The Syntheses and Hypotensive Activities of Some Substituted 1,4-Diazabicyclo[4.4.0]decanes

ALAN D. LOURIE AND ALLAN R. DAY

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

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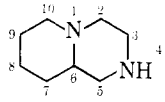
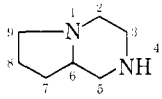
A number of substituted 1,4-diazabicyclo[4.4.0]decanes have been synthesized and evaluated for their pharmacological activity. Some of these compounds show marked hypotensive activity.

The present investigation is concerned with the synthesis of 1,4-diazabicyclo[4.4.0]decanes having substituents in the 4 and 10 positions. In 1960, Freed and Day[1] described the preparation of both 1,4-diazabicyclo[4.4.0]decane (I) and 1,4-diazabicyclo[4.3.0]nonane (II) by treating ethyl 2-piperidinecarboxylate and ethyl 2-pyrrolidinecarboxylate, respectively, with ethylenimine. The resulting lactams were reduced by lithium aluminum hydride to I and II.

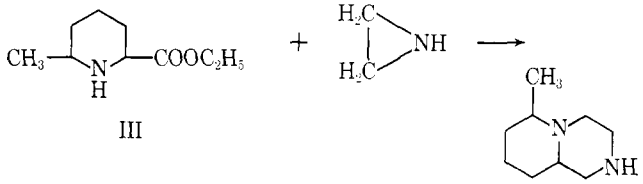


I



II

In the current study two new series of 1,4-diazabicyclo[4.4.0]decanes having substituents at the 4 and 10 positions were prepared. Treatment of ethyl 6-methyl-2-piperidinecarboxylate (III) with ethylenimine gave very poor yields of 10-methyl-1,4-diazabicyclo[4.4.0]-decan-5-one. The poor yield prompted the use of



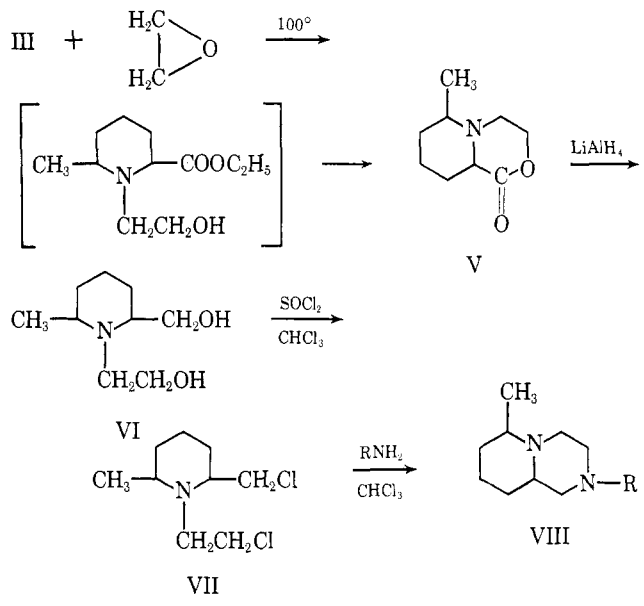
III IV

1-*p*-nitrobenzoylethylenimine as the amino-ethylating agent.[2] The resulting product, ethyl 1-(2-*p*-nitrobenzamidoethyl)-2-piperidinecarboxylate was heated with hydrochloric acid to give the desired product (IV) in good yield.

An alternative method, involving several steps shown in Scheme I, proved to be more useful. The pseudo-mustard (VII) was fairly stable and was kept in the cold for several months with minimal discoloration and quaternization. The 4-substituted 10-methyl-1,4-diazabicyclo[4.4.0]decanes are listed in Table I. Attempted distillation of XIV and XV resulted in decomposition and these compounds were isolated in pure form only as hydrochlorides. Compounds XVI and XVII were prepared by treating IX with phenyl isothiocyanate and 1-*p*-nitrobenzoylethylenimine, respectively. XIX is the reduction product of XVII and XVIII is the hydrolysis product of XIX.

