from acetone-H_2O gave material with mp 156° dec. *Anal.* ($C_{12}H_{14}ClN_5O_3S$), C, H, S, Cl.

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4-Oxo-1,2,3,4-tetrahydroquinazolines. 3.[1] Synthesis and Choleretic Activity of Quinazoline Derivatives

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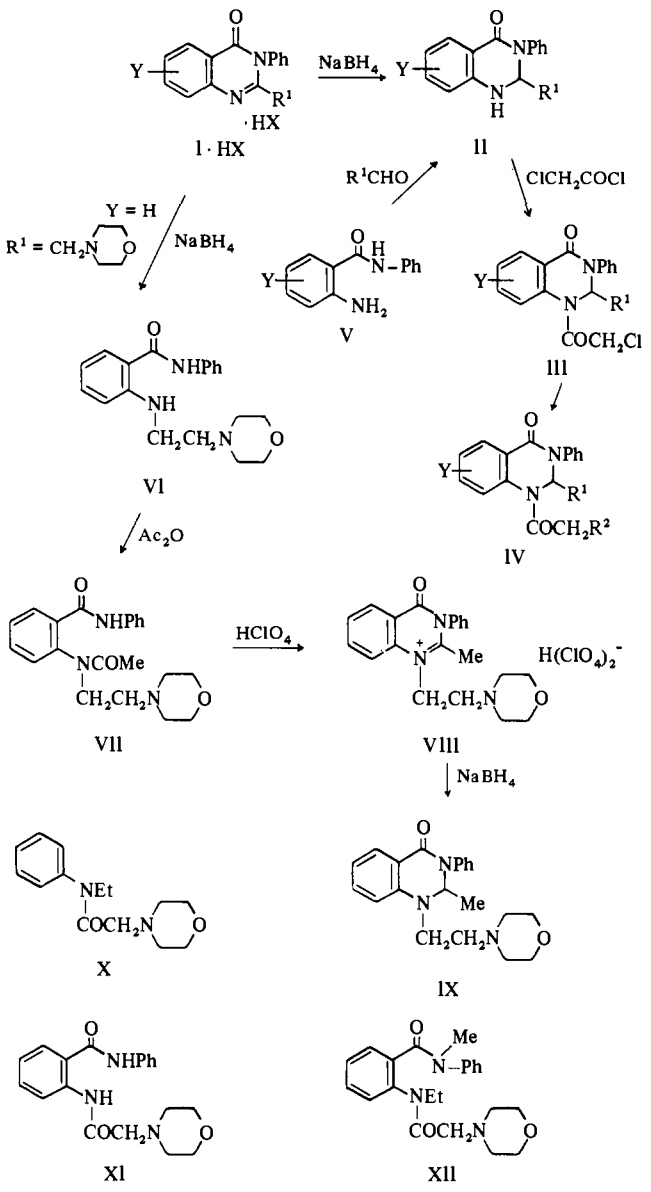
A series of 1-*tert*-aminoacetyl-2-alkyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazolines and their analogs has been synthesized and tested for choleretic activity. 1-Morpholinoacetyl-2-methyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline has been found to be a most effective choleretic agent. From the structure-activity relationship, it was concluded that the moiety, morpholino-C-C-N(alkyl)-Ph, is essential for choleretic activity.

Studies on 4-oxo-1,2,3,4-tetrahydroquinazolines,[1,2] directed toward new analgetic agents, have shown that some 1-*tert*-aminoacetyl-2-methyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazolines increased bile secretion. Especially 1-morpholinoacetyl-2-methyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline possessed high activity. Meanwhile, another group has independently reported the choleretic activity of similar compounds.[3-6] Since choleretic agents are useful for treatment of cholelithiasis and jaundice, it seemed of interest to synthesize additional derivatives in order to seek a more effective compound and, at the same time, to study their structure-activity relationships. 1-Dimethylaminoacetyl-, and 1-diethylaminoacetyl-2-methyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline did not show significant activity in contrast to the high potency of 1-morpholinoacetyl-2-methyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline. This suggested that the active center would be the cyclic amino or the O-containing amino moiety in the side chain rather than the quinazoline skeleton itself. The introduction of a substituent at the 2 position or on the fused benzene ring of the quinazoline moiety should have some effect on toxicity and activity. Therefore the new quinazoline derivatives were synthesized and subjected to pharmacological investigation.

Most of the quinazoline derivatives IV were prepared from the quinazolines I by methods developed in our laboratory.[2] Reduction of the quinazoline hydrochlorides I·HCl with $NaBH_4$ in THF-Diglyme gave the corresponding hydroquinazolines II in good yields. The reduction also proceeded readily in the reaction of the quinazoline-BF_3 complex with a 0.75 *M* ratio of $NaBH_4$ in THF to afford the hydroquinazoline in high yield (around 90%). Thus the reducing species in the reaction was diborane. In the case of 2-methyl-3-phenyl-8-chloro-4(3*H*)-quinazolinone·HCl, the hydroquinazoline IIi (Y = 8-Cl, $R^1 = CH_3$) was obtained in very low yield. This failure was due to the low yield of diborane that was generated in the reaction because of the low basicity of the quinazoline I (Y = 8-Cl, $R^1 = CH_3$). In fact the quinazoline·HCl (I·HCl, Y = 8-Cl, $R^1 = CH_3$) released HCl even on heat drying. Therefore, the reduction of the more acidic salt of the quinazoline I (Y = 8-Cl, $R^1 = CH_3$) was investigated. Treatment of the quinazoline hydroperchlorate (I-$HClO_4$, Y = 8-Cl, $R^1 = CH_3$) with $NaBH_4$ in Diglyme afforded IIi in an improved yield (42.6%). 2-Isopropyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline (IIb) was prepd by ring closure of 2-aminobenzanilide with isobutyraldehyde in the presence of *p*-TsOH. 2,3-Diphenyl-4-oxo-1,2,3,4-tetrahydroquinazoline (IId)[3] was obtained by the reaction of 2-aminobenzanilide with PhCHO in a similar manner. Yields and physical constants for the hydroquinazolines II are shown in Table I. Acylation of the hydroquinazolines II with $ClCH_2COCl$ was carried out in the presence of K_2CO_3, Et_3N, or pyridine (best) to afford the chloroacetylhydroquinazolines III. In the case of IId, the chloroacetyla-

