with gaseous HBr and allowed to stand at ambient temperature for 18 hr. The mixture was evaporated *in vacuo*. The residual oil was dissolved in a minimum of methanol, basified with 5% aqueous Na_2CO_3, and extracted with $CHCl_3$. The dried ($MgSO_4$) $CHCl_3$ extract was evaporated *in vacuo* leaving an oil (1.1 g.) which by infrared analysis was shown to be a mixture composed mainly of 2-methyl-2-(β-hydroxyphenethyl)nicotinic acid hydrazide and 2-methyl-2-(β-acetoxyphenethyl)nicotinic acid hydrazide; ν_{max} (film) 3390–3180 broad (OH, NH), 1726 (ester carbonyl), and 1695 (hydrazide carbonyl) cm.$^{-1}$.

New Sedative and Hypotensive 3-Substituted 2,4(1H,3H)-Quinazolinediones

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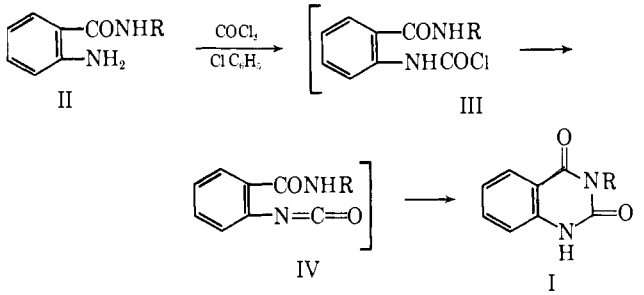
A series of 3-substituted 2,4(1H,3H)-quinazolinediones, mostly 3-(4-aryl-1-piperazinylalkyl)-2,4(1H,3H)-quinazolinediones, was prepared from the corresponding *o*-amino-N-substituted benzamides by treatment with phosgene in boiling chlorobenzene. 1-Methyl-3-substituted 2,4(1H,3H)-quinazolinediones were prepared by the reaction of *o*-methylamino-N-substituted benzamides with ethyl chloroformate, followed by heating at 200° to cyclize. These compounds showed varying degrees of sedative and hypotensive activity in experimental animals.

It has been reported that 2,4(1H,3H)-quinazolinedione[1,2] and 1,3-dimethyl-2,4(1H,3H)-quinazolinedione[1,2] possess anticonvulsant[3] activity against electroshock and pentylenetetrazol seizures in mice. 3-Alkyl-, 3-aralkyl-, and 3-aryl-2,4(1H,3H)-quinazolinediones[4] have been described but no pharmacological screening results were given. Our finding that some amides derived from 4-aryl-1-piperazinylalkylamines,[5] 4-aryl-1-piperazinylalkanoic acids,[5] and N-(4-aryl-1-piperazinylalkyl) derivatives of cyclic imides[6] have shown sedative and hypotensive activities led us to prepare 3-substituted [mostly 3-(4-aryl-1-piperazinylalkyl)-2,4(1H,3H)-] quinazolinediones (I).

The reaction of primary amines with isatoic anhydride gives mainly *o*-aminobenzamides[7] with minor quantities of 1-alkyl-3-(*o*-carboxyphenyl)ureas.[4b] The latter compounds are readily cyclized with dilute mineral acid to give I. In our hands, *o*-amino-N-alkyl- (or aralkyl-) benzamides (II) cyclized readily with phosgene in boiling chlorobenzene to give I in high yield.

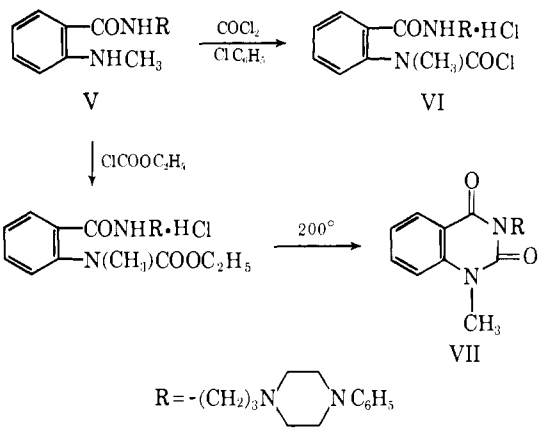
SCHEME I



I was also prepared by treating II with ethyl chloroformate, followed by heating at 200° to cyclize.

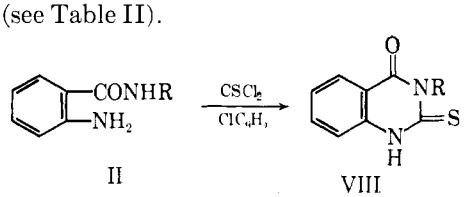
The formation of the quinazolinedione (I) (Scheme I) by treatment of *o*-amino-N-[3-(4-phenyl-1-piperazinyl)-propyl]benzamide (II) with phosgene at the boiling point of chlorobenzene was presumed to proceed through the intermediate isocyanate (IV) formed by dehydrochlorination of the carbamoyl chloride (III). Under the same conditions, *o*-methylamino-N-[3-(4-phenyl-1-piperazinyl)propyl]benzamide (V) gave the carbamoyl chloride (VI) in high yield (Scheme II).

SCHEME II



The dehydrochlorination of VI to give isocyanate is not possible in the latter case. 1-Methyl-3-[3-(4-phenyl-1-piperazinyl)propyl]-2,4(1H,3H)-quinazolinedione(VII) was obtained by treating V with ethyl chloroformate, followed by heating at 200°. See Table I for compounds I and VII.