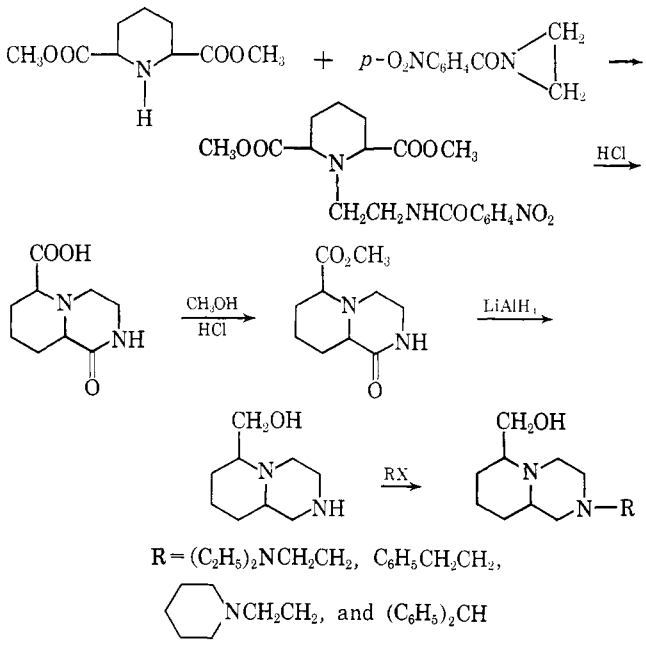
(1) M. E. Freed and A. R. Day, *J. Org. Chem.*, **25**, 2108 (1960).
(2) P. Thyrum and A. R. Day, *J. Med. Chem.*, **8**, 107 (1965).

SCHEME I



A second series of compounds was prepared from dimethyl piperidine-2,6-dicarboxylate as shown in Scheme II. These compounds are listed in Table II.

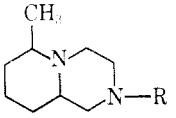
SCHEME II



R = $(C_2H_5)_2NCH_2CH_2$, $C_6H_5CH_2CH_2$, NCH_2CH_2, and $(C_6H_5)_2CH$

TABLE I

4-SUBSTITUTED 10-METHYL-1,4-DIAZABICYCLO[4.4.0]DECANES

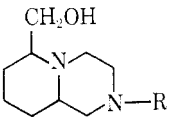


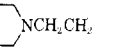
No.	R	Yield, %	Bp, °C (mm)	Formula	Calcd, % C	H	N	Cl	Found, % C	H	N	Cl
IX	H	80	66 (0.63)	$C_9H_{18}N_2$	70.07	11.76	18.17		70.10	11.75	18.31	
X	n-C_4H_9	57	158 (0.85)	$C_{13}H_{26}N_2$	74.22	12.46	13.32		74.04	12.61	13.51	
XI	$C_6H_5CH_2$	66	158–162 (3)	$C_{16}H_{24}N_2$	78.64	9.90	11.45		78.40	9.75	11.52	
XII	$(C_2H_5)_2NCH_2CH_2$	18	Dec	$C_{15}H_{31}N_3$	71.09	12.33	16.58		71.17	12.51	16.46	
XIII	$HOCH_2CH_2$	60	128 (0.85)	$C_{11}H_{22}N_2O$	66.62	11.18	14.12		66.83	11.30	14.10	
XIV	$(C_6H_5)_2CH$	40[a]	Dec	$C_{29}H_{30}Cl_2N_2$	67.17	7.69	7.12	18.03	67.32	7.56	7.32	17.86
XV		11[b]	Dec	$C_{16}H_{24}Cl_3N_3$	51.27	9.14	11.21	28.38	51.44	9.27	11.31	28.20
XVI	C_6H_5NHCS	70[c]		$C_{16}H_{24}N_3S$	66.39	8.01	14.52		66.59	8.20	14.39	
XVII	p-$O_2NC_6H_4CONHCH_2CH_2$	79[d]		$C_{18}H_{28}N_4O_3$	62.41	7.57	16.17		62.42	7.47	16.09	
XVIII	$H_2NCH_2CH_2$	35	105–110 (0.43)	$C_{11}H_{23}N_3$	66.96	11.75	21.30		66.91	11.55	21.19	
XIX	p-$H_2NC_6H_4CONHCH_2CH_2$	43[e]		$C_{18}H_{31}Cl_3N_4O$	50.77	7.34	13.16	28.73	50.69	7.21	13.09	28.51

[a] Isolated only as a dihydrochloride, mp 228–229° dec. [b] Isolated only as a trihydrochloride, mp 168.5–170. [c] Mp 168.5–170° dec. [d] Mp 128.5–129.5°. [e] Isolated only as a trihydrochloride, mp 250–253° dec.

TABLE II

4-SUBSTITUTED 10-HYDROXYMETHYL-1,4-DIAZOBICYCLO[4.4.0]DECANES



No.	R	Yield, %	Mp, °C	Formula	Calcd, % C	H	N	Cl	Found, % C	H	N	Cl
XX	H	72[a]		$C_9H_{18}N_2O$	63.49	10.65	16.44		63.24	10.77	16.21	
XXI	$(C_2H_5)_2NCH_2CH_2$	45[b]	243–246 dec	$C_{15}H_{34}Cl_3N_3O$	47.56	9.05	11.09	28.08	47.29	9.02	11.12	27.74
XXII	$C_6H_5CH_2CH_2$	55[c]	274–276 dec	$C_{17}H_{28}Cl_2N_2O$	58.78	8.13	8.07	20.42	58.68	8.11	7.83	20.62
XXIII		38[b]	277.5–279 dec	$C_{16}H_{34}Cl_3N_3O$	49.17	8.77	10.75	27.22	48.98	8.81	10.57	26.97
XXIV	$(C_6H_5)_2CH$	16	153–154	$C_{22}H_{28}N_2O$	78.53	8.39	8.33		78.46	8.32	8.14	

[a] Oil, bp 158–166° (2 mm). [b] Isolated only as a trihydrochloride. [c] Isolated only as a dihydrochloride.