Scheme I

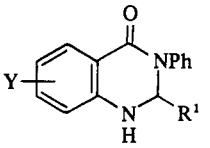


tion proceeded successfully only with pyridine to give 1-chloroacetyl-2,3-diphenyl-4-oxo-1,2,3,4-tetrahydroquinazoline (IIId) that had not been obtained by Bonola.[3] The hydroquinazolines with low basicity, or low solubility, 2-methyl-3-phenyl-8-chloro-4-oxo-1,2,3,4-tetrahydroquinazoline (IIi), 2-methyl-3-phenyl-6-nitro-4-oxo-1,2,3,4-tetrahydroquinazoline (IIm), and 2-methyl-3-phenyl-6-acetamido-4-oxo-1,2,3,4-tetrahydroquinazoline (IIn), could not be acylated under the same conditions. This was overcome by treating these hydroquinazolines (IIi, IIm, and IIn) with chloroacetic anhydride at 50-100° without solvent (see Table II). The target quinazoline derivatives IV were prepd in good yield by condensation of the chloroacetylhydroquinazolines (III) with amines (Table III).

1-Morpholinoethyl-2-methyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline (IX) was prepd from 2-morpholinomethyl-3-phenyl-4(3*H*)-quinazolinone[7] (I, Y = H, R^1 = morpholinomethyl) by the route illustrated in Scheme I. Reduction of the quinazoline I (Y = H, R^1 = morpholinomethyl) with excess $NaBH_4$ at 100-110° in Diglyme afforded 2-[*N*-(2-morpholinoethyl)amino]benzanilide (VI) in 64.6% yield. Acetylation of the anilide VI with Ac_2O gave 2-[*N*-(2-morpholinoethyl)acetamido]benzanilide (VII), which was converted to 1-(2-morpholinoethyl)-2-methyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline (IX) *via* 1-(2-morpholinoethyl)-2-methyl-3-phenyl-4-oxo-3,4-dihydroquinazolinium diperchlorate (VIII) as described previously.[1] The structurally related compounds, X, XI, and XII, were prepared from the corresponding starting materials for evaluation of the active part in the structure of the quinazoline derivatives IV for choleretic activity.

Choleretic Effect and Structure-Activity Relationship. The derivatives were screened in rats for their choleretic properties. The minimum doses which increased the bile flow by 50% during 30 min after the administration of these compounds are summarized in Table IV. Compd **9** showed the highest activity (50% increasing dose = 2.8 mg/kg), though Bonola[3] has reported that it has little activity. Most of the analogs that have the morpholino group in the side chain showed the same order of activity. Transformation of the morpholinoacetyl of **9** to the morpholinoethyl group reduced the activity slightly and so did the re-

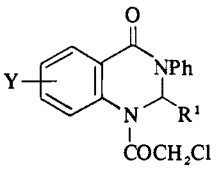
Table I. Hydroquinazolines II



No.	Y	R^1	Yield, %	Mp, °C	Recrystn[a] solvent	Formula
IIa	H	Et	89.8	151-153	A	$C_{16}H_{16}N_2O$
b	H	*i*-C_3H_7	62.3	184-186	A	$C_{17}H_{18}N_2O$[b]
c	H	*n*-C_4H_9	86.9	128-130	C	$C_{18}H_{20}N_2O$
d	H	Ph	95.5	207-209[c]	B	$C_{20}H_{16}N_2O$
e	H	FCH_2	80.0	148-150	A	$C_{15}H_{13}FN_2O$
f	5-Cl	Me	52.3	179-181	B	$C_{15}H_{13}ClN_2O$
g	6-Cl	Me	79.2	193-195	B	$C_{15}H_{13}ClN_2O$
h	7-Cl	Me	90.0	198-200	B	$C_{15}H_{13}ClN_2O$
i	8-Cl	Me	42.6	162-164	A	$C_{15}H_{13}ClN_2O$
j	6-Me	Me	91.0	177-178	B	$C_{16}H_{16}N_2O$
k	6-MeO	Me	94.2	160-161	B	$C_{16}H_{16}N_2O_2$
l	6-F	Me	87.3	167-169	A	$C_{15}H_{13}FN_2O$
m	6-NO_2	Me	97.8	280[d]	E	$C_{15}H_{13}N_3O_3$
n	6-NHAc	Me	55.0	255-258	D	$C_{17}H_{17}N_3O_2$
o	7-NO_2	Me	100	230-233[d]	B	$C_{15}H_{13}N_3O_3$
p	6,7-CH_2O_2	Me	87.0	230-231	B	$C_{16}H_{14}N_2O_3$

[a] A = *i*-PrOH; B = EtOH; C = EtOH–hexane; D = 50% EtOH; E = DMF. [b] Prepd by method C, C: calcd, 76.66; found, 76.24. [c] Ref 3. [d] Dec.

