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

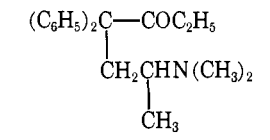
Osaka Research Laboratory, Tanabe Seiyaku Company, Ltd., Osaka, Japan

Received October 11, 1965

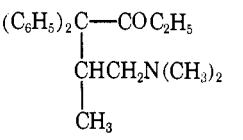
A number of 3- or 4-disubstituted amino-1-aryl-2-pyrrolidinone derivatives have been prepared, some of which were found to possess a potent antiinflammatory effect when administered intraperitoneally. These compounds were obtained by the reaction of 2-disubstituted aminobutyrolactones with aniline derivatives,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

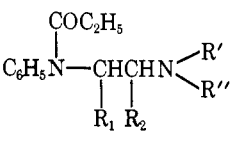
This paper is limited to a report on the synthesis and antiinflammatory activity of a series of 3- and 4-disubstituted amino-1-aryl-2-pyrrolidinones. 3-Disubstituted amino-1-aryl-2-pyrrolidinones and their 5-methyl homologs were prepared by methods A and B as illustrated below. Method A was applied to 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



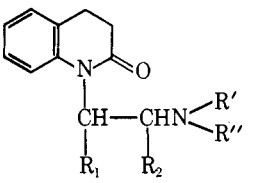
I



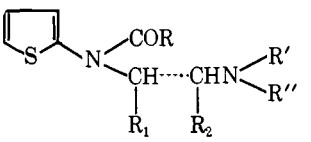
II



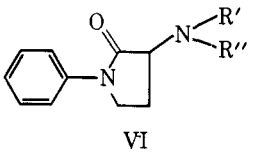
III



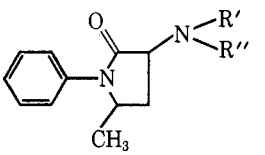
IV



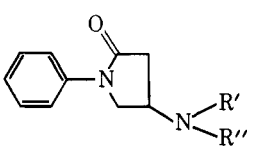
V



VI



VII



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

(1) W. B. Wright, Jr., H. J. Brabander, and R. A. Hardy, Jr., *J. Am. Chem. Soc.*, **81**, 1518 (1959).

(2) N. Shigematsu, *Chem. Pharm. Bull.* (Tokyo), **9**, 970 (1961); N. Sugimoto, K. Okumura, N. Shigematsu, and G. Hayashi, Annual Report of Tanabe Seiyaku Co., Ltd., Vol. 6, Tanabe Seiyaku Co., Ltd., Osaka, Japan, 1961, p 67.

(3) N. Sugimoto, K. Okumura, N. Shigematsu, and G. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **10**, 1061 (1962).

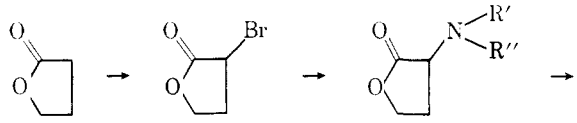
(4) K. Okumura and I. Inoue, *ibid.*, **12**, 718 (1964).

(5) Presented at the Kinki Local Meeting of the Pharmaceutical Society of Japan, Nov 23, 1962.

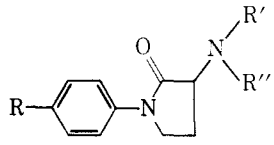
(6) F. A. Berti, *Gazz. Chim. Ital.*, **84**, 420 (1954).

(7) T. Scheradsky, Y. Knobler, and M. Frankel, *J. Org. Chem.*, **26**, 1482 (1961).