Pharmacological Test Results.[3]—Compounds XII–XV were first evaluated in a general behavioral screen (Table III). These four compounds were also tested in a series of antagonism studies. None of the compounds possessed any significant ability to reverse the effect of pentylenetetrazole (anticonvulsant action), reserpine (antidepressant effect), Tremorine (antiparkinsonism action), or electroshock (anticonvulsant action).

TABLE III

CENTRAL NERVOUS SYSTEM EFFECTS FOUND WITH 10-SUBSTITUTED 1,4-DIAZABICYCLO[4.4.0]DECANES

Response	Minimal dose at which response was observed, mg/kg Compound XII	XIII	XIV	XV
Hyperactivity to touch		400		
Tremors	400		127	400
Convulsions	400			
Decreased motor activity	40	127	127	40
Sedation ataxia	127		127	127
Righting reflex loss				127
Ptosis				127
Hypothermia			400	
Mydriasis	40		400	12.7
Hyperemia	40			
No. of deaths at 400 mg/kg	3/3	0/3	1/3	0/3

(3) The pharmacological evaluations were performed by Wyeth Laboratories, Inc., Radnor, Pa.

The remaining 10-methyl compounds and the four 10-hydroxymethyl compounds were also examined but showed no particular activity in the general behavior tests.

The first four compounds, XII–XV, were also tested for antihistaminic activity using sections of guinea pig ileum and chlorpheniramine as the control drug. The compounds showed some ability to inhibit the histamine response but not to a degree suggestive of clinical usefulness.

Nine of these compounds were tested for their hypotensive activity in 5,5-diallylbarbituric acid–urethan anesthetized cats. The compounds were injected intravenously and the blood pressure and heart rate were measured and compared with the values obtained before drug injection. A drop in blood pressure of 10–30 mm was considered slight, 31–60 mm was considered moderate, and >61 mm was considered marked. The results are shown in Table IV.

Compounds XIV, XVIII, XXI, XXIV, and XXIII exerted hypotensive activity, at the dosages listed in Table IV, XIV and XVIII being the most potent. Compound XII caused an initial small rise in blood pressure at all doses and a secondary fall at the higher dose levels. The marked activity of XIV and XVIII make them candidates for further work in order to determine their mechanism of action. Preliminary experiments not yet completed indicate that compound

TABLE IV

HYPOTENSIVE EFFECTS FOUND WITH 10-SUBSTITUTED 1,4-DIAZABICYCLO[4.4.0]DECANES

No.	Dose, mg/kg	Blood pressure (systolic/diastolic), mm — Before drug	Blood pressure (systolic/diastolic), mm — Max change	Heart rate, beats/min — Before drug	Heart rate, beats/min — Max change
XII	1.0	110/75	+25/+15		
			+25/+15		
	5.0	110/75	−20/−15		
			+25/+15		
	10.0	105/70	−20/−15		
XIII	1.0	145/95	0	156	0
	5.0	140/85	+10/0	162	0
	10.0	155/90	+5/+5	162	−6
XIV	0.5	190/140	−35/−30	150	−12
	5.0	195/145	−145/−110	144	−78
XV	1	140/80	+5/+5	132	0
	5	155/80	+10/+5	138	+12
	10	150/85	+10/+5	168	+6
XVIII	1.0	175/110	−75/−45	184	−24
	5.0	160/105	−75/−55	156	−30
XXI	1.0	135/100	0	138	+24
	5.0	140/100	−15/0	162	0
	10.5	145/105	−35/−20	168	−18
	20.5	145/110	−45/−35	162	−30
XXII	1.0	145/105	−5/−5	108	+12
	5.0	145/100	−10/−5	120	−6
	10.0	149/95	−35/−30	114	0
XXIII	1.0	145/90	+5/+5	180	−6
	5.0	150/95	0	174	−6
	10.0	145/95	−15/−15	162	−6
	20.0	125/85	−50/−50	144	−30
XXIV	1.0	135/90	−5/−10	150	0
	5.0	120/75	−35/−35	138	−24

XIV acts by a mechanism other than a ganglionic blocking action.

The presence of some hypotensive activity in six out of nine compounds tested, as well as the sharp differences between the 4-benzhydryl and 4-(2-aminoethyl) substituents in the two potent compounds, suggests that the hypotensive activity is primarily attributable to the 1,4-diazabicyclo[4.4.0]decane system but is augmented or diminished by the nature of the substituents. The hydroxymethyl group appears to have lowered the activity. Compound IX was observed to have little or no activity.