2-Thio-2,4(1H,3H)-quinazolinediones (VIII) were prepared by adding II to a solution of thiophosgene in chlorobenzene, followed by heating under reflux to cyclize (see Table II).



(1) J. H. Burckhalter and H. C. Scarborough, *J. Am. Pharm. Assoc., Sci. Ed.*, **44**, 545 (1955).

(2) B. Das and R. Mukherjee, *J. Indian Chem. Soc.*, **40**, 35 (1963); *Chem. Abstr.*, **59**, 6404 (1963).

(3) D. G. Wenzel, *J. Am. Pharm. Assoc., Sci. Ed.*, **44**, 550 (1955).

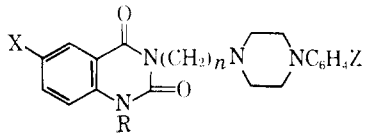
(4) (a) C. Paal, *Ber.*, **27**, 974 (1894); (b) R. P. Staiger and E. C. Wagner, *J. Org. Chem.*, **18**, 1427 (1935); (c) C. H. Wang, T. C. Feng, and B. E. Christensen, *J. Am. Chem. Soc.*, **72**, 4887 (1950); (d) B. Taub and J. B. Hino, *J. Org. Chem.*, **26**, 5238 (1961).

(5) S. Hayao and R. N. Schut, *ibid.*, **26**, 3414 (1961).

(6) S. Hayao and W. G. Strycker, unpublished data.

(7) R. H. Clark and E. C. Wagner, *J. Org. Chem.*, **9**, 55 (1944).

TABLE I



No.	X	R	n	Z	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
1	H	H	0	H	307–309 dec.	$C_{18}H_{18}N_4O_2$	67.1	5.59	17.4	67.3	5.66	17.4
					>260	$C_{18}H_{18}N_4O_2 \cdot 2HCl$			14.2			14.2
2	Cl	H	0	H	>250	$C_{18}H_{17}ClN_4O_2$	60.6	4.80	15.7	60.5	5.11	15.5
3	H	H	2	H	244–245	$C_{20}H_{22}N_4O_2$	68.5	6.29	16.0	68.9	6.33	16.0
					>270	$C_{20}H_{22}N_4O_2 \cdot HCl$	62.0	5.94	14.5	62.1	6.02	14.5
4	H	H	2	*m*-Cl	212.5–214.5	$C_{20}H_{21}ClN_4O_2$			14.6			14.5
					210.5–211.5 dec.	$C_{20}H_{21}ClN_4O_2 \cdot C_4H_4O_4$[a]			11.2			11.3
5	Cl	H	2	H	251–253	$C_{20}H_{21}ClN_4O_2$			3.64[b]			3.64
					230–231	$C_{20}H_{21}ClN_4O_2 \cdot C_4H_4O_4$	57.5	5.03	11.2	57.0	5.13	11.3
6	Cl	H	2	*m*-Cl	228–230	$C_{20}H_{20}Cl_2N_4O_2$			3.34[b]			3.36
					220–222	$C_{20}H_{20}Cl_2N_4O_2 \cdot C_4H_4O_4$			10.5			10.3
7	H	H	3	H	202–203	$C_{21}H_{24}N_4O_2$	69.3	6.60	15.4	68.8	6.96	15.4
					224–226 dec.	$C_{21}H_{24}N_4O_2 \cdot 2HCl \cdot H_2O$[c]			12.3			12.2
8	H	H	3	*o*-Cl	185–186	$C_{21}H_{23}ClN_4O_2$	63.2	5.76	14.0	63.1	6.19	13.8
					>260	$C_{21}H_{23}ClN_4O_2 \cdot HCl$[d]			12.9			12.7
9a	H	H	3	*m*-Cl	195–196	$C_{21}H_{23}ClN_4O_2$	63.3	5.76	14.0	63.3	6.17	14.2
b					240–241	$C_{21}H_{23}ClN_4O_2 \cdot HCl$[e]			12.9			12.6
c					204–206	$C_{21}H_{23}ClN_4O_2 \cdot (CH_3)_2SO_4$[f]	52.6	5.54	10.3	52.3	6.22	10.2
10	H	H	3	*p*-Cl	228.5–230	$C_{21}H_{23}ClN_4O_2$			14.1			13.8
					195–197 dec.	$C_{21}H_{23}ClN_4O_2 \cdot C_4H_4O_4$	58.3	5.25	10.9	58.1	5.44	10.7
11	H	H	3	*m*-CF_3	203–204.5 dec.	$C_{22}H_{23}F_3N_4O_2 \cdot C_4H_4O_4$	56.9	4.93	10.2	56.9	4.90	10.2
12	H	H	3	*p*-F	194–195	$C_{21}H_{23}FN_4O_2$	66.0	6.03	14.65	66.2	6.28	14.65
					259–260	$C_{21}H_{23}FN_4O_2 \cdot HCl$	60.2	5.74	13.4	59.9	5.91	13.2
13	Cl	H	3	H	227–230	$C_{21}H_{23}ClN_4O_2$			14.0			13.7
					213–216	$C_{21}H_{23}ClN_4O_2 \cdot C_4H_4O_4$	58.3	5.28	10.9	58.4	5.50	10.7
14	Cl	H	3	*m*-Cl	198–199	$C_{21}H_{22}Cl_2N_4O_2$			3.24[b]			3.21
					223–225	$C_{21}H_{22}Cl_2N_4O_2 \cdot C_4H_4O_4$	54.7	4.77	10.2	54.8	4.96	10.3
15	Cl	H	3	*p*-Cl	259–262	$C_{21}H_{22}Cl_2N_4O_2$			3.24[b]			3.25
					203–205	$C_{21}H_{22}Cl_2N_4O_2 \cdot C_4H_4O_4$	54.7	4.77	10.2	55.0	4.90	10.0
16	NO_2	H	3	H	208–210	$C_{21}H_{23}N_5O_4$	61.6	5.64	17.2	61.4	5.64	17.3
17	CH_3CONH	H	3	H	256–258 dec.	$C_{23}H_{27}N_5O_3$	65.5	6.41	16.6	64.9	6.50	16.7
					245–246 dec.	$C_{23}H_{27}N_5O_3 \cdot C_4H_4O_4$	60.3	5.77	13.0	60.0	5.56	13.0
18	H	H	4	H	196.5–197.5	$C_{22}H_{26}N_4O_2$	69.9	6.88	14.8	70.1	6.99	15.0
					276–277	$C_{22}H_{26}N_4O_2 \cdot 2HCl$[g]			3.11[b]			3.11
19	H	H	4	*m*-Cl	192–193	$C_{22}H_{25}ClN_4O_2$	63.9	6.05	13.6	63.7	6.39	13.8
					243–245	$C_{22}H_{25}ClN_4O_2 \cdot HCl$[h]			12.5			12.2
20	Cl	H	4	H	205–210	$C_{22}H_{25}ClN_4O_2$			3.40[b]			3.66
					220–222	$C_{22}H_{25}ClN_4O_2 \cdot C_4H_4O_4$	59.0	5.53	10.6	58.7	5.55	10.4
21	H	H	5	H	172–173	$C_{23}H_{28}N_4O_2$	70.5	7.15	14.3	70.1	7.17	14.2
					211–213 dec.	$C_{23}H_{28}N_4O_2 \cdot 2HCl$[i]			12.0			11.8
22	H	H	5	*m*-Cl	180–184	$C_{23}H_{27}ClN_4O_2$	64.5	6.32	13.1	64.5	5.97	13.1
					206–208 dec.	$C_{23}H_{27}ClN_4O_2 \cdot HCl$	59.6	6.05	12.1	59.3	6.21	12.2
23	Cl	H	5	H	185–187	$C_{23}H_{27}ClN_4O_2$			13.1			13.6
					226–230	$C_{23}H_{27}ClN_4O_2 \cdot HCl$	59.6	6.10	12.1	59.1	6.08	12.1
24		H	6	H	173–174	$C_{24}H_{30}N_4O_2$	71.0	7.38	13.8	70.6	7.38	13.7
					259–261 dec.	$C_{24}H_{30}N_4O_2 \cdot HCl$[j]			12.7			13.0
		CH_3	3	H	99–101	$C_{22}H_{26}N_4O_2$	69.8	6.88	14.8	68.5	6.87	14.6
					247–249	$C_{22}H_{26}N_4O_2 \cdot 2HCl$[k]	58.5	6.21	12.4	58.5	6.29	12.3
26	H	CH_3	3	*m*-Cl	103–105	$C_{22}H_{25}ClN_4O_2$	63.9	6.05	13.6	63.6	6.23	13.2
					256–258	$C_{22}H_{25}ClN_4O_2 \cdot HCl$[l]	58.8	5.80	12.5	58.1	5.97	12.2
27	Cl	CH_3	3	H	>250	$C_{22}H_{25}ClN_4O_2 \cdot HCl$[m]	58.8	5.80	12.5	58.1	5.95	12.6