Method A

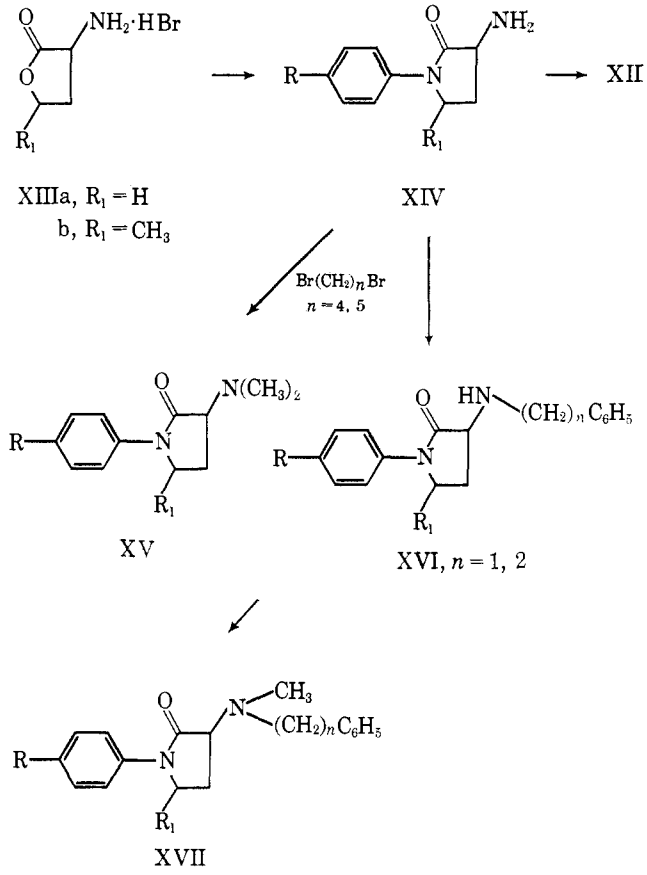


IX X XIa, R′, R″ = $-(CH_2)_4-$
b, R′, R″ = $-(CH_2)_5-$
c, R′, R″ = $-(CH_2)O(CH_2)-$



XII

Method B



XIIIa, $R_1 = H$
b, $R_1 = CH_3$

XIV

$Br(CH_2)_nBr$
$n = 4, 5$

XV

XVI, $n = 1, 2$

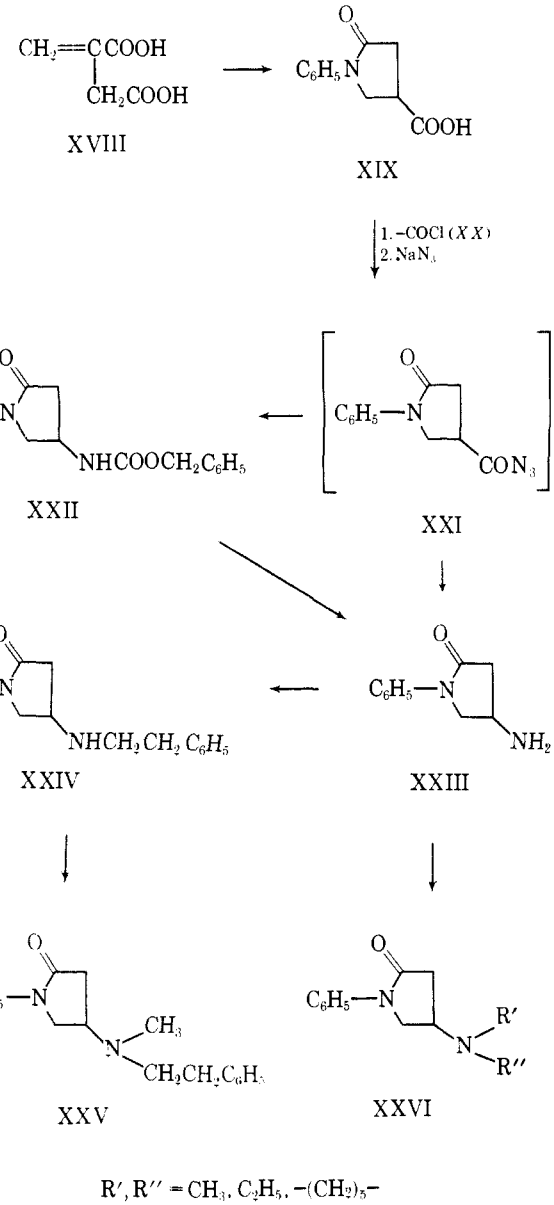
XVII

derivatives. The other compounds were synthesized by method B. In this method, the key intermediate was 3-amino-1-aryl-2-pyrrolidinone (XIV), which was synthesized by the reaction of α-amino-γ-butyrolactone hydrobromide with aniline derivatives. Further treatment of XIV with formic acid and formaldehyde gave the N-dimethylamino derivatives (XV).