Experimental Section

The melting points reported are uncorrected and were determined in a Thomas–Hoover melting point apparatus.

Ethyl 6-methyl-2-piperidinecarboxylate was prepared from 6-methyl-2-pyridinecarboxylic acid.[4] The free base boiled at 89–91° (4 mm), $n^{25}D$ 1.4510, lit.[4] bp 99–100° (13 mm).

Anal. Calcd for $C_9H_{17}NO_2$: C, 63.12; H, 10.01; N, 8.18. Found: C, 62.98; H, 10.17; N, 8.21.

Reference 4 gives mp 213–215° for the hydrochloride but our hydrochloride decomposed at 232–234°.

Anal. Calcd for $C_9H_{18}ClNO_2$: C, 52.01; H, 8.73; N, 6.74. Found: C, 51.94; H, 8.94; N, 6.46.

Ethyl 6-Methyl-1-(2-*p*-nitrobenzamidoethyl)-2-piperidinecarboxylate.—Ethyl 6-methyl-2-piperidinecarboxylate (5.0 g, 0.029 mole) was heated on the steam bath with 1 *p*-nitrobenzoylethylenimine[2] (5.63 g, 0.029 mole) for 3 hr. After cooling, the oil was stirred with hexane until the oil solidified. The solid was recrystallized from hexane–petroleum ether (30–60°); mp 76–78°, yield 70%.

Anal. Calcd for $C_{18}H_{25}N_3O_5$: C, 59.49; H, 6.94; N, 11.56. Found: C, 59.55; H, 7.11; N, 11.66.

10-Methyl-1,4-diazabicyclo[4.4.0]decan-5-one.—Ethyl 6-methyl-1-(2-*p*-nitrobenzamidoethyl)-2-piperidinecarboxylate (11.5 g, 0.032 mole) was suspended in 100 ml of 6 *N* HCl and the mixture was refluxed for 24 hr. It was cooled and the *p*-nitrobenzoic acid was removed by filtration. The filtrate was evaporated and the residue was heated with 2-propanol to yield a crystalline hydrochloride. A sample was recrystallized from ethanol, dec pt 266°.

Anal. Calcd for $C_9H_{17}ClN_2O$: C, 52.80; H, 8.37. Found: C, 52.62; H, 8.47.

The hydrochloride was dissolved in water, the solution was made basic (NaOH) and extracted with chloroform. The extract was evaporated, and the residue was recrystallized from ethyl acetate; mp 124–127°, yield 53%.

Anal. Calcd for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.65. Found: C, 64.11; H, 9.65; N, 16.43.

10-Methyl-1,4-diazabicyclo[4.4.0]decane (IX).—A solution of 1.5 g (0.009 mole) of 10-methyl-1,4-diazabicyclo[4.4.0]decan-5-one in 15 ml of tetrahydrofuran was added dropwise to a slurry of 0.57 g (0.015 mole) of $LiAlH_4$ in 20 ml of tetrahydrofuran, and the mixture was refluxed for 12 hr. The excess $LiAlH_4$ was decomposed by the cautious addition of 2.5 ml of water. 2-Propanol was added, and the mixture was stirred until the solid was colorless. The solid was removed by filtration and washed with 2-propanol. The solvents were evaporated and the resulting oil was dissolved in dry ether and treated with dry HCl. The dihydrochloride (very hygroscopic) was recrystallized from 2-propanol–acetone and obtained in 20% yield, mp 255–258° dec.

Anal. Calcd for $C_9H_{20}Cl_2N_2$: C, 47.58; H, 8.87; Cl, 31.21; N, 12.33. Found: C, 47.48; H, 8.93; Cl, 30.97; N, 12.42.

A larger batch of product was prepared from 21.5 g (0.128 mole) of 10-methyl-1,4-diazabicyclo[4.4.0]decan-5-one and 7.3 g (0.192 mole) of $LiAlH_4$. The reaction mixture was worked up as above to the point where the solvents were evaporated. The residual oil was distilled at 66° (0.63 mm), yield of free base 80%, $n^{25}D$ 1.5006.

1-(2-Hydroxyethyl)-6-methyl-2-piperidinecarboxylic Acid δ-Lactone (V).—Ethyl 6-methyl-2-piperidinecarboxylate (6.8 g, 0.04 mole) was dissolved in 25 ml of methanol. To this was added a solution of 2.22 g (2.5 ml, 0.05 mole) of ethylene oxide in 10 ml of methanol. The mixture was heated, in a pressure bottle, on a steam bath for 24 hr. The solvent was removed *in vacuo* and the remaining oil distilled, bp 129–134° (2 mm), $n^{25}D$ 1.4894, yield 70%.