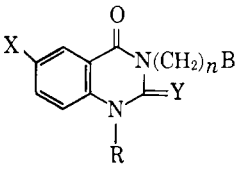
[a] Maleate. [b] Basic nitrogen. Titrated by $HClO_4$. [c] *Anal.* Calcd.: HCl, 16.0. Found: HCl, 16.0. [d] *Anal.* Calcd.: HCl, 8.40. Found: HCl, 8.48. [e] *Anal.* Calcd.: HCl, 8.38. Found: HCl, 8.38. [f] Methosulfate. [g] *Anal.* Calcd.: HCl, 16.2. Found: HCl, 16.1. [h] *Anal.* Calcd.: HCl, 8.13. Found: HCl, 8.12. [i] *Anal.* Calcd.: HCl, 15.7. Found: HCl, 15.8. [j] *Anal.* Calcd.: HCl, 8.25. Found: HCl, 8.40. [k] *Anal.* Calcd.: HCl, 16.2. Found: HCl, 16.1. [l] *Anal.* Calcd.: HCl, 8.12. Found: HCl, 8.18. [m] *Anal.* Calcd.: HCl, 8.13. Found: HCl, 8.08.

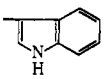
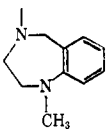
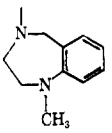
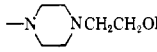
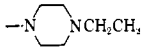
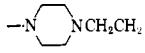
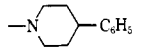
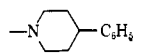
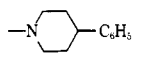
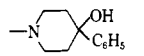
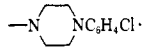
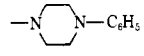
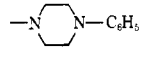
Pharmacology.—These compounds show varying degrees of sedative and hypotensive activity. One of the best compounds as a potential psychosedative was **9b** (Table I). Its activity in experimental animals was comparable to that of chlorpromazine (CPZ). This is shown by the following tests: (1) double blind behavioral observations in dogs and cats, (2) locomotor activity using a rotarod,[8] (3) activity cages[9] with mice,

(8) N. W. Dunham and T. S. Miya, *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 208 (1957).