Reductive alkylation of XIV with benzaldehyde or phenylacetaldehyde gave the corresponding benzylamino or phenethylamino derivatives (XVI), respectively. These compounds were converted to the N-methyl derivatives (XVII) by the Eschweiler–Clark methylation procedure.[8] Cyclization of XIV with 1,4-dibromobutane or 1,5-dibromopentane gave the pyrrolidino (XIIa) or piperidino (XIIb) derivatives, which had previously been obtained by method A. In the case of the 5-methyl homologs which possess two asymmetric centers, the diastereoisomers were isolated, and the stereoconfiguration of these epimers was established by analysis and synthesis as described in a previous paper.[9]

Conversion of 5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid[10] (XIX) *via* the acid chloride (XX) to the azide (XXI), with subsequent hydrolysis and rearrangement of the azide (XXI) by dilute hydrochloric acid gave the 4-amino derivative (XXIII), which was also obtained *via* the benzylurethan (XXII) according to Sugasawa–Saito's modification of the Curtius method.[11] Alkylation and cyclization of the 4-amino derivative (XXIII) by the same manner as for the 3-amino homologs gave 4-disubstituted amino derivatives such as XXIV–XXVI (Scheme I).

SCHEME I



XVIII XIX

1. $-COCl$ (XX)
2. NaN_3

XXII XXI XXIV XXIII XXV XXVI

R′, R″ = CH_3, C_2H_5, $-(CH_2)_5-$

(8) M. L. Moore, *Org. Reactions*, **5**, 307 (1949).

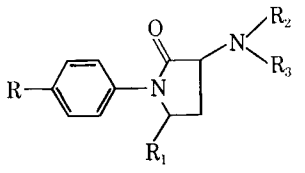
(9) K. Okumura, K. Kotera, and I. Inoue, *Chem. Pharm. Bull.* (Tokyo), **12**, 725 (1964).

(10) P. L. Paytash, E. Sparrow, and J. C. Gathe, *J. Am. Chem. Soc.*, **72**, 1415 (1950).

(11) S. Sugasawa and J. Saito, *Yakugaku Zasshi*, **64**, A4 (1944).

