13.9 g of an oil. The oily residue was dissolved in 180 ml of EtOH and was stirred together with 180 ml of 2 *N* NH_4OH for 1 hr at room temp. Satd NaCl was added and the soln was extd with $CHCl_3$-EtOH (2:1). Removal of the solvent from the dried (Na_2SO_4) exts by warming *in vacuo* afforded 12.3 g of an oily residue. Chilling of a soln of this residue in 25 ml of Et_2O gave 4 g of **49**, mp 93–98°. The mother liquor was chromatog on 100 g of silica gel. Elution with Et_2O afforded 4.2 g of crude starting material. Elution with 100% THF gave another 3.1 g of **49** (80% yield based on starting material consumed). Recrystallization from Et_2O afforded 4.2 g of **49**, mp 113–115°. *Anal.* ($C_{10}H_{17}NO_4$) C, H, N.

(±)-Tropane-2β,3α-diol (50). A soln of 0.47 g (22 mmoles) of **49** in 6 ml of THF was added to 0.22 g of LAH in 21 ml of THF and the mixt was heated under reflux for 6.5 hr. A 1:1 mixt (4 ml) of H_2O and THF was added, then more H_2O and the mixt was extd with $CHCl_3$-EtOH (2:1). The ext was dried (Na_2SO_4) and concd by heating *in vacuo* to afford 0.41 g of an oil that partially crystd. Recrystallization from C_6H_6 afforded 0.15 g of rhombic crystals of **50**,[9] mp 100–101°, ir ($CHCl_3$) 3438 and 3628 cm^{-1} (bonded and nonbonded OH bands).

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Diazirines. 3.[1] Synthesis of a Series of Diazirine-Containing Molecules and Their Pharmacological Evaluation

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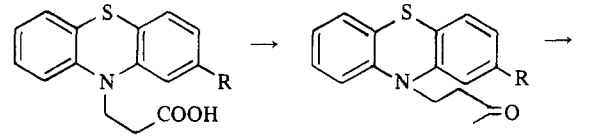
Several diazirine-containing congeners of biologically active molecules were synthesized. In addition, as a result of observations of biological activity for some small diazirine-containing molecules not related to compounds with established biological activity, a series of simple diazirines were prepared.

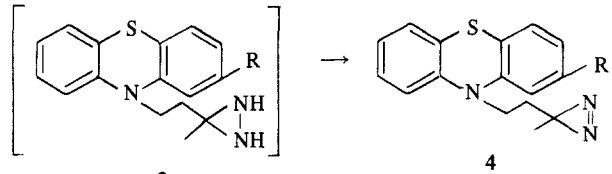
In an earlier report[2] we described the synthesis of several steroids containing the diazirine group and noted the favorable effect on the anabolic to androgenic ratio of certain of these derivatives. Since there were only a few other reports[3] concerning the biological properties of diaziridine and diazirine-containing molecules, we were encouraged to investigate the biological effects of this novel group.

Our initial approach was aimed at the preparation of diazirines congeneric with substances of established utility. Thus, we prepared the phenothiazine diazirine **4a** from phenothiazine acid **1a**[4] *via* ketone **2a**.† However, repeated attempts to effect the transformation of 2-chloro-*N*-(3-ketobutyl)phenothiazine **2b**, prepared from the corresponding acid **1b**, to the more interesting diazirine **4b** were unsuccessful. Although the reason for this failure is not known, this result, as well as the meager yield (15%) obtained in the preparation of **4a** from **2a**, further illustrates the less-than-satisfactory nature, in many instances, of the ketone-to-diazirine transformation.‡

The unreliable nature of this transformation with more complex molecules persuaded us to shift our approach and base our syntheses on the utilization of relatively simple, otherwise functionalized, diazirine-containing substances. Toward this end we prepared, among others, the acids **5** (n = 2–4), the alcohols **6** (n = 1–3), the acetals **7** (n = 0–2), and the amines **8** (n = 1 and 2). The preparation and properties of these useful simple molecules, as well as selected



1 **2**



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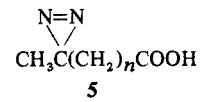
a series, R = H
b series, R = Cl

4

derivatives, are described in detail in an earlier paper.[1,§]

By unexceptional procedures, the following diazirine-



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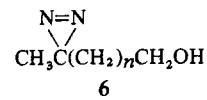

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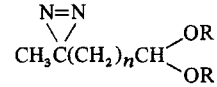

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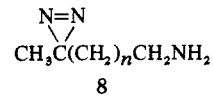

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containing analogs of clinically useful pharmaceutical agents were obtained: amides **9** and **10**, respectively, of psychic stimulants tranylcypramine and amphetamine, the phenyl-

†It should be noted that all attempts to isolate the diaziridine **3a**, a more pertinent analog of the aminoalkylphenothiazines, were unsuccessful.