(9) C. A. Winter and L. Flataker, *J. Pharmacol. Exptl. Therap.*, **103**, 93 (1951).

TABLE II



No.	X	R	Y	n	B	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
28	H	H	O	0		>260	$C_{13}H_9N_3O_2$			17.6			17.6
						265–267 dec.	$C_{13}H_9N_3O_2 \cdot HCl$[a]	56.6	3.63	15.3	56.9	4.14	15.3
29	H	H	O	1		238–239	$C_{14}H_{11}N_3O_2$	66.5	4.35	16.6	66.3	4.40	16.7
						245–247	$C_{14}H_{11}N_3O_2 \cdot HCl$[b]	58.0	4.15	4.83[c]	57.4	4.33	4.72
30	H	H	O	2	C_6H_5	215–216	$C_{16}H_{14}N_2O_2$			10.5			10.8
31	H	H	O	2	$C_6H_3(OCH_3)_2$-3, 4	202–203	$C_{18}H_{18}N_2O_4$	66.3	5.53	8.60	66.1	5.45	8.83
32	H	H	O	2		275–278	$C_{18}H_{15}N_3O_2$	70.9	4.92	13.8	70.2	5.01	13.7
33	H	H	O	2		210 dec.	$C_{20}H_{22}N_4O_2 \cdot 2HCl \cdot CH_4O$[d,e]			12.3			12.2
34	H	H	O	3		217–218	$C_{21}H_{24}N_4O_2 \cdot 2HCl$	57.7	5.99	12.8	57.4	6.08	12.8
35	H	H	O	3	$N(C_2H_5)_2$	227–228	$C_{15}H_{21}N_3O_2 \cdot HCl$	57.7	7.06	13.5	58.0	7.62	13.7
36	H	H	O	3		168–169	$C_{15}H_{19}N_3O_3$	62.5	6.25	14.6	61.9	6.57	14.7
						242–243	$C_{15}H_{19}N_3O_3 \cdot HCl$[f]			12.9			12.8
37	H	H	O	3		181–183 dec.	$C_{17}H_{24}N_4O_3 \cdot 2C_4H_4O_4$[g]	53.2	5.67	9.93	53.8	5.90	9.86
38	H	H	O	3		166–167	$C_{23}H_{28}N_4O_2$	70.5	7.15	14.3	70.2	7.21	14.5
						>260	$C_{23}H_{28}N_4O_2 \cdot 2HCl$[h]			12.1			12.1
39	Cl	H	O	3		233–234	$C_{23}H_{27}ClN_4O_2 \cdot 2C_4H_4O_4$[g]	56.5	5.35	8.50	56.7	5.44	8.50
40	H	H	O	3		172–176	$C_{22}H_{25}N_3O_2$	72.8	6.90	11.6	72.6	6.40	11.9
						210–202	$C_{22}H_{25}N_3O_2 \cdot C_4H_4O_4$[g]	65.2	6.05	8.77	65.0	5.66	8.88
41	H	CH_3	O	3		185–188 dec.	$C_{23}H_{26}N_3O_2 \cdot C_4H_4O_4$[g]	65.7	6.09	8.52	65.6	6.45	8.72
42	Cl	H	O	3		198–199.5	$C_{22}H_{24}ClN_3O_2$			10.6			10.7
						221.5–222.5 dec.	$C_{22}H_{24}ClN_3O_2 \cdot C_4H_4O_4$[g]	60.8	5.45	8.18	61.1	5.94	8.08
43	H	H	O	3		250–250.5 dec.	$C_{22}H_{25}N_3O_3 \cdot HCl$[i]			10.1			10.3
44	H	H	S	3		212–213	$C_{21}H_{23}ClN_4OS \cdot C_4H_4O_4$[g]	56.7	5.14	10.5	56.9	6.02	10.6
45	Cl	H	S	3		213–215	$C_{21}H_{23}ClN_4OS$	60.8	5.55	13.5	60.8	5.95	13.1
						>280	$C_{21}H_{23}ClN_4OS \cdot HCl$[j]	55.9	5.33	3.13[c]	55.7	5.74	3.23
46	H	H	S	5		262–264	$C_{23}H_{28}N_4OS \cdot 2HCl$	57.4	6.29	11.6	57.7	6.58	11.7

[a] *Anal.* Calcd.: HCl, 13.2. Found: HCl, 13.2. [b] *Anal.* Calcd.: HCl, 12.7. Found: HCl, 12.3. [c] Basic nitrogen. Titration with $HClO_4$. [d] Methanolate. [e] *Anal.* Calcd.: HCl, 16.1. Found: HCl, 16.0. [f] *Anal.* Calcd.: HCl, 11.3. Found: HCl, 11.4. [g] Maleate. [h] *Anal.* Calcd.: HCl, 15.7. Found: HCl, 15.7. [i] *Anal.* Calcd.: HCl, 8.79. Found: HCl, 8.73. [j] *Anal.* Calcd.: HCl, 8.10. Found: HCl, 8.05.