TABLE I

3-DISUBSTITUTED AMINO-1-ARYL-2-PYRROLIDINONES

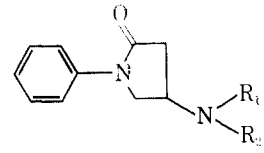


Compd[a]	R	R_1	R_2	R_3	Yield, %	Mp, °C of base	Mp, °C of salt	Formula[b]	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Anti-inflammatory effect % inhibition of edema	Toxicity MLD[c] (mice), mg/kg ip
1	H	H	H	H	33	62–65	HCl, 214–215	$C_{10}H_{12}N_2O \cdot HCl \cdot H_2O$	51.41	6.35	12.14	51.65	6.29	12.80	10.0	300
2	H	H	CH_3	CH_3	93		Picrate, 154–155	$C_{12}H_{16}N_2O \cdot C_6H_3N_3O_7$	49.88	4.42	16.16	50.05	4.43	16.56	15.0	300
3	H	H	$-(CH_2)_4-$		35[d]	83–85	HCl, 210–212	$C_{14}H_{18}N_2O$	73.01	7.88	12.17	72.31	7.33	12.35	28.0	250
4	H	H	$-(CH_2)_5-$		28[d]	84–85	HCl, 209–210	$C_{16}H_{20}N_2O \cdot HCl$	64.16	7.48	9.97	63.89	7.46	9.70	30.0	230
5	H	H	$-(CH_2)_2O(CH_2)_2-$		25	104–105	HCl, 177–178	$C_{14}H_{18}N_2O_2 \cdot HCl$	59.46	6.72	9.91	59.54	6.53	9.70	8.5	200
6	H	H	H	$CH_2Cl_2C_6H_5$	72[b]		HCl, 235–236	$C_{18}H_{20}N_2O \cdot HCl$	68.14	6.62	8.83	68.43	6.46	9.05	1.5	300
7	H	H	CH_3	$CH_2CH_2C_6H_5$	73		HCl, 109–111	$C_{19}H_{22}N_2O \cdot HCl \cdot H_2O$	65.42	6.65	8.03	65.61	6.81	8.12	3.5	250
8	OCH_3	H	H	H	15	120–122	HCl, 230–232	$C_{11}H_{14}N_2O_2$	64.06	6.84	13.58	63.77	6.46	14.30	—	—
9	OCH_3	H	$-(CH_2)_4-$		55[d]	94–96	HCl, 158–160	$C_{75}H_{20}N_2O_2$	69.20	7.74	10.76	69.29	7.24	10.44	6.5	200
10	OCH_3	H	$-(CH_2)_5-$		41[d]	124–126	HCl, 197–198	$C_{76}H_{22}N_2O_2 \cdot HCl$	61.08	7.46	9.01	61.25	7.23	8.85	22.5	400
11	CH_3	H	H	H	29	94–97	HCl, 233–235	$C_{11}H_{14}N_2O$	69.44	7.42	14.73	69.89	3.71	13.75	—	—
12	CH_3	H	$-(CH_2)_4-$		21[d]	117–119		$C_{15}H_{20}N_2O$	73.73	8.25	11.47	73.62	7.40	11.74	—	200
13	CH_3	H	$-(CH_2)_5-$		22[d]	108–110	HCl, 220–222	$C_{16}H_{22}N_2O$	74.38	8.58	10.84	74.34	8.45	10.74	34.5	400
14	CH_3	H	CH_3	CH_3	61		HCl, 185–187	$C_{13}H_{18}N_2O \cdot HCl$	61.40	7.51	10.99	61.70	7.21	10.43	—	—
15	OH	H	$-(CH_2)_5-$		28	191–192	HCl, 243–245	$C_{16}H_{20}N_2O_2$	69.20	7.74	10.76	69.30	7.34	10.81	−7.5	400
16	Cl	H	H	H	29	88–89	HCl, 228–230	$C_{10}H_{11}ClN_2O$	57.01	5.26	13.30	56.63	5.07	12.71	25.5	400
17	Cl		$-(CH_2)_4-$		20	142–145	HCl, 158–160								—	—
18	Cl	H	$-(CH_2)_5-$		19	136–138	HCl, 214–216	$C_{15}H_{19}ClN_2O$	64.62	6.87	10.05	64.54	6.52	10.27	4.5	200
19	F	H	H	H	47	89–91	HCl, 203–205	$C_{10}H_{11}FN_2O$	61.84	5.71	14.43	61.64	5.74	14.20	—	800
20	F	H	$-(CH_2)_5-$		44	96–98	Picrate, 171–173	$C_{15}H_{19}FN_2O$	68.70	7.25	10.69	67.46	7.66	9.69	43.3	200
21α	H	CH_3	H	H	15	57–60	HCl, 96–98	$C_{11}H_{14}N_2O$	69.44	7.42	14.73	69.55	7.12	14.79	−7.0	300
21β	H	CH_3	H	H	12	94–96	HCl, 215–220	$C_{11}H_{14}N_2O$	69.44	7.42	14.73	69.88	7.04	14.58	13.2	300
22α	H	CH_3	CH_3	CH_3	60		HCl, 206–209	$C_{13}H_{18}N_2O \cdot HCl$	61.29	7.46	11.00	61.01	7.26	11.25	4.7	300
22β	H	CH_3	CH_3	CH_3	81		HCl, 194–197	$C_{13}H_{18}N_2O \cdot HCl$	61.29	7.46	11.00	61.08	7.05	10.93	12.0	300
23α	H	CH_3	$-(CH_2)_5-$		27	79–81	HCl, 208–210	$C_{16}H_{22}N_2O \cdot HCl$	65.19	7.81	9.50	65.34	7.97	9.51	0	200
23β	H	CH_3	$-(CH_2)_5-$		29	75–77	HCl, 222–225	$C_{16}H_{22}N_2O \cdot HCl$	65.19	7.81	9.50	64.99	7.26	9.61	19.7	250
24α	H	CH_3	H	$CH_2C_6H_5$	53		Picrate, 214–215	$C_{18}H_{20}N_2O \cdot C_6H_3N_3O_7$	56.58	4.55	13.75	56.26	4.39	13.85	10.5	300
24β	H	CH_3	H	$CH_2C_6H_5$	46	107–109		$C_{18}H_{20}N_2O$	77.11	7.19	9.99	77.44	7.05	10.05	—	—
25α	H	CH_3	CH_3	$CH_2C_6H_5$	87		Picrate, 128–130	$C_{19}H_{22}N_2O \cdot C_6H_3N_3O_7$	57.36	4.81	13.38	57.68	4.77	13.61	15.0	200
25β	H	CH_3	CH_3	$CH_2C_6H_5$	76		Picrolonate, 187–189	$C_{19}H_{22}N_2O \cdot C_{10}H_8N_4O_5$	62.35	5.41	15.05	62.46	5.12	15.06	—	—
26α	H	CH_3	H	CH_3	65	72–73.5	HCl, 216–217	$C_{12}H_{16}N_2O \cdot HCl$	59.82	7.06	11.63	60.16	6.91	11.62	7.5	350
26β	H	CH_3	H	CH_3	78		HCl, 228–230	$C_{12}H_{16}N_2O \cdot HCl$	59.82	7.06	11.63	59.98	6.90	11.84	0.7	300
27α	H	CH_3	H	$CH_2CH_2C_6H_5$	44		HCl, 216–218	$C_{19}H_{22}N_2O \cdot HCl$	68.98	7.00	8.47	68.86	6.80	8.52	1.5	150
27β	H	CH_3	H	$CH_2CH_2C_6H_5$	39[e]		HCl, 232–234	$C_{19}H_{22}N_2O \cdot HCl$	68.98	7.00	8.47	68.65	6.80	8.44	6.5	200
28α	H	CH_3	CH_3	$CH_2CH_2C_6H_5$	56[f]		Picrolonate, 204–205	$C_{20}H_{24}N_2O \cdot C_{10}H_8N_4O_5$	62.92	5.63	14.68	62.77	5.66	14.25	27.2	200
28β	H	CH_3	CH_2	$CH_2CH_2C_6H_5$	74[f]		Picrolonate, 215–217	$C_{20}H_{24}N_2O \cdot C_{10}H_4N_4O_5$	62.92	5.63	14.68	62.99	5.40	15.00	7.5	200
Aminopyrine															31.0	200
Phenylbutazone															28.5	200