‡For additional examples see ref 1 and 2.

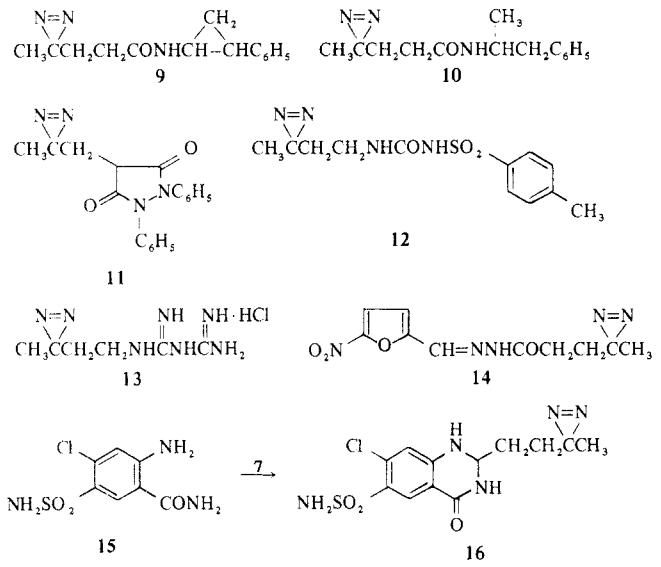
§The use of these compounds for the preparation of cephalosporins containing the diazirine group has been reported; see ref 5.