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28. Found: C, 63.81; H, 8.90; N, 8.14.

1-(2-Hydroxyethyl)-2-hydroxymethylpiperidine (VI). Method 1.—A solution of 4.3 g (0.025 mole) of V in 25 ml of anhydrous ether was slowly added to a stirred suspension of 1.1 g (0.029 mole) of $LiAlH_4$ in 35 ml of anhydrous ether. The mixture was refluxed for 12 hr. The excess $LiAlH_4$ was decomposed by the careful addition of 5 ml of water. The resultant white precipitate was removed by filtration and washed with 2-propanol. The combined washings and filtrate were evaporated to dryness and the resulting oil was distilled, bp 164° (5 mm), $n^{25}D$ 1.5015, yield 40%.

Anal. Calcd for $C_9H_{19}NO_2$: C, 62.39; H, 11.05; N, 8.09. Found: C, 62.14; H, 10.93; N, 8.18.

Method 2.—Ethyl 6-methyl-2-piperidinecarboxylate (0.05 mole) in 25 ml of dry ether was slowly added to a stirred suspension of 4.4 g (0.116 mole) of $LiAlH_4$ in 150 ml of dry ether. The mixture was refluxed for 20 hr. The excess $LiAlH_4$ was carefully decomposed with water and the precipitate was removed by filtration and washed with 2-propanol. The combined filtrate and washings was evaporated *in vacuo* and the 2-hydroxymethyl-6-methylpiperidine was recrystallized from petroleum ether, mp 83–83.5°, yield 71%.

Anal. Calcd for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 64.93; H, 11.53; N, 10.73.

2-Hydroxymethyl-6-methylpiperidine (6.8 g, 0.053 mole) was dissolved in 25 ml of methanol. To this solution was added a solution of 2.58 g (0.059 mole) of ethylene oxide in 15 ml of methanol. The solution was heated in a pressure bottle on a steam bath for 36 hr. The solvent was removed *in vacuo* and the oily semisolid was recrystallized from petroleum ether. This solid proved to be starting material (50%). The filtrate was evaporated, the oily residue was dissolved in 15 ml of methanol con-

(4) M. V. Rubtsov, E. S. Nikitskaya, and V. S. Usovskaya, *J. Gen. Chem. USSR*, **26**, 129 (1956).

taining 2.58 g of ethylene oxide, and the solution was heated as before, on a steam bath, for 5 days. Evaporation of the solvent and distillation of the residual oil gave a 29% yield of VI, based on 0.053 mole of starting material.

1-(2-Chloroethyl)-2-chloromethyl-6-methylpiperidine (VII).—1-(2-Hydroxyethyl)-2-hydroxymethyl-6-methylpiperidine (13.9 g, 0.08 mole) in 50 ml of chloroform was added dropwise to a stirred solution of 23.8 g (0.2 mole) of $SOCl_2$ in 50 ml of $CHCl_3$. The solution was gently refluxed for 2 hr. The solvent was evaporated *in vacuo*. The resulting dark residue was dissolved in water, and the solution was made basic (Na_2CO_3) and then extracted with ether. After removing the ether, the residual oil was distilled to give a 57% yield of product, bp 127° (6 mm), $n^{25}D$ 1.4997.

Anal. Calcd for $C_9H_{17}Cl_2N$: C, 51.43; H, 8.16; Cl, 33.74; N, 6.67. Found: C, 51.36; H, 8.11; Cl, 33.99; N, 6.84.

4-Butyl-10-methyl-1,4-diazabicyclo[4.4.0]decane (X). Method A.—Butylamine (4.2 g, 0.0576 mole) was added dropwise to 3 g (0.0143 mole) of VII. To this mixture was added 50 ml of acetone and 25 ml of water. The resulting solution was refluxed for 12 hr. The bulk of the solvent was removed *in vacuo*, the remaining solution made basic (NaOH) and extracted with ether. After removing the ether, the remaining oil was distilled *in vacuo* (Table I). The **dipicrate** decomposed at 240°.

Anal. Calcd for $C_{25}H_{32}N_8O_{14}$: C, 44.91; H, 4.83; N, 16.76. Found: C, 44.81; H, 4.64; N, 16.72.

4-Benzyl-10-methyl-1,4-diazabicyclo[4.4.0]decane (XI). Method B.—Benzylamine (4.1 g, 0.0383 mole) in 25 ml of chloroform was added dropwise to a solution of 7.3 g (0.0348 mole) of VII and 7.0 g (0.0696 mole) of triethylamine in 50 ml of $CHCl_3$. The solution was refluxed for 18 hr. The solvent was evaporated, the residue was dissolved in water, and the solution was made basic with NaOH. The mixture was then extracted ($CHCl_3$). After removing the chloroform by distillation, the residual oil was distilled *in vacuo* (Table I). The **dipicrate** decomposed at 240–260°.