Table II. Chloroacetylhydroquinazolines III



No.	Y	R^1	Yield, %	Mp, °C	Recrystn[a] solvent	Formula
IIIa	H	Et	46.2	138–139	A	$C_{18}H_{17}ClN_2O_2$
b	H	*i*-C_3H_7	70.0	121–123	B	$C_{19}H_{19}ClN_2O_2$
c	H	*n*-C_4H_9	53.7	114–116	A	$C_{20}H_{21}ClN_2O_2$
d	H	Ph	70.0	179–181	C	$C_{22}H_{17}ClN_2O_2$
e	H	FCH_2	81.0	128–129	A	$C_{17}H_{14}ClFN_2O_2$
f	5-Cl	Me	83.2	192–194	B	$C_{17}H_{14}Cl_2N_2O_2$
g	6-Cl	Me	71.4	199–201	D	$C_{17}H_{14}Cl_2N_2O_2$
h	7-Cl	Me	89.2	149–150	A	$C_{17}H_{14}Cl_2N_2O_2$
i	8-Cl	Me	71.0[b]	114–115	A	$C_{17}H_{14}Cl_2N_2O_2$
j	6-Me	Me	89.2	199–201	C	$C_{18}H_{17}ClN_2O_2$
k	6-MeO	Me	91.7	174–176	C	$C_{18}H_{17}ClN_2O_3$
l	6-F	Me	93.9	169–171	B	$C_{17}H_{14}ClFN_2O_2$
m	6-NO_2	Me	78.0[b]	231–232	E	$C_{17}H_{14}ClN_3O_4$
n	6-NHAc	Me	89.0	248–249	E	$C_{19}H_{18}ClN_3O_3$
o	7-NO_2	Me	71.0	196–198	B	$C_{17}H_{14}ClN_3O_4$
p	6,7-CH_2O_2	Me	81.0	220–222	B	$C_{18}H_{15}ClN_2O_4$

[a] A = *i*-PrOH; B = EtOH; C = PhH; D = THF; E = DMF–EtOH. [b] Prepd by method B.

placement of 2-Me with a longer alkyl group.

It is difficult to find a definite relation between the substituents on the fused benzene ring of the quinazolines and the choleretic activity. However, in view of the low activity of **4** and **5** and the maintenance of activity in X and XII which contain structural moiety of **9**, the morpholino-C-C-N(alkyl)-Ph appears to be the active center and the quinazoline moiety to be an auxiliary group.

Experimental Section

Pharmacological Method. (1) **Choleretic Activity.** Adult male Wister King rats (250–300 g) were anesthetized with urethane (1.2 g/kg) sc and placed on the animal board in the spin position. The abdomen was opened and a polyethylene tube was inserted centrally into the common bile duct. After the control bile flow was detd, the test compds which were dissolved in saline or suspended in 0.5% CMC soln were injected into the carotid vein. Then the bile flow was detd volumetrically for 30 min.

(2) **Behavioral Observation.** Adult male ddk strain mice (20–22 g) were used, in 4 groups consisting each of 6 mice. The test compds were dissolved in saline or suspended in 0.5% CMC soln so that each dose could be delivered at 0.1 ml/10 g of body weight. After the test compds were administered ip, the behavioral changes which were shown in Table IV were observed.†

Chemical Methods.‡ **2-Methyl-6-fluoro-4-oxo-3,1-benzoxazine.** A mixt of 5-fluoroanthranilic acid[8] (20.0 g, 0.129 mole) and Ac_2O (132 g, 1.29 moles) was refluxed for 2.5 hr. The mixt was concd under reduced pressure and the residue was triturated with *i*-Pr_2O to afford almost pure product (19.0 g, 82.3%). Recrystn from EtOAc afforded a pure sample as colorless needles, mp 129–130°. *Anal.* ($C_9H_6FNO_2$) C, H, N.

Other substituted 4-oxo-3,1-benzoxazines were prepd from the corresponding anthranilic acid in the same manner.

2-Methyl-6,7-methylenedioxy-4-oxo-3,1-benzoxazine was obtained as pale yellow needles (EtOAc), mp 166–168°. *Anal.* ($C_{10}H_7NO_4$) C, H, N.

2-Methyl-7-nitro-4-oxo-3,1-benzoxazine was obtained as pale yellow prisms (EtOAc), mp 138–140°. *Anal.* ($C_9H_6N_2O_4$) C, H, N.

Quinazolines (I). Method A. From **Substituted 4-Oxo-3,1-benzoxazine. 2-Methyl-3-phenyl-6-fluoro-4(3*H*)-quinazolinone.** A mixt of 2-methyl-6-fluoro-4-oxo-3,1-benzoxazine (20.0 g, 0.112 mole) and $PhNH_2$ (11.5 g, 0.123 mole) was heated at 160° for 2 hr. The mixt which crystd on cooling was triturated with *i*-PrOH and the crystals were collected by filtration to give almost pure product (21.8 g, 76.8%), mp 172–174°. Recrystn from EtOH afforded an analytically pure sample as colorless prisms, mp 174–176°. *Anal.* ($C_{15}H_{11}FN_2O$) C, H, N.

Other new quinazolines were prepd in the same manner.

2-Methyl-3-phenyl-8-chloro-4(3*H*)-quinazolinone was obtained as colorless needles (dioxane), mp 237–238°. *Anal.* ($C_{15}H_{11}ClN_2O$) C, H, N.

2-Methyl-3-phenyl-6,7-methylenedioxy-4(3*H*)-quinazolinone was obtained as colorless prisms (EtOH), mp 163–165°. *Anal.* ($C_{16}H_{12}N_2O_3$) C, H, N.

2-Methyl-3-phenyl-7-nitro-4(3*H*)-quinazolinone was obtained as pale yellow prisms (DMF–EtOH), mp 203–205°. *Anal.* ($C_{15}H_{11}N_3O_3$) C, H, N.