(4) hexobarbital sleeping time prolongation in mice,[10] (5) lowering the threshold current for psychomotor seizure in mice,[11] and (6) lowering the acute *d*-amphetamine toxicity in aggregated mice.[12] Equal prolongation of the hexobarbital sleeping times (mg. for mg.) were obtained with **9b** and CPZ. At a dose 5–10 times that of CPZ, **9b** depressed spontaneous motor activity in mice and rats to the same extent as did CPZ. In the rotarod test, the ED_{50} of **9b** was 2.9 mg./kg. and that of CPZ was 1.6 mg./kg. In a blind crossover behavioral study in dogs and cats, **9b** at 5 mg./kg. (*p.o.*) produced sedation equal to that produced by CPZ in dogs and produced greater (1.9 times) sedation in cats than did CPZ at the same dose. The toxicity of **9b** was very low: LD_{50} >7650 (rat, *p.o.*), 3290 (rat, i.p.), and 2160

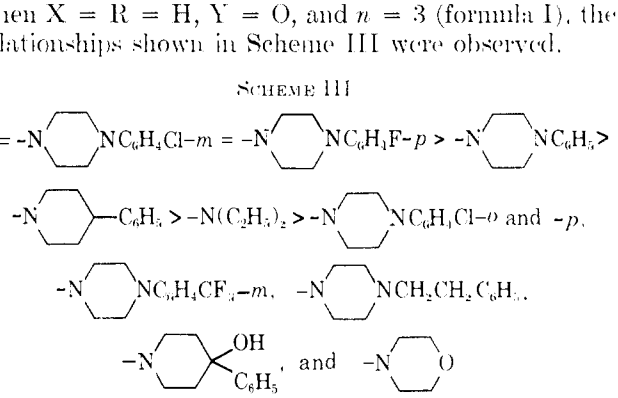
(10) C. A. Winter, *J. Pharmacol. Exptl. Therap.*, **94**, 7 (1948).

(11) G. Chen, C. R. Enson, and B. Bohner, *Proc. Soc. Exptl. Biol. Med.* **86**, 507 (1954).

(12) (a) J. H. Burn and R. Hobbs, *Arch. intern. pharmacodyn.*, **113**, 290 (1958); (b) G. S. Stone, B. M. Bernstein, W. E. Hambourger, and V. A. Drill, *ibid.*, **127**, 85 (1960).

mg./kg. (mouse, i.p.). Sedative and hypotensive activities are found principally in compounds having a 4-aryl-1-piperazinylalkyl group. The following sedative activity–structure relationships were found in this series. When X = R = Z = H (Table I), $n = 0 \ll n = 2 < n = 3 \geqq n = 4 \geqq n = 5 \gg n = 6$, and when X = R = H, Y = O, and $n = 3$ (formula I), the relationships shown in Scheme III were observed.

SCHEME III



The introduction of a 1-methyl group or a C=S at position 2 seems to destroy the activity. The most potent hypotensive compounds were **7** and **18**. At 5 mg./kg. (normotensive anesthetized dog, i.v.), **7** caused a 54% drop in blood pressure which lasted 58 min. A drop of 25% was maintained more than 3 hr. Similarly, at 5 mg./kg. (dog, i.v.), **18** caused a 58% drop in blood pressure for 57 min. and a 25% drop was sustained for more than 5 hr. These compounds reversed the pressor effect of epinephrine, but did not block the action of acetylcholine. Introduction of a halogen (Z or X = Cl, see Table I) in these compounds decreased the hypotensive activity drastically, although the sedative activity was maintained. The details of the pharmacology will be published elsewhere.[13]

Experimental Section[14]

1-Arylpiperazines were prepared readily according to the procedure of Pollard.[15] 4-Aryl- and 4-hydroxy-4-phenylpiperidines were prepared by the procedure of Janssen, *et al.*[16] Isatoic anhydride and 6-chloro-, 6-nitro-, and 1-methylisatoic anhydrides were obtained from Manmee Chemical Co.[17] C^{14}-labeled phosgene was obtained from New England Nuclear Corp.[18]

o-Amino-N-[3-(4-*m*-chlorophenyl-1-piperazinyl)propyl]benzamide.—To a solution of 1-(3-aminopropyl)-4-*m*-chlorophenylpiperazine (607 g., 2.4 moles) in 800 ml. of dimethylformamide (DMF) was added 440 g. (2.7 moles) of isatoic anhydride during 15 min. with stirring. The inner temperature rose to 59° and soon dropped as CO_2 was given off. As the temperature fell to *ca.* 40°, the mixture began to solidify and 1500 ml. of water was added all at once with vigorous stirring. The mixture was stirred for an additional hour and cooled in an ice bath. The solid was collected, washed with water then with 2-propanol, and dried at 100°, m.p. 152–153°, yield 748 g.

Anal. Calcd. for $C_{20}H_{25}ClN_4O$: N, 15.0. Found: N, 14.8.

3-[3-(4-*m*-Chlorophenyl-1-piperazinyl)propyl]-2,4(1H,3H)-quinazolinedione (9).—A stream of phosgene was bubbled into a boiling solution of the above amine (748 g., 2.0 moles) in 4000 ml. of chlorobenzene during 2 hr. (280 g. was absorbed). The reaction mixture was cooled in an ice bath and the solid product was collected by suction, washed with 2-propanol, and dried in air. The crude product was recrystallized from a mixture of 1000 ml. of glacial acetic acid and 3000 ml. of water (activated charcoal) to give a light cream colored solid which was collected and washed with 500 ml. of 25% acetic acid and then with acetone. After drying at 100°, the monohydrochloride melted at 240–241°, yield 740 g. (85%).