[a] The compound number suffixed with α and β represent *trans* and *cis*, respectively. [b] Formula used for analysis. [c] Minimum lethal dose. [d] Yield by method A. [e] Yield as hydrochloride. [f] Yield by phenethylation of **26**.

TABLE II

4-DISUBSTITUTED AMINO-1-ARYL-2-PYRROLIDINONE



Compd	R_1	R_2	Yield, %	Mp, °C of base	Mp, °C of salt	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Antiinflammatory effect, % inhibition of edema	Toxicity MLD[a] (mice), mg/kg ip
29	H	H	78		HCl, 178–180	$C_{10}H_{12}N_2O \cdot HCl$	56.47	6.12	13.18	56.36	6.24	13.10	0.4	300
30	CH_3	CH_3	58	105–107	HCl, 203–204	$C_{12}H_{16}N_2O$	70.56	7.90	13.72	70.73	7.74	13.75	−3.0	300
31	C_2H_5	C_2H_5	29		HCl, 187	$C_{14}H_{20}N_2O \cdot HCl$	62.56	7.82	10.42	62.77	7.42	10.68	—	—
32	H	$CH_2CH_2C_6H_5$	41	89–91	HCl, 216–218	$C_{18}H_{20}N_2O$	77.11	7.19	9.99	77.35	6.95	9.83	3.5	150
33	CH_3	$CH_2CH_2C_6H_5$	61	76–77	HCl, 192–193.5	$C_{19}H_{22}N_2O$	77.52	7.53	9.52	77.37	7.18	9.45	10.0	150
34		$-(CH_2)_5-$	18	91–93	HCl, 225–227	$C_{16}H_{20}N_2O$	73.73	8.25	11.47	73.61	8.20	11.38	19.5	200

[a] Minimum lethal dose.

Pharmacology

Antiinflammatory Effect. Methods.—The antiinflammatory activity of the test compounds was evaluated by measuring the inhibition of edema produced acutely by injection of 0.1 ml of 10% egg white in saline into the planter tissue of the hind paw of Wister king rats.[12] The compounds to be tested were administered intraperitoneally at a dose level of 100 mg/kg of body weight 30 min before the egg white injection. Intensity of the hind paw swelling was measured plethysmographically at 1, 2, 3, and 4 hr after the induction of the inflammation. The percentage edema was obtained from the following formula: % edema = $(V_a - V_b) \times 100/V_b$, where V_b is the mean volume of the hind paw before, and V_a the mean volume of the hind paw after the egg white injection. Antiinflammatory effect was expressed as a percentage inhibition of edema: % inhibition of edema = $(E_c - E_t) \times 100/E_c$, where E_c is the percentage edema in the control animals and E_t is that in the animals treated with the test compound. Every experimental group consisted of five animals, weighing 130–150 g.