Anal. Calcd for $C_{28}H_{30}N_8O_{14}$: C, 47.86; H, 4.30; N, 15.95. Found: C, 48.01; H, 4.52; N, 15.61.

4-(2-Diethylaminoethyl)-10-methyl-1,4-diazabicyclo[4.4.0]-decane (XII).—Method B was used with the same molar quantities as above. The free base could not be distilled without decomposition. It was converted to its trihydrochloride by dissolving in dry ethanol, passing in dry hydrogen chloride, and finally adding dry ether. It was quite hygroscopic. It was recrystallized from methanol and acetone, mp 236–242° dec.

Anal. Calcd for $C_{15}H_{34}Cl_3N_3$: C, 49.65; H, 9.45; Cl, 29.32; N, 11.58. Found: C, 49.39; H, 9.73; Cl, 29.26; N, 11.48.

The free base was obtained by dissolving the hydrochloride in water, neutralizing the solution (NaOH), and extracting with chloroform. After drying (K_2CO_3), the $CHCl_3$ was removed to yield the pure base (Table I).

4-(2-Hydroxyethyl)-10-methyl-1,4-diazabicyclo[4.4.0]decane (XIII).—Method B was used with the same molar quantities. The free base was quite hygroscopic; dihydrochloride, mp 255–257°, from methanol–2-propanol–acetone.

Anal. Calcd for $C_{11}H_{24}Cl_2N_2O$: C, 48.71; H, 8.92; Cl, 26.14; N, 10.33. Found: C, 48.73; H, 8.86; Cl, 26.12; N, 10.14.

Compound XIII was also prepared from IX. 10-Methyl-1,4-diazabicyclo[4.4.0]decane (5 g, 0.0325 mole) and 1.79 g (0.0407 mole) of ethylene oxide in 50 ml of methanol were placed in a pressure bottle and heated for 12 hr. After removing the methanol *in vacuo*, the residual oil was distilled *in vacuo*. This method gave somewhat better yields (Table I).

4-Benzhydryl-10-methyl-1,4-diazabicyclo[4.4.0]decane (XIV).—Method B was used with the same molar quantities. The dihydrochloride of XIV was prepared by dissolving the oil, from the $CHCl_3$ solution, in dry acetone and adding dry HCl. The addition of petroleum ether or diethyl ether precipitated a gum. This was dissolved in 2-propanol and acetone was carefully added to produce a solid. The latter was recrystallized from methanol–ethyl acetate (Table I). A pure sample of the free base could not be obtained.

4-(2-Piperidinoethyl)-10-methyl-1,4-diazabicyclo[4.4.0]decane (XV).—Method B was used and the oil was converted to a trihydrochloride by the procedure used for XIV. The salt was recrystallized from ethanol–acetone.

4-Phenylthiocarbamyl-10-methyl-1,4-diazabicyclo[4.4.0]decane (XVI).—Phenyl isothiocyanate (0.875 g, 0.0065 mole) was added dropwise to a solution of IX (1 g, 0.0065 mole) in 10 ml of cyclohexane. The resulting precipitate was recrystallized from cyclohexane (Table I).

4-(2-*p*-Nitrobenzamidoethyl)-10-methyl-1,4-diazabicyclo-[4.4.0]decane (XVII).—A solution of 3 g (0.0195 mole) of IX and 3.74 g (0.0195 mole) of 1-*p*-nitrobenzoylethylenimine in 100 ml of acetone was refluxed for 24 hr. The solvent was removed *in vacuo* and the residual oil was solidified by the addition of petroleum ether. The product was recrystallized from cyclohexane (Table I).

4-(2-Aminoethyl)-10-methyl-1,4-diazabicyclo[4.4.0]decane (XVIII).—A solution of XVII in 6 *N* HCl was refluxed for 2 hr. The precipitated *p*-nitrobenzoic acid was removed by filtration. The filtrate was made basic (NaOH) and extracted ($CHCl_3$). After removing the chloroform, the remaining oil was distilled *in vacuo* (Table I). The trihydrochloride of this base was formed from an acetone solution by adding dry HCl. It was recrystallized from a mixture of methanol and 2-propanol; mp 265–268° dec.

Anal. Calcd for $C_{11}H_{26}Cl_3N_3$: C, 43.07; H, 8.55; Cl, 34.68; N, 13.70. Found: C, 43.05; H, 8.38; Cl, 34.58; N, 13.62.

4-(2-*p*-Aminobenzamidoethyl)-10-methyl-1,4-diazabicyclo-[4.4.0]decane (XIX).—A solution of 3.46 g (0.01 mole) of XVII in 100 ml of ethanol was hydrogenated over platinum. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo*. The semisolid residue could not be obtained in analytically pure form. It was dissolved in a mixture of chloroform and acetone and treated with dry HCl. The resulting hydrochloride was recrystallized from a mixture of methanol and 2-propanol (Table I).

