4,5]decan-2,4-dione (IIId,e,f)——A mixture of IIIa (0.1 mole), KOH (0.11 mole) and *n*-propyl iodide (ethylene bromohydrin or benzyl chloride 0,1 mole) in 250 ml of methylcellosolve was heated under reflux for 2 hr. After being cooled, resulting precipitates were collected and recrystallized from suitable solvent.

General Procedure for the Synthesis of III from II and Isocyanates——A mixture of II (0.1 mole) and isocyanate (0.2 mole) in 100 ml of anhydrous ether was heated under reflux for 3 hr and concentrated under reduced pressure. The residue was recrystallized from suitable solvent. As to methyl isocyanate, the refluxing time was increased to 15 hr. Results are summarized in Table III.

8-Benzyl-3-aryl-4-arylcarbamoylimino-1-oxa-3,8-diazaspiro[4,5]decan-2-one (IVa,b)——To a mixture of I (0.1 mole) and aryl isocyanate (0.2 mole) in 100 ml of anhydrous benzene was added 2 ml of triethylamine to catalyze the reaction. After an exothermic reaction ensued, the reaction mixture was allowed to stand at room temperature overnight. After evaporation of 70% of the solvent under reduced pressure precipitated crystals were collected by filtration and recrystallized from suitable solvent to give IV. The filtrate was concentrated under reduced pressure and the residue was recrystallized from suitable solvent to yield Va (or Vb). Results are shown in Table I and II.

8-Benzyl-3-alkyl-4-imino-1-oxa-3,8-diazaspiro[4,5]decan-2-one (VIa,b)——To a mixture of I (0.1 mole) and alkyl isocyanate (0.2 mole) in 100 ml of anhydrous benzene was added 2 ml of triethylamine. After standing at room temperature the solution was concentrated under reduced pressure. By fractional distillation under reduced pressure of the residue there were obtained Vc (or Vd) and 1-benzyl-4-piperidone (boiling at 142—146° under 4 mm Hg). The resulting residue was chromatographed on basic alumina (80 g). Elution with $CHCl_3$ gave crystalline mass which was recrystallized from ether to give VI. VIa, Mass Spectrum *m/e*: 273 (M^+). VIb, Mass Spectrum *m/e*: 301 (M^+).

8-Benzyl-3-acyl-4-imino-1-oxa-3,8-diazaspiro[4,5]decan-2-one (VIIa,b)——To a mixture of I (0.1 mole) and acyl isocyanate (0.2 mole) in 100 ml of anhydrous benzene was added 2 ml of triethylamine under stirring. After the addition the resulting solution was allowed to stand overnight. The precipitated crystals were collected and recrystallized from suitable solvent.

General Procedure for Hydrolysis of 4-Imino Compounds (IV,VI,VII,VIII)——A solution of 4-imino compound (0.05 mole) in a mixture of 150 ml of EtOH and 50 ml of conc. HCl was heated on a steam bath for 2 hr. After being cooled, the precipitates were collected and recrystallized from suitable solvent to yield III in quantitative yields.

1-Benzyl-4-imino-1-oxa-3,8-diazaspiro[4,5]decan-2-one (VIII)——A solution of 0.5 g of VIIa and 5 ml of diethylamine in 15 ml of EtOH was heated under reflux for 2 hr. After being cooled, the precipitates were collected and recrystallized from a mixture of pyridine and ether to give 0.33 g (77%) of VIII, mp 281—283°.

Anal. Calcd. for $C_{14}H_{17}O_2N_3$: C, 64.84; H, 6.61; N, 16.21. Found: C, 64.74; H, 6.55; N, 16.00.

General Procedure for Debenzylation of III by Catalytic Hydrogenation——Into 80 ml of glacial acetic acid were added III (0.05 mole) and 1 g of 10% palladium-carbon, and the reduction was carried out at elevated temperatures of 50—80° under ordinary pressure. After the theoretical amount of H_2 was absorbed, the catalyst and the solvent were removed. The residue was dissolved into water and basified with NH_4OH. The precipitated crystals were collected and recrystallized from suitable solvent to give IXa,b,f,g. When precipitated material was oily product, that oil was extracted with $CHCl_3$ and dried over Na_2SO_4. After the solvent was removed, the residue was converted into hydrochloride by ethanolic HCl and recrystallized from suitable solvent to give IXc—e·HCl.

General Procedure for the Preparation of XI·HCl——A mixture of X (or *p*-fluorobenzoylpropyl chloride, 0.03 mole), IX (0.03 mole), potassium carbonate (0.04 mole) and potassium iodide (0.01 mole) in 150 ml of methyl ethyl ketone was heated under reflux for 8 hr. After being cooled, the insoluble matter was removed by filtration and the filtrate was concentrated. The residue was converted into hydrochloride by ethanolic HCl and recrystallized from suitable solvent. Results are shown in Table V and VI.

New Procedure for the Preparation of 10-(3-Chloropropyl)-2-chlorophenothiazine (XIa)——To an ice-cooled and stirred mixture of bromochloropropane (0.2 mole) and 20 ml of dimethylformamide (DMF) was added dropwise NaH (60% mineral oil dispersion, 0.15 mole), and to the suspension a solution of 2-chlorophenothiazine (0.1 mole) in 35 ml of DMF was added keeping the reaction temperature below 25°. After stirring at room temperature for 30 min the mixture was warmed at 40° for 3 hr. Precipitates were removed by filtration and the filtrate was concentrated under reduced pressure at the oil-bath temperature of 140—150°. The residue was extracted with hexane and the extract was concentrated. The resulting residue was examined by gas chromatography. Three peaks were detected and identified as Xa (t_R: 3.6 min,[14] yield 32.1%), 10-(3-bromopropyl)-2-chlorophenothiazine (5.0 min,[14] 43.4%) and 10-allyl-2-chlorophenothiazine[15] (9.2

14) GC was performed with a Nihon Denshi JGC-750 (column, Silicone OV-17 3% Chromosorb WAW 80—100 mesh 3 —0.75 m: detector temperature 310°, column temperature 240°, injection temperature 368°, He 10 psi).

15) K. Fujii, *Yakugaku Zasshi*, **76**, 640 (1956).

min,[16] 9.6%) by the comparison with the standard samples. Those samples were prepared as follows: Xa was prepared by chlorination of 10-(3-hydroxypropyl)-2-chlorophenothiazine[17] with thionyl chloride and 10-(3-bromopropyl) analogue by bromination of 10-(3-hydroxypropyl) compound with phosphorus tribromide.

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16) GC was performed with a Nihon Denshi JGC-20KFP (column, Silicone OV-1 2% Chromosorb WAW 60—80 mesh 2 —2 m: detector temperature 300°, column temperature 240—270°/15, injection temperature 300°, He 1.3 kg/cm^2).
17) L. Toldy and I. Fabricius, *Chem. Ind.*, **1957**, 665.