Results.—Compounds showing an activity better than 20% inhibition were considered to be effective. Compound **1** was only slightly active, but introduction of a *p*-chlorine atom (**16**) in the phenyl group increased activity. Replacement of the 3-amino group in **1** by either a 3-pyrrolidino (**3**) or a 3-piperidino (**4**) group markedly increased the activity, which was nearly the same as that of aminopyrine and phenylbutazone. Orally **4** showed the same activity as that of these standard drugs. However, the replacement by a dimethylamino (**2**), morpholino (**5**), or phenethylamino (**6**) group did not increase the activity. Introduction of a *p*-fluorine substituent (**20**) in the active compound, 1-phenyl-3-piperidino-2-pyrrolidinone (**4**), further enhanced the activity, while that of a *p*-hydroxy group (**15**) resulted in loss of activity of **4**. This fact suggests that the compound having a phenolic hydroxy group has a tendency to be easily conjugated. Unexpectedly, activity of **4** was abolished by the introduction of a *p*-chlorine atom (**18**). Introduction of *p*-methyl (**13**) or *p*-methoxy (**10**) into **4** did not affect activity. A methyl group at the 5-position of 1-phenyl-2-pyrrolidinone derivatives (**21**–**27**) failed to increase activity with exception of **28**α. Generally, the α form of the 5-methyl compounds such as **21**α, **22**α, and **23**α showed less activity than the β form. Compounds with benzylamino (**24**), methylbenzylamino (**25**), phenethylamino (**6** and **27**), or methyl phenethylamino (**7** and **28**β) groups also were less active (see Table I).

The antiinflammatory activity of 4-aminopyrrolidinone derivatives shown in Table II was weaker than that of 3-aminopyrrolidinone derivatives. The acute toxicity of the compounds was investigated using mice weighing 18–19 g. Toxicity of 1-phenyl-3-piperidino-2-pyrrolidinone (**4**) was reduced by introduction of a *p*-hydroxyl (**15**), *p*-methoxyl (**10**), and *p*-methyl group (**13**). On the other hand, substitution by either a *p*-chlorine (**18**) or *p*-fluorine atom (**20**) did not lower the toxicity, although the *p*-fluoro derivative (**19**) of 1-phenyl-3-amino-2-pyrrolidinone (**1**) had decreased acute toxicity.

Experimental Section[13]

Since the details of the preparation of 1-phenyl-3-disubstituted amino-2-pyrrolidinone derivatives were given in a previous paper[4] only one example of the respective method is described here.

α-Pyrrolidino-γ-butyrolactone (XIa).—To well-cooled α-bromo-γ-butyrolactone[14] (50.0 g, 0.303 mole) was added 49.7 g (0.7 mole) of pyrrolidine with stirring. The reaction mixture was kept at room temperature for 2 days, then poured into ether, and the precipitated pyrrolidine hydrobromide was filtered off. Distillation of the ethereal layer afforded 10.13 g (27.5%) of XIa, bp 88–92° (0.08 mm); **picrate**, yellow needles from aqueous ethanol, mp 172–175°.

Anal. Calcd for $C_8H_{13}NO_2 \cdot C_6H_3N_3O_7$: C, 43.75; H, 4.20; N, 14.58. Found: C, 43.69; H, 3.87; N, 15.15.

3-Amino-1-(*p*-anisyl)-2-pyrrolidinone (8).—A mixture of 3 g (0.0164 mole) of α-aminobutyrolactone hydrobromide (XIIIa) and 12.2 g (0.099 mole) of *p*-anisidine was heated at 240–250° for 3 hr. The excess *p*-anisidine was removed *in vacuo* and the residue was dissolved in 10% HCl. The insoluble oily layer was removed by extraction ($CHCl_3$). After neutralization of the acidic aqueous layer, the basic product was extracted ($CHCl_3$). The extract was dried (K_2CO_3) and concentrated. The residue crystallized on standing, and was recrystallized from isopropyl ether to give 0.5 g (14.7%) of white prisms, mp 120–122°; **hydrochl ride** from ethanol, mp 230–232° dec.