A sample was treated with aqueous NH_3 and the resulting free base was recrystallized from aqueous methanol–DMF to give a colorless solid of m.p. 195–196°; ν_{max}^{KCl} 1712 and 1667 cm.$^{-1}$ (imide carbonyls),[19] no amide II band.

o-Amino-N-methylbenzamide and 1-o-Carboxyphenyl-3-methylurea.—To 255 g. of 40% aqueous methylamine was added portionwise isatoic anhydride (163 g., 1.0 mole). A vigorous reaction occurred with evolution of CO_2 and heat. The resulting milky solution was kept at room temperature overnight and then was heated on a steam bath for 1 hr. to give a clear solution. When the solution was cooled in an ice bath, a heavy oil separated and soon solidified. The solid was collected, washed with water, and dried at 50°, m.p. 70–74°, yield 133.7 g. (89.4%). It was recrystallized from aqueous methanol to give 114.2 g. of *o*-amino-N-methylbenzamide, m.p. 74–77°. The aqueous methylamine solution was acidified with dilute HCl to give a light tan solid of m.p. 180–181° dec., yield 8.1 g. (4.2%). It was recrystallized from acetone–Skelly B to give a colorless solid of m.p. 188–189° (lit.[20] m.p. 183°), yield 3.6 g. This compound showed a correct analysis for 1-*o*-carboxyphenyl-3-methylurea.

Anal. Calcd. for $C_9H_{10}N_2O_3$: N, 14.4. Found: N, 14.8.

3-Methyl-2,4(1H,3H)-quinazolinedione. A.—The above 1-*o*-carboxyphenyl-3-methylurea (2.9 g.) was suspended in 18% HCl and heated on a hot plate for a few minutes. The solid product was collected, m.p. 240–241°, yield 2.6 g. It was recrystallized from aqueous methanol–DMF to give a pure sample of m.p. 240–241° (lit.[20] m.p. 241°).

Anal. Calcd. for $C_9H_8N_2O_2$: N, 15.9. Found: N, 15.9.

B.—*o*-Amino-N-methylbenzamide (75.0 g., 0.5 mole) was added all at once to ice-cold chlorobenzene (250 ml.) containing 68.4 g. (0.69 mole) of phosgene, and the resulting suspension was stirred at room temperature overnight. It was then stirred under reflux for 2 hr. and cooled in an ice–water bath. The solid was collected and dried in air, m.p. 215–222°, yield 89.8 g. (100.2%). It was recrystallized from acetone–DMF to give a slightly yellow solid of m.p. 241–243°, yield 34.7 g. No mixture melting point depression was observed with the sample from A.

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.5; H, 4.55; N, 15.9. Found: C, 61.62; H, 4.89; N, 16.1.

The filtrate from the recrystallization gave an additional 7.5 g. of the product melting at 238–241°.

1-(2-Carboxy-4-nitrophenyl)-3-[3-(4-phenyl-1-piperazinyl)propyl]urea and 2-Amino-5-nitro-N-[3-(4-phenyl-1-piperazinyl)propyl]benzamide.—A mixture of 1-(3-aminopropyl)-4-phenylpiperazine (70.9 g., 0.325 mole) and 6-nitroisatoic anhydride (67.5 g., 0.325 mole) was heated on a steam bath for 1 hr. after the initial reaction had subsided to give a dark yellow solid mass. This was dissolved in hot DMF, treated with carbon, filtered, and diluted with acetone and with a large volume of ether to give 13.4 g. (10.4%) of a light yellow solid of m.p. 242° dec. It was 1-(2-carboxy-4-nitrophenyl)-3-[3-(4-phenyl-1-piperazinyl)propyl]urea.

Anal. Calcd. for $C_{21}H_{25}N_5O_5$: C, 59.0; H, 5.85; N, 16.4. Found: C, 58.8; H, 5.76; N, 16.5.

The filtrate was concentrated by heating on a hot plate and water was added to give a dark oil which slowly solidified on scratching. The yield was 97.0 g. (77.9%), m.p. 143–145°, with softening at 138°. It was dissolved in hot DMF and added to a large amount of water to give a yellow powder of m.p. 140–144°. It was again recrystallized to give an analytical sample of m.p. 141–144°; $\nu_{max}^{CHCl_3}$ 3500 and 3330 (NH_2 and NH), 1645 (amide C=O), 1550 (amide II), 1505 and 1330 cm.$^{-1}$ (NO_2).

Anal. Calcd. for $C_{21}H_{25}N_5O_5$: N, 18.30; N(basic), 3.56. Found: N, 18.24; N(basic), 3.60.

6-Nitro-3-[3-(4-phenyl-1-piperazinyl)propyl]-2,4(1H,3H)-quinazolinedione. (16). A.—Into a boiling solution of 2-amino-5-nitro-N-{3-(4-phenyl-1-piperazinyl)propyl}benzamide (95.2 g., 0.249 mole) in 400 ml. of chlorobenzene was passed a

(13) H. Fujimori and D. P. Cobb, *J. Pharmacol. Exptl. Therap.*, **148**, 151 (1965).

(14) All melting points are corrected and were determined using a (Swiss) Büchi apparatus. Infrared spectra were determined with a Perkin-Elmer Model 237 grating spectrophotometer. Titrations were done with a Sargent Model D recording titrator.

(15) C. B. Pollard and L. G. MacDowell, *J. Am. Chem. Soc.*, **56**, 2199 (1934); **76**, 1853 (1954).

(16) P. A. J. Janssen, *et al.*, *J. Med. Pharm. Chem.*, **1**, 281 (1959).

(17) Toledo, Ohio.

(18) Boston 18, Mass.