Dimethyl 2,6-Pyridinedicarboxylate.—A solution of 43 g (0.258 mole) of 2,6-pyridinedicarboxylic acid in 150 ml $SOCl_2$ was refluxed for 18 hr. The $SOCl_2$ was evaporated *in vacuo* leaving a solid residue. Methanol was added carefully with cooling and stirring; yield of ester 98%, mp 123–125°.[5]

Dimethyl 2,6-Piperidinedicarboxylate.—Dimethyl 2,6-pyridinedicarboxylate (49.5 g, 0.254 mole) was dissolved in 250 ml of warm glacial acetic acid and hydrogenated over platinum.[5] It is advisable to keep the solution at 50–60° to keep the solute from precipitating; yield 60%, mp 92–93°.

Dimethyl 1-(2-(*p*-Nitrobenzamidoethyl)piperidine-2,6-dicarboxylate.—A solution of 3.23 g (0.0161 mole) of dimethyl 2,6-piperidinedicarboxylate and 3.08 g (0.0161 mole) of 1-*p*-nitrobenzoylethylenimine in 50 ml of dry ethanol was refluxed for 12 hr. The solvent was evaporated *in vacuo*, and the resulting solid was extracted with benzene. The benzene solution was extracted with dilute HCl, and the acid solution was made basic (Na_2CO_3) and extracted ($CHCl_3$). The chloroform solution was dried (K_2CO_3) and then evaporated. The remaining solid was recrystallized from petroleum ether; yield 81%, mp 101–104°.

Anal. Calcd for $C_{18}H_{23}N_3O_7$: C, 54.95; H, 5.89; N, 10.68. Found: C, 54.91; H, 5.88; N, 10.45.

5-Oxo-1,4-diazabicyclo[4.4.0]decane-10-carboxylic Acid.—A solution of 3 g (0.0077 mole) of dimethyl 1-(2-*p*-nitrobenzamidoethyl)piperidine-2,6-dicarboxylate in 100 ml of 6 *N* HCl was refluxed for 4 hr. The precipitated *p*-nitrobenzoic acid was removed by filtration, the filtrate was extracted with ether, and then the filtrate was evaporated to dryness. The residue was washed with acetone and then with dimethylformamide; yield of hydrochloride 84%, mp 272–274° dec. The product was analytically pure without further purification.

Anal. Calcd for $C_9H_{15}ClN_2O_3$: C, 46.06; H, 6.44; Cl, 15.11; N, 11.94. Found: C, 46.05; H, 6.60; Cl, 15.12; N, 11.72.

Methyl 5-Oxo-1,4-diazabicyclo[4.4.0]decane-10-carboxylate.—5-Oxo-1,4-diazabicyclo[4.4.0]decane-10-carboxylic acid was suspended in methanol and saturated with dry HCl, and the mixture refluxed for 12 hr. The methanol was removed *in vacuo* and the residue was dissolved in water. The water solution was made basic (KOH) and extracted ($CHCl_3$). The chloroform solution was dried (K_2CO_3) and the chloroform then was removed by distillation. The residue was recrystallized from benzene–petroleum ether; yield 63%, mp 155.5–156.5°.

Anal. Calcd for $C_{10}H_{16}N_2O_3$: C, 56.68; H, 7.60; N, 13.20. Found: C, 56.63; H, 7.72; N, 13.11.

10-Hydroxymethyl-1,4-diazabicyclo[4.4.0]decane (XX).—A solution of 15 g (0.071 mole) of methyl 5-oxo-1,4-diazabicyclo-[4.4.0]decane-10-carboxylate in 100 ml of warm tetrahydrofuran

(5) R. A. Barnes and H. M. Fales, *J. Am. Chem. Soc.*, **75**, 975 (1953).

was added dropwise to a suspension of 8.1 g (0.212 mole) of $LiAlH_4$ in 50 ml of tetrahydrofuran The mixture was refluxed for 48 hr. The excess hydride was destroyed by the careful addition of water, and the white precipitate was removed by filtration and washed with 2-propanol. The combined washings and filtrate was evaporated to leave a heavy oil. The latter was distilled *in vacuo*, bp 156–166° (2 mm) (Table II).

4-(2-Diethylaminoethyl)-10-hydroxymethyl-1,4-diazabicyclo[4.4.0]decane (XXI). General Procedure.—A solution of 3 g (0.0176 mole) of XX in 50 ml of acetone was added dropwise to a stirred solution of 2.79 g (0.0176 mole) of 2-diethylaminoethyl chloride hydrochloride and 3.55 g (0.0352 mole) of triethylamine in 50 ml of water. The solution was refluxed for 24 hr, evaporated to half volume, made basic (KOH solution), and extracted ($CHCl_3$). The chloroform extract was dried (K_2CO_3) and evaporated to yield an oil. The latter was dissolved in dry acetone and treated with dry HCl. The resulting trihydrochloride was recrystallized from a mixture of methanol and 2-propanol (Table II).