1-Phenyl-3-pyrrolidino-2-pyrrolidine (3). Method A.—A mixture of 15.0 g (0.96 mole) of α-pyrrolidino-γ-butyrolactone (XIa) and 27.0 g (0.288 mole) of aniline was heated in a sealed tube at 240–250° for 4 hr. Treatment of the reaction mixture as in the preceding experiment afforded 5 g of a colorless oil, bp 140–160° (0.3 mm), which crystallized on standing. Recrystal-

(12) G. V. Wilhelmi and R. Domenjoz, *Arzneimittel-Forsch.*, 1, 151 (1951).

(13) Melting points are corrected.

(14) J. E. Lival, E. C. Britton, J. C. Vander Weele, and M. F. Murray, *J. Am. Chem. Soc.*, **67**, 2218 (1945).

lization from isopropyl ether gave 4.5 g (31.4%) of colorless needles, mp 83–85°; **hydrochloride** from ethanol, mp 207–212° dec.

Method B.—A solution of 3 g (0.017 mole) of **1** and 3.67 g (0.017 mole) of 1,4-dibromobutane in 70 ml of absolute toluene was refluxed with stirring for 4 hr. To the mixture was added 2.9 g of $NaHCO_3$ and stirring under refluxing was continued further for 10 hr. After cooling, the basic mixture was extracted with 10% HCl, and the acid solution was made alkaline (K_2CO_3) and extracted ($CHCl_3$). The extract was dried (K_2CO_3) and evaporated under reduced pressure. Distillation of the residue gave 1.75 g of a colorless oil, bp 140–160° (0.3 mm), which crystallized on standing. Recrystallization from isopropyl ether gave 1.6 g (41%) of white needles, mp 82–84°. The infrared spectrum of this product was identical with that of the product from method A.

3-Dimethyl-1-(*p*-tolyl)-2-pyrrolidinone (14).—A mixture of 1 g (0.0052 mole) of 3-amino-5-(*p*-tolyl)-2-pyrrolidinone (XIVa), 5 ml of 97% formic acid, and 5 ml of 35% formaldehyde was heated on a water bath for 8 hr. Evaporation of excess formic acid and formaldehyde left a viscous oil, which was distilled at 0.08 mm (bath temperature, 150–170°) to give 0.7 g (61%) of a colorless oil. The **hydrochloride** crystallized as white needles from ethanol, mp 185–187°; **picrate**, yellow needles from aqueous ethanol, mp 209–211° dec.

4-Carbobenzoxyamino-1-phenyl-2-pyrrolidine (XXII).—A mixture of 19.5 g (0.0945 mole) of 5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid (XIX), 23 g of $SOCl_2$, 1 drop of pyridine, and 95 ml of chloroform was refluxed for 3 hr. Solvent and excess $SOCl_2$ were evaporated *in vacuo* to leave the crude chloride (XX). The chloride, dissolved in 40 ml of dioxane, was added to a mixture of 8.4 g (0.13 mole) of NaN_3, 43 ml of water, and 19 ml of dioxane at 0° with stirring. Further stirring at the same temperature gave a crystalline precipitate. Filtration and drying afforded 20 g of the crude azide (XXI), mp 87–89° dec. The azide was refluxed with 9.5 g of benzyl alcohol in 300 ml of benzene for 2 hr. After removal of the solvent, the residue was recrystallized from ethanol to give 16.0 g (55%) of XXII, mp 149–151°.

Anal. Calcd for $C_{18}H_{18}N_3O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.62; H, 5.47; N, 9.16.

4-Amino-1-phenyl-2-pyrrolidinone (29). Method A. Catalytic Reduction of XXII.—To 60 ml of a dioxane–acetone (1:1) solution containing 1.0 g (0.0032 mole) of XXII was added 0.4 g of 15% Pd–C catalyst and 1.5 ml of 10% NaOH. The mixture was subjected to hydrogen at room temperature under atmospheric pressure. After the theoretical amount of hydrogen was consumed, the reaction mixture was neutralized with dilute HCl. Removal of the catalyst and solvent left a colorless oil, which was dissolved in 10% HCl. After neutralization of the acid solution, a basic product was extracted ($CHCl_3$). The extract was dried (K_2CO_3) and concentrated. Distillation of the residue yielded 0.4 g (78%) of **29,** bp 135–140° (0.06 mm). The **hydrochloride** crystallized as colorless needles from ethanol, mp 178–180°.

Anal. Calcd for $C_{10}H_{12}N_2O \cdot HCl$: C, 56.47; H. 6.12; N, 13.18. Found: C, 56.36; H, 6.24; N, 13.10.

The **picrate** crystallized as yellow needles from the aqueous ethanol, mp 232–235° dec.