(19) H. Culbertson, J. C. Decius, and B. E. Christensen, *J. Am. Chem. Soc.*, **74**, 4834 (1952). Reported carbonyl absorptions at 1690–1720 and 1650–1668 cm.$^{-1}$ for 1- or 3-(4-methyl-2,4(1H,3H)-quinazolinedione)s or 1,3-dimethyl-2,4(1H,3H)-quinazolinedione.

slow stream of phosgene during 90 min. to give a tan solid. The reaction mixture was kept at room temperature overnight and the solid was collected on a filter, m.p. 170–210° with softening at 120°, yield 99.1 g. The free base was obtained by treating the crude hydrochloride with aqueous NH_3. The base was recrystallized twice from aqueous methanol–DMF to give a deep yellow solid of m.p. 208–210°; yield 50.0 g.; $\nu_{max}^{CHCl_3}$ 1725 and 1670 (imide carbonyls), 1540 and 1340 cm.$^{-1}$ (NO_2). From the recrystallization mother liquor, 29.5 g. of crude starting material was obtained by adding excess water, m.p. 129–139°.

B.—1-(2-Carboxy-4-nitrophenyl)-3-[3-(4-phenyl-1-piperazinyl)propyl]urea (13 g.) was recrystallized twice from aqueous DMF–methanol to give a yellow solid of m.p. 208–210°, yield 8.0 g. The melting point of a mixture with the product from method A was not depressed. The infrared spectra were identical.

Anal. Calcd. for $C_{21}H_{23}N_5O_5$: N, 17.14. Found: N, 17.07.

6-Amino-3-[3-(4-phenyl-1-piperazinyl)propyl]-2,4(1H,3H)-quinazolinedione.—The above nitro compound (50.0 g., 0.123 mole) was hydrogenated using 10 g. of palladium on charcoal (5% Pd by weight) in 400 ml. of glacial acetic acid under 3.5 kg. (50 lb.) initial hydrogen pressure at room temperature. The calculated amount of hydrogen was taken up in 30 min. The catalyst was removed, and the solvent was evaporated *in vacuo* to leave a brown viscous syrup which was treated with aqueous NH_3 to give a solid of m.p. 229–235°, yield 46.9 g. This was recrystallized from aqueous methanol–DMF (carbon) to give a brown powder of m.p. 234–238°, yield 37.9 g. The amino derivative is unstable in air.

6-Acetamido-3-[3-(4-phenyl-1-piperazinyl)propyl]-2,4(1H,3H)-quinazolinedione Maleate (17).—The above amino derivative (30.2 g.) was hydrogenated again in a mixture of glacial acetic acid (200 ml.) and acetic anhydride (50 ml.) with 5 g. of palladium on carbon (5% Pd by weight) to reduce any oxidized material. The product was obtained as described above, yield 27.2 g., m.p. 258–262° (softening at 252°). It was recrystallized from aqueous methanol–DMF to give a tan powder of m.p. 257–261° dec., yield 18.1 g. It was suspended in methanol, maleic acid (5.8 g., 0.05 mole) was added to give a slurry which was dissolved in aqueous methanol–DMF, and the solution was treated with charcoal and concentrated. Addition of ethyl acetate gave a pure maleate of m.p. 245–246° dec.; yield 19.7 g.; ν_{max}^{KCl} 1710 and 1650 (imide carbonyls), 1650 cm.$^{-1}$ (AcNH).

Anal. Calcd. for $C_{29}H_{27}N_5O_3 \cdot C_4H_4O_4$: C, 60.3; H, 5.77; N, 13.0. Found: C, 60.0; H, 5.50; N, 13.0.

***o*-Methylamino-N-[3-(4-phenyl-1-piperazinyl)propyl]benzamide.**—A mixture of 1-methylisatoic anhydride (54.0 g., 0.305 mole) and 1-(3-aminopropyl)-4-phenylpiperazine (66.9 g., 0.305 mole) was heated on a steam bath for 1 hr. after the initial reaction had subsided. The resulting solid was recrystallized from aqueous acetone to give a colorless crystalline solid of m.p. 127–129°; yield 91.2 g. (86%); $\nu_{max}^{CHCl_3}$ 3345 (broad NH), 1640 (amide C=O), 1520 cm.$^{-1}$ (amide II).

Anal. Calcd. for $C_{21}H_{28}N_4O$: N, 15.9. Found: N, 16.1.

***o*-(N-Chlorocarbonylmethylamino)-N-[3-(4-phenyl-1-piperazinyl)propyl]benzamide Hydrochloride.**—Dry phosgene was bubbled into a boiling solution of *o*-methylamino-N-[3-(4-phenyl-1-piperazinyl)propyl]benzamide (49.1 g., 0.14 mole) in 250 ml. of chlorobenzene during 45 min. with vigorous stirring to give a slightly tan solid. After cooling to room temperature, ethyl acetate was added, and the solid was collected on a filter, washed with ethyl acetate and ether, and dried in air; m.p. 227–228° dec.; yield 61.4 g.; ν_{max}^{KCl} 1780 (COCl), 1750, 1645 cm.$^{-1}$ (amide C=O), no amide II band.

Anal. Calcd. for $C_{22}H_{27}ClN_4O_2 \cdot HCl$: N, 12.4. Found: N, 12.5.

The above hydrochloride (50.6 g.) was recrystallized twice from aqueous 2-propanol containing HCl to give the trihydrochloride of the starting material, m.p. 218–219° dec., yield 39.5 g.