4-Phenylethyl-10-hydroxymethyl-1,4-diazabicyclo[4.4.0]decane (XXII) was prepared by the general procedure, for XXI, with phenethyl bromide as the halide, and using 0.120 *M* amounts. The mixture was evaporated to dryness and the residue was heated with a small amount of 2-propanol and cooled to cause crystallization. It was then recrystallized from a mixture of methanol and 2-propanol (Table II).

4-(2-Piperidinoethyl-10-hydroxymethyl)-1,4-diazabicyclo[4.4.0]decane (XXIII) was prepared by the general procedure with 1-(2-chloroethyl)piperidine as the halide and using 0.020 *M* quantities of the reagents (Table II).

4-Benzhydryl-10-hydroxymethyl-1,4-diazabicyclo[4.4.0]decane (XXIV).—The general procedure was followed in this case with benzhydryl chloride as the halide, and using 0.020 *M* quantities of the reagents. The dihydrochloride was recrystallized from methanol–ethyl acetate; mp 213–214° dec. The salt was dissolved in water and the solution made basic (NaOH). The resulting free base was removed, washed with water, and dried (Table II).

Synthesis and Antiinflammatory Activity of a Series 1-Aryl-2-pyrrolidinone Derivatives

K. OKUMURA, I. INOUE, M. IKEZAKI, G. HAYASHI, S. NURIMOTO, AND K. SHINTOMI

Osaka Research Laboratory, Tanabe Seiyaku Company, Ltd., Osaka, Japan

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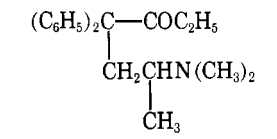
A number of 3- or 4-disubstituted amino-1-aryl-2-pyrrolidinone derivatives have been prepared, some of which were found to possess a potent antiinflammatory effect when administered intraperitoneally. These compounds were obtained by the reaction of 2-disubstituted aminobutyrolactones with aniline derivatives, or by alkylation of 3- or 4-amino-1-aryl-2-pyrrolidinones.

Some new derivatives of propionanilide, N-*t*-aminoalkylpropionanilides (III), were reported by Wright and co-workers[1] as effective analgesic agents. The compounds in this series are considered analogs of methadone (I) and isomethadone (II), in which the quaternary carbon atom and one of the phenyl groups are replaced by a nitrogen atom. We had previously prepared various analogs of N-*t*-aminoalkylpropionanilides such as IV,[2] V,[3] VI,[4] VII,[4] and VIII,[5] in order to study the relation between their chemical structure and pharmacological activity, and found that some of them have strong analgesic, antipyretic, and antiinflammatory activities.

This paper is limited to a report on the synthesis and antiinflammatory activity of a series of 3- and 4-disubstituted amino-1-aryl-2-pyrrolidinones. 3-Disubstituted amino-1-aryl-2-pyrrolidinones and their 5-methyl homologs were prepared by methods A and B as illustrated below. Method A was applied to the compounds, in which R′ and R″ form a morpholino, piperidino, and pyrrolidino ring. According to Berti's[6] or Scheradsky's[7] method, α-bromo-γ-butyrolactone



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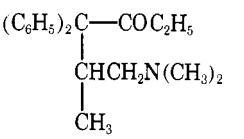

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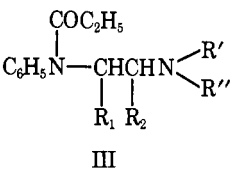

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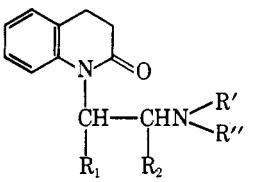

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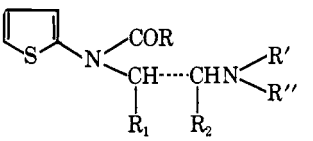

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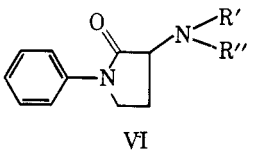

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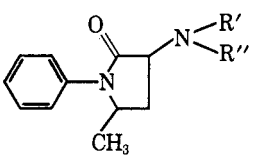

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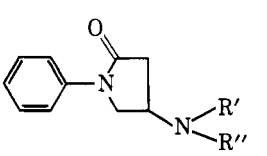

VIII

(X) was treated with morpholine, piperidine, and pyrrolidine to give 2-disubstituted aminobutyrolactone (XI), which yielded 3-disubstituted amino-1-aryl-2-pyrrolidinone (XII) on reaction with aniline or its

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