Method B. Hydrolysis of Crude XXI.—A solution of 1.0 g (0.00435 mole) of XXI in 20 ml of dioxane was heated at 90–95° for 30 min. After cooling, 5 ml of concentrated HCl was added and the mixture was stirred at 60° for 20 min. The reaction mixture was concentrated to dryness under reduced pressure, and the residue was recrystallized from ethanol to give 0.44 g (47%) of the **hydrochloride** of **29,** mp 180–183°, which was identified by the comparison of its infrared spectrum with that of the sample prepared by method A.

4-Dimethylamino-1-phenyl-2-pyrrolidinone (30).—To a mixture of 0.8 g (0.0045 mole) of **29,** 1.36 g (0.016 mole) of $NaHCO_3$ and 10 ml of water was added 2.35 g (0.0152 mole) of diethyl sulfate at room temperature, and the mixture was stirred at 50–60° for 2 hr. The oily product was extracted ($CHCl_3$) and dried (K_2CO_3), and the solvent was evaporated. After removal of the starting material and secondary amine in the usual way, the residue was distilled at 0.1 mm (bath temperature, 200–210°) to give 0.3 g (29%) of XXVIc. The **hydrochloride** crystallized as prisms from isopropyl alcohol, mp 187–187.5°.

Anal. Calcd for $C_{14}H_{20}N_2O \cdot HCl$: C, 62.56; H, 7.82; N, 10.42. Found: C, 62.77; H, 7.42; N, 10.68.

4-Phenethylamino-1-phenyl-2-pyrrolidinone (32).—To a solution of 0.1 g (0.0057 mole) of XXIII and 0.82 g (0.0068 mole) of phenylacetaldehyde in 40 ml of absolute ethanol was added 0.1 g of prereduced PtO_2, and the mixture was shaken in an atmosphere of hydrogen until the uptake of hydrogen stopped. Removal of the catalyst and solvent left a colorless oil, which crystallized on standing. Recrystallization from benzene–ether gave 0.65 g (40.5%) of XXIV, mp 89–90°.

Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.35; H, 6.95; N, 9.83.

The hydrochloride was obtained as colorless needles from ethanol, mp 216–218°.

Synthesis of *trans*-2-Cyclohexyloxycyclopropylamine and Derivatives

JACOB FINKELSTEIN, ELLIOT CHIANG, F. M. VANE, AND JOHN LEE

Department of Chemical Research, Research Division, Hoffmann-La Roche, Inc., Nutley, New Jersey 07110

Received November 13, 1965

In continuing the study of the relationship between chemical constitution and monoamine oxidase inhibition, *trans*-2-cyclohexyloxycyclopropylamine was synthesized. The compound was discovered to be 20–50 times as active as iproniazid in the six biological tests employed. Comparative data were also obtained for the clinically active tranylcypromine and isocarboxazid.

In our further investigation of 2-substituted cyclopropylamines as monoamine oxidase inhibitors (MAO),[1] we synthesized 2-cyclohexyloxycyclopropylamine and discovered it to be a potent compound. After the completion of this work, Kaiser and co-workers,[2] in an extensive study, synthesized the closely related compound, 2-cyclohexylcyclopropylamine, and Zirkle and co-workers[3] reported that it was almost completely devoid of MAO inhibition, as determined by *in vivo* potentiation of tryptamine convulsions in rats. As a result of this and other findings, they concluded that the structural requirements for a potent *in vivo* MAO inhibitor in this class of compounds are (a) a cyclopropyl ring, (b) an amino group attached directly to the cyclopropyl ring, and (c) a 2-substituent containing an aromatic moiety. Since 2-cyclohexyloxycyclopropylamine (**9**) is a potent inhibitor, requirement c must be modified.

The synthesis of 2-cyclohexyloxycyclopropylamine (**9**) was accomplished by the series of reactions shown in

(1) J. Finkelstein, E. Chiang, and J. Lee, *J. Med. Chem.*, **8**, 432 (1965).
(2) C. Kaiser, B. M. Lester, C. L. Zirkle, A. Burger, C. S. Davis, T. J. Delia, and L. Zirngibl, *ibid.*, **5**, 1243 (1962).
(3) C. L. Zirkle, C. Kaiser, D. H. Tedeschi, R. E. Tedeschi, and A. Burger, *ibid.*, **5**, 1265 (1962).