Anal. Calcd. for $C_{21}H_{31}Cl_3N_4O$: HCl, 23.7. Found: HCl, 23.7.

1-Methyl-3-[3-(4-phenyl-1-piperazinyl)propyl]-2,4(1H,3H)-quinazolinedione (25).—To a boiling solution of *o*-methylamino-N-[3-(4-phenyl-1-piperazinyl)propyl]benzamide (54.6 g., 0.155 mole) in 250 ml. of dry tetrahydrofuran was added a solution of ethyl chloroformate (17.4 g., 0.16 mole) in 50 ml. of tetrahydrofuran dropwise during 10 min. to give a milky solution which was heated under reflux for 1 hr. and then kept at room temperature overnight. The solvent was removed *in vacuo* and the residue (sticky semisolid) was heated at 200–235° in a wax bath for 5 hr. to give a brown solid mass. This was dissolved in hot methanol and treated with dry HCl to give a light tan solid of m.p. 248–252° dec., yield 58.3 g. Recrystallization from aqueous methanol containing HCl and ethyl acetate gave 48.1 g. of a colorless solid of m.p. 248–250° dec. This was dissolved in water and made basic with aqueous NH_3 to give a colorless sirup which soon solidified on scratching. Recrystallization from aqueous acetone gave a colorless solid of m.p. 97–98°; yield 39.0 g.; $\nu_{max}^{CHCl_3}$ 1660 and 1705 (imide carbonyls), no amide II and NH.

The free base was dissolved in 200 ml. of methanol and added to 200 ml. of methanol saturated with dry HCl to give a colorless solid. This was collected on a filter, washed with ethyl acetate and ether, and dried in air; m.p. 247–249° (dark melt); yield 44.1 g.; ν_{max}^{KCl} 1660 and 1705 (imide carbonyls), no amide II.

6-Chloro-3-[3-(4-phenyl-1-piperazinyl)propyl]-2-thio-2,4(1H,3H)-quinazolinedione (45).—To a suspension of 2-amino-5-chloro-N-[3-(4-phenyl-1-piperazinyl)propyl]benzamide (25.0 g., 0.067 mole) in 250 ml. of chlorobenzene at room temperature was added a solution of thiophosgene (8.0 g., 0.076 mole) in 50 ml. of chlorobenzene dropwise during 10 min. with stirring to give a milky suspension. Heating at reflux for 1 hr. gave a mixture of a light solid and a very dark blue solid. The solid was collected on a filter and washed with ethyl acetate and ether, and the still solvated solid was treated with aqueous ammonia to give a light tan oil which partly solidified. This was extracted with chloroform and an insoluble solid was collected on a filter. The chloroform layer was separated and dried. The solvent was removed *in vacuo* to give a mixture of tan and greenish blue solids. The mixture was triturated with ether and the insoluble solid was collected on a filter; yield 7.7 g., m.p. 184–200°. The chloroform-insoluble solid melted at 198–205°, yield 16.7 g. Both solids were combined and recrystallized from aqueous methanol–DMF (carbon) to give a light greenish blue solid of m.p. 201–210°, yield 19.9 g. Two more recrystallizations gave a light greenish yellow solid of m.p. 213–215°, yield 16.0 g.

The base in methanol was treated with dry HCl to give a purple solid. Enough aqueous DMF was added to the boiling suspension to yield a clear solution which was filtered hot. The filtrate deposited a colorless hydrochloride on cooling; yield 14.2 g.; m.p. >280°; ν_{max}^{KCl} 3180 (NH), 1680 (imide C=O), 1535 (thioimide II), 1330 (thioimide III), 1170 and 1150 cm.$^{-1}$ (thioimide C=S).[20]

N-Methyl-N-phenethylenediamine.—N-Methylaniline (321 g., 3 moles) was added to a mixture of 37% formalin (243 ml., 3 moles) and sodium bisulfite (312 g., 3 moles) in 1000 ml. of water. The mixture was stirred at 70–80° for 2 hr. and 195 g. (3 moles) of KCN was added. After refluxing for 3 hr., the reaction mixture was extracted with ether. The ether extract was dried, and the solvent was removed *in vacuo* to leave a liquid of b.p. 97–98° (0.5 mm.), yield 332.8 g. (75.5%). This was N-methyl-N-cyanomethylaniline. The nitrile was hydrogenated in methanolic ammonia using a Raney nickel catalyst at 100° at 70.3 kg. (1000 lb.) pressure. The crude amine was distilled at 148° (13 mm.), yield 226.5 g. (67%), lit.[21] b.p. 145° (13 mm.).

2,3,4,5-Tetrahydro-1-methyl-1,4-benzodiazepine.—N-Methyl-N-phenylethenediamine (166.2 g., 1.1 moles) was added slowly to 250 ml. of 90% formic acid at *ca.* 10°. After the addition of 90 ml. (1.11 moles) of 37% formalin, the mixture was heated at 90° for *ca.* 60 hr. with stirring. The cooled solution was added to ice and basified with NaOH solution, and the resulting amine was extracted with chloroform. The extract was dried and evaporated *in vacuo* to give the N-formyl derivative, which was hydrolyzed by heating in 18% HCl overnight. The acidic solution was concentrated *in vacuo*, and the residue was basified with NaOH solution. The resulting amine was extracted with ether and dried. After removing the solvent, the amine distilled at 87–93° (0.43 mm.), yield 45 g. (25%).

Anal. Calcd. for $C_{10}H_{14}N_2$: N(basic), 8.64. Found: N(basic), 8.63 (titration with $HClO_4$).

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