Table I. Diazirine-Containing Compounds

Compound No.	Structure R = $CH_3CCH_2CH_2-$ (3-methyl-3-diazirinylpropyl)	Preparation	Recrystn solvent	Mp or bp (mm), °C	Formula	Anal.
9	RCONHCH(CH$_2$)–CHC$_6$H$_5$	2A	$CHCl_3$–petr ether	81–81.5	$C_{14}H_{17}N_3O$	C, H, N
10	$RCONHC(CH_3)HCH_2C_6H_5$	2A	C_6H_6–petr ether	68–69	$C_{14}H_{19}N_3O$	C,[a] H, N
14	RCONHN=CH–(5-nitro-2-furyl)	1A	CH_2Cl_2–hexane then EtOH–H_2O	146–148	$C_{10}H_{11}N_5O_4$	C, H, N
17	$RCON(CH_3)_2$	2A		58 (0.2)	$C_7H_{13}N_3O$	C, H, N
18	RCON(1-methylcyclopropyl)	2A		Oil	$C_8H_{13}N_3O$	C, H, N[b]
19	RCONH–cyclopropyl	2A	Et_2O–hexane	39–41	$C_8H_{13}N_3O$	C, H, N
20	$RCONHC_6H_{11}$	2A	Hexane	70.5–72.5	$C_{11}H_{19}N_3O$	C, H, N
21	$RCON(CH_2C_6H_5)_2$	2A		Oil	$C_{19}H_{21}N_3O$	C, H, N
22	$RCONHC_6H_5$	2A	Hexane	81.5–82	$C_{11}H_{13}N_3O$	C, H, N
23	RCON(4-methylpiperazino)·HCl	2B	*i*-PrOH	164–165	$C_{10}H_{16}N_4O\cdot HCl$	C, H, N, Cl
24	RCON(4-phenylpiperazino)·HCl	2B	EtOAc–Et_2O	151–154	$C_{15}H_{20}N_4O\cdot HCl$	C, H, N, Cl
25	$RCONHCH_2C_6H_5$	2A	C_6H_6–petr ether	64–65	$C_{12}H_{15}N_3O$	C, H, N
26	$RCONHCH_2CH_2C_6H_5$	2A	C_6H_6–petr ether	65–66	$C_{13}H_{17}N_3O$	C, H, N
27	$RCONC(CH_3)HCH_2C_6H_{11}$	2A		90–95 (0.14)	$C_{15}H_{27}N_3O$	C, H, N
28	RCONH(2-pyridyl)·HCl	2C	EtOH–Et_2O	147–148	$C_{10}H_{12}N_4O\cdot HCl$	C, H, N, Cl
29	RCONH(2-pyridyl)	2B	$CHCl_3$–hexane	78.5–80	$C_{10}H_{12}N_4O$	C, H, N
30	RCONH(2-pyrimidyl)	2C	EtOAc–hexane	96–97	$C_9H_{11}N_5O$	C, H, N
31	RCONH(2-thiazolyl)	2A	Acetone–hexane	112.5–114.5	$C_8H_{10}N_4SO$	C, H, N, S
32	RCONH(4-methylpiperazino)	2B	Et_2O	130–137	$C_{10}H_{19}N_5O$	C, H, N
33	$RCONHN(CH_3)_2\cdot HCl$	2B	EtOH–Et_2O	120–121	$C_7H_{14}N_4O\cdot HCl$	C,[c] H, N, Cl
34	$RCH_2CH_2CONH_2$	2D	CH_2Cl_2–hexane	94–96	$C_7H_{13}N_3O$	C, H,[d] N
35	$RNHCOC_6H_5$	2A		Oil	$C_{11}H_{13}N_3O$	C, H, N[e]
36	$RCONHN{=}C(CH_3)_2$	1A	Acetone (−78°)	50.5	$C_8H_{14}N_4O$	C, H, N
37	$RCONHN{=}CHC_6H_4$-*m*-OCH_3	1A	EtOH–H_2O	98–100	$C_{13}H_{16}N_4O_2$	C, H, N
38	$RCONNHC_6H_5$ (C_6H_5)	1B	CH_2Cl_2–hexane	128–130	$C_{17}H_{18}N_4O$	C, H, N
39	$RCH_2CONHCHCH_2C_6H_5$ (CH_3)	2A	Hexane	88–90	$C_{20}H_{23}N_3O$	C, H, N
40	RCOOCH$_2$(pyridyl)·maleate salt	2B	Acetone–Et_2O	70–72	$C_{15}H_{17}N_3O_6$	C, H, N
41	RCH_2COOCH_3	3		50 (3.0)	$C_7H_{12}N_2O_2$	C, H, N
42	$RCH_2CH_2COOCH_3$	3		45 (0.3)	$C_8H_{14}N_2O_2$	C, H, N
43	$ROCOC_6H_5$	2A		82 (0.1)	$C_{11}H_{12}N_2O_2$	C, H, N
44	RCONHNHCOR	2A	Acetone–hexane	150.5–152	$C_{10}H_{16}N_6O_2$	C, H, N
45	RCON(piperazino)NCOR	2A	C_6H_6–petr ether	83.5–84	$C_{14}H_{22}N_6O_2$	C, H, N
46	$RCONHC_6H_4NHCOR$-*p*	2A	Acetone	208–210	$C_{16}H_{20}N_6O_2$	C, H, N
47	RCON(RCON)(pyridyl)	2E	Hexane	62–63	$C_{14}H_{17}N_7O_2$	C, H, N
48	$CH_3CCH_2CHCONHCH_2$ ($N{=}N$, C_6H_5) $CH_3CCH_2CHCONHCH_2$ ($N{=}N$, C_6H_5)	2A	Acetone–hexane	120–121	$C_{24}H_{28}N_6O_2$	C, H, N

[a] C: calcd, 68.54; found, 67.93. [b] N: calcd, 25.18; found, 24.38. [c] C: calcd, 40.68; found, 41.23. [d] H: calcd, 8.44; found, 7.91. [e] N: calcd, 20.68; found, 19.65.

butazone congener **11**, analogs **12** and **13**, respectively, of the hypoglycemic agents tolbutamide and phenformin, the nitrofuran derivative **14**, and analog **16** of the diuretic quinethazone.



The heat sensitivity of the diazirine group precluded the application of the usual route to biguanide **13**, namely heating together dicyandiamide and an amine. For the preparation of **13**, we therefore used the room temp reaction[6] of *N*-guanyl-*O*-methylisourea·HCl with 3,3-azobutylamine.