2-Methyl-3-phenyl-6-methoxy-4(3*H*)-quinazolinone was obtained as colorless needles (EtOH), mp 180–181°. *Anal.* ($C_{16}H_{14}N_2O_2$) C, H, N.

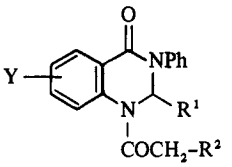
Method B. 2-Fluoromethyl-3-phenyl-4(3*H*)-quinazolinone. A mixt of 2-chloromethyl-3-phenyl-4(3*H*)-quinazolinone[7] (20.0 g, 0.075 mole), KF (13.0 g, 0.225 mole), and ethylene glycol (14 ml) was heated with stirring at 145–155° (inner temp) for 2 hr. After cooling, the mixt was poured into H_2O and extd with PhH. The PhH layer was washed, dried, and evapd. The residual oil was triturated with *i*-PrOH (40 ml) to afford crude cryst product (12.6 g), mp 91–99°. Recrystn from *i*-PrOH (30 ml) gave pure material (11.0 g, 57.7%) as colorless needles, mp 101–103°. The mother liquor was collected and distd under reduced pressure (bp 160–165°, 0.07 mm) to give an oil (2.5 g) which crystd on cooling, mp 95–99°. Recrystn from *i*-PrOH afforded another crop (2.2 g, 11.5%), mp 99–102°. Total yield 13.2 g (69.2%). *Anal.* ($C_{16}H_{13}FN_2O$) C, H, N. The hydrochloride had mp 195–198° dec. *Anal.* ($C_{16}H_{13}FN_2O \cdot HCl$) C, H, N.

Method C. 2-Butyl-3-phenyl-4(3*H*)-quinazolinone. To a stirred soln of anthranilic acid (40.5 g, 0.34 mole) in 0.2 *N* NaOH (1700 ml) were added gradually valeryl chloride (46.5 g, 0.34 mole) and 0.2 *N* NaOH (1700 ml) during 1 hr at 0°. The mixt was stirred for 50 min at 0° and then for 40 min at room temp. The reaction mixt was acidified with 5 *N* HCl (88 ml) and the crystals were collected by filtration. Recrystn from 50% aq EtOH gave 2-(*N*-valerylamino)-benzoic acid (31 g) as colorless prisms, mp 117–119°. To a soln of this acid (26 g, 0.118 mole) and $PhNH_2$ (11 g, 0.118 mole) in PhMe (300 ml) was added PCl_3 (6.5 g, 0.047 mole) at room temp. The mixt was refluxed for 3 hr. After cooling, it was decompd with 10%

†In general, lachrymation, salivation, and soft defecation were observed when the known choleretic agents, such as dehydrocholic acid, *N*-(4-hydroxyphenyl)salicylamide, and 2-(1-hydroxycyclohexyl)butyric acid, were administered. These behavioral changes were mainly tested.

‡Melting points were uncorrected and were detd on a Yamato apparatus MP-1. The nmr spectra were detd on a Hitachi Perkin-Elmer R-20A instrument (Me_4Si). Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

Table III. Quinazoline Derivatives IV



Compd No.	Y	R^1	R^2	Yield, %	Mp, °C	Recrystn[a] solvent	Formula
1	H	Me	Pyrrolidino	87.5	234-236[b]	G	$C_{21}H_{23}N_3O_2 \cdot HCl$
2	H	Me	$NH(CH_2)_2OMe$	70.0	203-205[b]	G	$C_{20}H_{23}N_3O_3 \cdot HCl$
3	H	Me	$NH(CH_2)_3OMe$	86.0	202-203[b]	G	$C_{21}H_{25}N_3O_3 \cdot HCl$
4	H	Me	$N(CH_2CH_2OMe)_2$	100.0	Amorph		
5	H	Me		71.0	198-200[b]	E	$C_{22}H_{26}N_4O_2 \cdot 2HCl \cdot 1.5H_2O$[c]
6	H	Me		75.5	135-137	A	$C_{27}H_{28}N_4O_2$
					165-167[b]	G	$C_{27}H_{28}N_4O_2 \cdot HCl \cdot 2H_2O$[d]
7	H	Me		60.5	106-108	B	$C_{21}H_{23}N_3O_2S$
					237-238[b]	E	$C_{21}H_{23}N_3O_2S \cdot HCl$
8	H	H		60.0	140-142	B	$C_{20}H_{21}N_3O_2S$
					236-237[b]	I	$C_{20}H_{21}N_3O_2S \cdot HCl \cdot 0.5H_2O$
9	H	Me	Morpholino	94.0	133-135	B	$C_{21}H_{23}N_3O_3$
					239-240[b]	I	$C_{21}H_{23}N_3O_3 \cdot HCl$
10	H	CH_2F	Morpholino	95.0	130-132	B	$C_{21}H_{22}FN_3O_3$
					253-254[b]	I	$C_{21}H_{22}FN_3O_3 \cdot HCl$
11	H	Et	Morpholino	90.2	243-244[b]	E	$C_{22}H_{25}N_3O_3 \cdot HCl$
12	H	Et	$NH(CH_2)_2OMe$	74.4	215-216[b]	G	$C_{21}H_{25}N_3O_3 \cdot HCl$
13	H	i-C_3H_7	Morpholino	95.0	241-242[b]	E	$C_{23}H_{27}N_3O_3 \cdot HCl$
14	H	n-C_4H_9	Morpholino	85.0	244-245[b]	E	$C_{24}H_{29}N_3O_3 \cdot HCl$
15	H	n-C_4H_9		60.8	233-235[b]	E	$C_{30}H_{34}N_4O_2 \cdot HCl$
16	H	Ph	Morpholino	74.0	133-134	C	$C_{26}H_{25}N_3O_3$
					260-261[b]	I	$C_{26}H_{25}N_3O_3 \cdot HCl$
17	5-Cl	Me	Morpholino	83.0	146-148	B	$C_{21}H_{22}ClN_3O_3$
					244-246[b]	I	$C_{21}H_{22}ClN_3O_3 \cdot HCl \cdot 0.5H_2O$
18	6-Cl	Me	Morpholino	86.9	175-176	B	$C_{21}H_{22}ClN_3O_3$
					248-250[b]	I	$C_{21}H_{22}ClN_3O_3 \cdot HCl \cdot 0.5H_2O$
19	7-Cl	Me	Morpholino	94.0	128-130	B	$C_{21}H_{22}ClN_3O_3$
					234-235[b]	I	$C_{21}H_{22}ClN_3O_3 \cdot HCl$
20	8-Cl	Me	Morpholino	69.5	110-112	D	$C_{21}H_{22}ClN_3O_3$
					221-223[b]	I	$C_{21}H_{22}ClN_3O_3 \cdot HCl$
21	6-Me	Me	Morpholino	92.0	122-123	D	$C_{22}H_{25}N_3O_3$[e]
					239-240[b]	E	$C_{22}H_{25}N_3O_3 \cdot HCl$
22	6-MeO	Me	Morpholino	83.8	116-118	D	$C_{22}H_{25}N_3O_4$
					230-231[b]	I	$C_{22}H_{25}N_3O_4 \cdot HCl \cdot 0.5H_2O$
23	6-F	Me	Morpholino	94.3	169-171	E	$C_{21}H_{22}FN_3O_3$
					244-246[b]	I	$C_{21}H_{22}FN_3O_3 \cdot HCl$
24	6-NO_2	Me	Morpholino	92.0	171-173	E	$C_{21}H_{22}N_4O_5$
					236-238[b]	I	$C_{21}H_{22}N_4O_5 \cdot HCl \cdot H_2O$
25	6-NHAc	Me	Morpholino	84.8	253-254	F	$C_{23}H_{26}N_4O_4$
					235-237[b]	I	$C_{23}H_{26}N_4O_4 \cdot HCl$
26	7-NO_2	Me	Morpholino	91.0	182-184	E	$C_{21}H_{22}N_4O_5$
					230-231[b]	H	$C_{21}H_{22}N_4O_5 \cdot HCl$
27	7-NH_2	Me	Morpholino	63.0[g]	207-209	B	$C_{21}H_{24}N_4O_3$[f]
					242-244[b]	E	$C_{21}H_{24}N_4O_3 \cdot HCl$
28	7-NHAc	Me	Morpholino	27.0	222-225	B	$C_{23}H_{26}N_4O_4$
29	6,7-CH_2O_2	Me	Morpholino	72.0	163-167	B	$C_{22}H_{23}N_3O_5$
					258-260[b]	I	$C_{22}H_{23}N_3O_5 \cdot HCl$
30	6-NHOH	Me	Morpholino	3.8[g,h]	201-203	E	$C_{21}H_{24}N_4O_4$
31	6-NH_2	Me	Morpholino	4.0[g,h]	174-176	B	$C_{21}H_{24}N_4O_3$
32	7-NHOH	Me	Morpholino	96.0[g]	195-197[i]	E	$C_{21}H_{24}N_4O_4$
33	7-N(COMe)(OCOMe)	Me	Morpholino	54.0	146-148	E	$C_{25}H_{28}N_4O_6$

[a] A = dioxane-i-PrOH; B = i-PrOH; C = i-Pr_2O; D = i-PrOH-i-Pr_2O; E = EtOH; F = DMF-EtOH; G = EtOH-Et_2O; H = MeOH; I = MeOH-Et_2O. [b] Dec of hydrochloride. [c] H: calcd, 6.53; found, 6.08. [d] C: calcd, 63.19; found, 63.70. [e] N: calcd, 11.08; found, 11.49. [f] C: calcd, 66.30; found, 65.89. [g] Prepd by reduction of the corresponding NO_2-compds. [h] Isolation yield. [i] Dec.

aqueous Na_2CO_3 soln. The PhMe layer was sepd, washed with H_2O, dried (Na_2SO_4), concd, and distd under reduced pressure to give an oil [4.7 g, bp 230° (bath temp), 0.05 mm] which on cooling crystd, mp 109-111°. Recrystn from i-PrOH gave an analytically pure sample as colorless prisms, mp 110-112°. *Anal.* ($C_{18}H_{18}N_2O$) C, H, N. The hydrochloride had mp 200-207° dec. *Anal.* ($C_{18}H_{18}N_2O \cdot HCl$) C, H, N.

Hydroquinazolines (II). Method A. Reduction of Quinazaline·HCl (I·HCl) with $NaBH_4$. 2,6-Dimethyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline (IIj). To a stirred suspension of 2,6-dimethyl-3-phenyl-4(3*H*)-quinazoline·HCl[9] (14.3 g, 0.05 mole) in THF (200 ml) was added a soln of $NaBH_4$ (2.25 g, 0.06 mole) in Diglyme (70 ml) during 2 hr at 5-7°. The mixt was stirred for 30 min at the same temp. Dil aqueous AcOH was added to the mixt until H_2 evolution ceased, and the solvent was removed under reduced pressure. The residue was treated with H_2O (600 ml) to

Table IV. Summary of Pharmacological Observation

Drug No.	Max tolerated dose, mg/kg ip	Behavior in max tolerated dose, ip	Choleretic act.,[a] mg/kg iv
1	100	rr	13.0
2	100	sed	25.9
3	100	s, sed	
4	⩾300	sed, rr	47.6[b]
5	⩾300	a, tr, j, rr	50.8[b]
6	⩾300	sed	
7	⩾300	Unchanged	
8	⩾300	Unchanged	
9	⩾300	l, s, d	2.8
10	⩾300	l, s, d	3.3
11	100	l, s, d	6.9
13	100	t, v, tr	15.7
14	100	l, s	6.8
16	300	l, s, d, a, t, tr, st	
17	⩾100	t, v, l	26.7
18	100	l	6.0
19	100	s	8.4
20	100	l	12.4
21	⩾300	l, d, rr	8.5
22	⩾300	l, s, d, a	4.1
23	100	l, s, d	7.5
24	100	l, s, m	15.6
25	⩾300	l, s	15.4
26	⩾300	l, s, t	8.8
27	⩾300	l, s, a, rd	10.8
28	⩾300	l, rr	8.5
IX	100	l, s, d	8.2
X	⩾300	s, t, tr, l	8.0
XI	⩾300	sed	
XII	⩾300	a, t, tr, l	8.2
Moquizone[c]	⩾300	l, s, d	5.7
Dehydrocolic acid		l, s	10.3
p-Hydroxyphenyl salicylamide		l, s	10.2

[a]Dose which increased the bile flow by 50%. Blanks were not tested because of insolubility. Behavior; l: lacrimation, s: salivation, d: soft defecation, rr: loss of righting reflex, tr: tremor, v: vocalization, sed: slight sedation, t: occasional elevation of the tail, a: ataxia, j: jumping, st: stretching, rd: slight respiratory depression, m: elevation of the motility. [b]Calcd value. [c]See ref 6.

give a cryst product. The product was collected by filtration and dried to afford 12.2 g of IIj. Recrystn from EtOH (80 ml) gave 11.5 g (91%) of colorless prisms, mp 176–178°. *Anal.* ($C_{16}H_{16}N_2O$) C, H, N.

Method B. Reduction of 2-Methyl-3-phenyl-8-chloro-4(3*H*)-quinazolinone Hydroperchlorate (I·HClO$_4$, Y = 8-Cl, R^1 = Me) with NaBH$_4$. To a stirred suspension of the quinazoline hydroperchlorate (I·HClO$_4$) (Y = 8-Cl, R^1 = Me, 12.0 g, 0.033 mole) in Diglyme (250 ml) was added gradually a soln of $NaBH_4$ (1.6 g, 0.042 mole) in Diglyme (80 ml) during 5 hr at 0–2°. The mixt was stirred for 2 hr at this temp. Dil aqueous AcOH was added until H_2 evolution ceased and the mixt was poured into cold H_2O (4000 ml) to give a cryst product. This was collected by filtration to afford crude 2-methyl-3-phenyl-8-chloro-4-oxo-1,2,3,4-tetrahydroquinazoline (IIi, 8 g). Recrystn from EtOH gave unchanged quinazoline (3.65 g, 41.5%) as colorless needles. The mother liquor was concd under reduced pressure and the residue was recrystd from *i*-PrOH to afford pure IIi (3.75 g, 42.6%) as colorless prisms, mp 162–163°. *Anal.* ($C_{15}H_{13}ClN_2O$) C, H, N.

Method C. Reaction of 2-Aminobenzanilide with Aldehyde. 2-Isopropyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline (IIb). To a soln of 2-aminobenzanilide (21.2 g) and *p*-TsOH (0.4 g) in EtOH (300 ml) was added isobutyraldehyde (21 g) and the mixt was stirred at room temp for 6 hr. The crystals were collected by filtration to give crude product (12.5 g), mp 180–182°. A second crop (5.0 g) was obtd from the filtrate by evapn of the solvent. Recrystn from EtOH afforded pure IIb as colorless prisms, mp 184–186°. *Anal.* ($C_{17}H_{18}N_2O$) C, H, N.

Chloroacetylhydroquinazolines (III). Method A. Chloroacetylation with Chloroacetyl Chloride. 1-Chloroacetyl-2-methyl-3-phenyl-6-fluoro-4-oxo-1,2,3,4-tetrahydroquinazoline (IIIl). To a stirred soln of IIl (6.4 g, 0.025 mole) and pyridine (3.55 g, 0.045 mole) in PhH (400 ml) was added dropwise $ClCH_2COCl$ (4.25 g, 0.0375 mole) at room temp. The mixt was stirred at the same temp for 2.5 hr, then washed (H_2O), dried, and concd to dryness under reduced pressure to give almost pure product (7.8 g, 93.9%), mp 167–169°. Recrystn from EtOH gave colorless leaflets, mp 169–171°. *Anal.* ($C_{17}H_{14}ClFN_2O_2$) C, H, N.

Method B. Chloroacetylation with Chloroacetic Anhydride. 1-Chloroacetyl-2-methyl-3-phenyl-6-nitro-4-oxo-1,2,3,4-tetrahydroquinazoline (IIIm). A mixt of IIm (8.0 g, 0.0288 mole) and chloroacetic anhydride (14.4 g, 0.0864 mole) was heated at 100° for 20 hr. After cooling the mixt was crystd by trituration with Et_2O. The crystals were collected by filtration and washed with EtOH to afford crude product (9.0 g), mp 210–215°. Recrystn from DMF–EtOH (1:1, 350 ml) gave pure sample (8.1 g, 78.2%) as colorless prisms, mp 231–232°. *Anal.* ($C_{17}H_{14}ClN_3O_4$) C, H, N.

Quinazoline Derivatives. Method A. 1-Morpholinoacetyl-2-methyl-3-phenyl-6-fluoro-4-oxo-1,2,3,4-tetrahydroquinazoline. A soln of 1-chloroacetyl-2-methyl-3-phenyl-6-fluoro-4-oxo-1,2,3,4-tetrahydroquinazoline (IIIl, 3.0 g, 0.009 mole) and morpholine (3.9 g, 0.045 mole) in THF (150 ml) was stirred at 50° for 5 hr. The mixt was concd under reduced pressure and the residue was dissolved in PhH. The PhH soln was washed with H_2O, dried (K_2CO_3), and concd to dryness under reduced pressure to give cryst residue, which was triturated with *i*-Pr_2O to afford almost pure product (3.25 g, 94.3%), mp 168–170°. Recrystn from EtOH gave pure sample as colorless prisms, mp 168–170°. *Anal.* ($C_{21}H_{22}FN_3O_3$) C, H, N.

Method B. 1-Morpholinoacetyl-2-methyl-3-phenyl-7-amino-4-oxo-1,2,3,4-tetrahydroquinazoline·HCl. A mixt of 1-morpholinoacetyl-2-methyl-3-phenyl-7-nitro-4-oxo-1,2,3,4-tetrahydroquinazoline·HCl (2.0 g, 0.0045 mole), 5% Pd/C (0.4 g), and MeOH (200 ml) was shaken under H_2 (2.5 kg/cm^2), the theoretical vol of H_2 being absorbed in 3 hr at room temp. The catalyst was filtered off and the filtrate was concd under reduced pressure. The residue was recrystd from EtOH to give almost pure product (0.87 g) as colorless needles, mp 238–240° dec. A further crop (0.31 g) was obtd from the mother liquors, total yield 1.18 g (63%). Recrystn from EtOH gave pure sample as colorless needles, mp 242–244°. *Anal.* ($C_{21}H_{24}N_4O_3$·HCl) C, H, N. The free base was obtd from the hydrochloride by neutralization of the aqueous soln with $NaHCO_3$, followed by filtration. It crystallized from *i*-PrOH as colorless prisms, mp 207–209°. *Anal.* ($C_{21}H_{24}N_4O_3$) H, N; C: calcd, 66.30; found, 65.89.

2-[*N*-(2-Morpholinoethyl)amino]benzanilide (VI). To a soln of 2-morpholinomethyl-3-phenyl-4(3*H*)-quinazolinone[7] (13.0 g, 0.04 mole) in Diglyme (100 ml) was added portionwise $NaBH_4$ (2.0 g, 0.053 mole) and the mixt was stirred at 100–110° for 6 hr. The mixt was concd under reduced pressure and the residue was decompd with dil aqueous AcOH. The crystals which had formed were collected by filtration to give crude product (10.5 g), mp 115–118°. Recrystn from *i*-PrOH afforded a pure sample (8.4 g, 64.6%) as colorless prisms, mp 125–127°. *Anal.* ($C_{19}H_{23}N_3O_2$) C, H, N.

2-[*N*-(2-Morpholinoethyl)acetamido]benzanilide (VII). A mixt of VI (6.0 g, 0.018 mole) and Ac_2O (24.0 g) was heated with stirring at 50–60° for 4 hr. Excess Ac_2O evapd under reduced pressure and the residue was poured into aqueous K_2CO_3 soln. The oil was extd with PhH. The benzene layer was dried (K_2CO_3) and concd to dryness. The residue was triturated with Et_2O and the crystals were collected by filtration to give VII (6.5 g, 94.2%), mp 139–141°. Recrystn from *i*-PrOH–*i*-Pr_2O (1:1) afforded pure sample as colorless prisms, mp 140–142°. *Anal.* ($C_{21}H_{25}N_3O_3$) C, H, N.

1-(2-Morpholinoethyl)-2-methyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline (IX). To a soln of VII (5.5 g) in EtOH (100 ml) was added excess 60% $HClO_4$. The mixt was warmed at 60–70° for 1 hr and concd under reduced pressure. After cooling, the pptd crystals were collected by filtration to give crude 1-(2-morpholinoethyl)-2-methyl-3-phenyl-4-oxo-3,4-dihydroquinazolinium diperchlorate (VIII, 7.8 g, 94.8%), mp 232–233° dec, ir (Nujol) 1721, 1621, 1553, 1493 cm^{-1}. To a stirred suspension of VIII (5.5 g, 0.01 mole) in EtOH (100 ml) was added dropwise a soln of $NaBH_4$ in EtOH (50 ml) at −5–0° during 4.5 hr. The mixt was concd under reduced pressure. The residue was poured into H_2O and extd with PhH, the PhH layer was dried and concd under reduced pressure to give a paste which was crystd by trituration with *i*-Pr_2O. The crystals were collected by filtration to afford almost pure IX (2.7 g, 77%), mp 132–134°. Recrystn from *i*-PrOH gave pure sample as colorless prisms, mp 132–134°. *Anal.* ($C_{21}H_{25}N_3O_2$) C, H, N. The oxalate of IX melts at 135–137° which was recrystd from EtOH. *Anal.* ($C_{23}H_{27}N_3O_6$·0.5H_2O) C, H, N.

***N*-Ethylmorpholinoacetanilide (X).** A soln of *N*-ethylchloroacetanilide (3 g) and morpholine (4 g) in PhH (100 ml) was re-

fluxed for 14 hr. After cooling, the mixt was washed with H_2O and extd with 10% HCl. The ext was made alk with K_2CO_3 and the oil which had sepd was extd with Et_2O. The ext was dried (K_2CO_3) and concd to dryness to give crude X as an oil. This was crystd as the oxalate. Recrystn from EtOH gave pure sample (2.8 g) as colorless prisms, mp 97–98° dec. *Anal.* ($C_{14}H_{20}N_2O_2 \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H; N: calcd, 8.06; found, 7.41.

2-(*N*-Ethylamino)-*N*'-methylbenzanilide. A mixt of *N*-ethylisatoic anhydride[2] (5.75 g) and PhNHMe (3.60 g) was heated at 100° for 4 hr, at 130° for 2 hr, and at 160° for 1 hr. The mixt which crystd on cooling was recrystd from *i*-PrOH to afford pure product (5.2 g, 64%) as colorless prisms, mp 97–99°. *Anal.* ($C_{16}H_{18}N_2O$) C, H, N.

2-(*N*-Ethylchloroacetamido)-*N*'-methylbenzanilide. To a stirred mixt of 2-(*N*-ethylamino)-*N*'-methylbenzanilide (4.0 g, 0.016 mole) and anhyd K_2CO_3 (4.0 g, 0.028 mole) in PhH (130 ml) was added dropwise $ClCH_2COCl$ (2.8 g, 0.024 mole) at room temp during 10 min. The mixt was stirred at room temp for 1 hr and then washed with H_2O. The dried PhH layer was concd to dryness under reduced pressure and the crystalline residue was triturated with *i*-PrOH to afford almost pure product (4.4 g, 83%), mp 137–139°. Recrystn from *i*-PrOH gave a pure sample as colorless leaflets, mp 138–140°, nmr ($CDCl_3$) δ 1.15 (t, J = 8 Hz, 3 H), 3.23 (d, q, J = 16 Hz, 8 Hz, 1 H), 3.32 (broad s, 2 H), 3.44 (s, 3 H), 4.29 (d, q, J = 16 Hz, 8 Hz, 1 H), 6.9–7.5 (m, 9 H). *Anal.* ($C_{18}H_{19}ClN_2O_2$) C, H, N.

2-(*N*-Ethylmorpholinoacetamido)-*N*'-methylbenzanilide (XII). A soln of 2-(*N*-ethylchloroacetamido)-*N*'-methylbenzanilide (2.0 g, 0.006 mole) and morpholine (2.6 g, 0.03 mole) in PhH (30 ml) was warmed at 50° for 3 hr and then washed with H_2O. The dried PhH layer was concd to dryness under reduced pressure to give almost pure product as a colorless oil, nmr ($CDCl_3$) δ 1.13 (t, J = 7 Hz, 3 H), 2.46 (m, 4 H), 2.63 (s, 2 H), 3.19 (d, q, J = 14 Hz, 7 Hz, 1 H), 3.40 (s, 3 H), 3.65 (m, 4 H), 4.17 (d, q, J = 14 Hz, 7 Hz, 1 H), 6.9–7.5 (m, 9 H).

2-(Morpholinoacetamido)benzanilide (XI). A soln of 2-(chloroacetamido)benzanilide (5.57 g) and morpholine (4.3 g) in dioxane (180 ml) was stirred at 60–65° for 20 hr. The reaction mixt was concd under reduced pressure and the residue was poured into H_2O. The crystals were collected by filtration to give crude XI (6.9 g). Recrystn from dioxane afforded 6.2 g (94%) of XI as colorless prisms, mp 189–191°; the analytical sample melted at 190–192°. *Anal.* ($C_{19}H_{21}N_3O_3$) C, H, N. The hydrochloride was obtained as colorless needles (aqueous MeOH), mp 230–231° dec. *Anal.* ($C_{19}H_{21}N_3O_3 \cdot HCl$) C, H, N.

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Basic Ethers of 2-Anilinobenzothiazoles and 2-Anilinobenzoxazoles as Potential Antidepressants

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Some 2-[4-(β-*tert*-aminoethoxy)anilino]benzothiazoles and the corresponding benzoxazoles reversed reserpine-induced hypothermia in mice at low doses. The effects of structural variation of these molecules have been systematically examined. General pharmacology of selected compounds classifies them as antidepressants with a mild stimulant component. Anilinobenzazoles were advantageously prepared from substituted anilines and 2-chlorobenzazoles in DMF or *sym*-tetrachloroethane.

Routine pharmacological screening in these laboratories of compounds prepared for another purpose[1] revealed significant activity of 2-[4-(β-diethylaminoethoxy)phenyl]benzothiazole (**1**) in reversing reserpine-induced hypothermia in mice. This paper describes structural modifications leading to compounds having greatly increased antireserpine activity and a general pharmacological profile which suggests that they may be of value in depressive illness.

It soon became clear that in the 2-phenylbenzothiazole and 2-phenylbenzoxazole series, antireserpine activity was limited to a few basic ethers such as **1** in which a variety of substituents in the benzene ring did not greatly alter the activity. The 2'- and 3'-diethylaminoethoxy isomers of **1** were inactive, as were several 2-phenylbenzothiazoles having groups other than a basic ether in the 4' position. The introduction of bridging groups Y (Table I) between the benzazole and Ph rings led to the considerable increase in potency of the anilino basic ether **3**, other N-containing bridging groups being less effective and those without N giving weak or inactive compds. Compd **3** has been reported to have hypocholesterolemic activity.[2] The importance of the anilino H atom is shown by the poor activity of the *N*-Me and *N*-Ac derivs **17** and **18**.

Tests on intermediates (Table II) suggested that the basic structural unit required for antireserpine activity was *p*-$ZNHC_6H_4O(CH_2)_nNR_2$ and that potency was greatly increased when Z was an electron-attracting aromatic group. When Z was *p*-nitrophenyl the diphenylamine basic ether[2] **52**, although a potent antireserpine compd, caused a severe stereotyped response in the cat (see below). Other nuclei employed as Z produced compds which, as potential antidepressants, had pharmacological profiles inferior to those of the anilinobenzazoles (*e. g.*, **3**, **14**). Since the benzimidazole **16** was almost inactive, further variations were made in the basic ethers of 2-anilinobenzothiazoles and benzoxazoles (Tables I and III).

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