Thermal sensitivity was also the apparent cause of our inability to prepare the next lower homolog of the quinethazone congener **16**. Whereas the preparation of **16** from the *o*-aminobenzamide **15** and 1,1-diethoxy-4,4-azopentane (**7**, n = 2, R = Et) proceeded normally, the same procedure, employing 1,1-dimethoxy-3,3-azobutane (**7**, n = 1, R = Me), afforded only low yields of an impure material which appeared to be a mixture of quinazolines substituted with olefinic side chains. Presumably the olefinic function is due to decomposition of the diazirine group. It is conceivable that this apparent increase in thermal instability results from an enhanced interaction between the diazirine and the neighboring electron-withdrawing HC=O function. We also were unable to prepare the 2-C side-chain analog of **16** from **15** and 1,1-diethoxy-2,2-azopropane (**7**, n = 0, R = Et); in this instance no reaction occurred, there being recovered only starting acetal and benzamide **15**. This inability to hydrolyze acetal **7** (n = 0) is presumably another manifestation of the strong electron-withdrawing nature of the diazirine group.[1]

During the course of this investigation, routine pharmacological screening of the simple diazirine-containing molecules (noted above) revealed interesting activity in several assays. These positive results encouraged us to prepare on an empirical basis a variety of derivatives of these compounds for broad biological evaluation. These derivatives, which were obtained by standard procedures, are listed in Table I.

Biological Evaluation. Among the congeners and derivatives of biologically active molecules (**4**, **9–14**, and **16**) only two, **9** and **16**, elicited significant activity in assays for which the compounds were intended. Compd **9**, an analog of tranylcypramine, was active at 6 mg/kg as an antidepressant in the tetrabenazine-reversal assay[7] (rat, ip dose), and the quinethazone congener **16** induced diuresis[8] in both the rat and the dog, although it was less potent than quinethazone itself.

A broad variety of biological activities, summarized in Table II, were exhibited by the simple diazirine-containing molecules and their derivatives. Several of the compounds exhibited a strong diuretic effect in the rat but none were of substantial interest when tested in the dog. The most striking of these activities was hypoglycemia, however this initially exciting observation is probably the result of a marked alteration in liver lipid metabolism. Thus, three compounds [**6**, (n = 2), **5** (n = 2, Me ester), 4,4-azopimelic acid[1]] which did not induce a hypoglycemic response at the dose employed also did not produce an alteration in liver lipids. In contrast, the livers of mice treated with **6** (n = 1), **5** (n = 2, 4-pyridylmethyl ester maleate salt), **7** (n = 1, R = Me), **8** (n = 1), **22**, **30**, or **33**, all active hypoglycemics (38 to 69% decrease in blood glucose), showed increased weight and exhibited fatty infiltration.#,**

Table II. Biologically Active Compounds

Test[a]	Active compounds
Antidepressant	**9**
Diuretic	**5** (n = 2, Me ester, amide or hydrazide), **6** (n = 2), **7** (n = 0 or 2, R = Et; n = 1, R = Me), **16**, **18**, **19**, **25**, **33**, **36**, **37**, **40**, **44**, **47**
Antihypertensive	**25**, **30**, **47**
Analgetic	**5** (n = 2, hydrazide), **5** (n = 3, Me ester), **12**, **17**, **22**, **28**, **30**, **33**, **36**, **37**, **41**.
Antiinflammatory	**5** (n = 3), **10**
Hypoglycemic	**5** (n = 2 and its Me and 4-pyridylmethyl esters, amide, and hydrazide), **5** (n = 3, and its Me ester); **6** (n = 1, 2), **7** (n = 1, R = Me), **8** (n = 1), **17**, **22**, **25**, **29**, **30**, **33**, **36**, **37**

[a] See Experimental Section.

Experimental Section

Melting points were taken on a Mel-Temp apparatus in open capillary tubes and are corrected. Boiling points are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values. Petr ether used as a solvent is that fraction boiling at 30–60°. Solns were dried (Na_2SO_4) unless otherwise indicated.

Biological Methods. Antidepressant Test.[7] Compds that inhibited tetrabenazine depression of exploratory behavior in 4 or more of 15 mice were considered active.

Diuretic Test.[8] The compd to be tested was given to male Wistar nonhydrated rats by gavage at a dose of 100 mg/kg, and urine was collected during the first 0–5 hr period and during the following 5–24 hr period. Compds that increased urine vol by 100% or more were considered active.

Compds shown to be active by the rat test were given to hydrated dogs at the same dose level, and urine was collected during the first 0–6 hr period and the following 6–24 hr period. Active compds were those that increased urine vol by 100% or more.

Antihypertensive Test.[14] The test compds (100 mg/kg) were suspended in 2% starch and administered to conscious normotensive rats by gavage. Active compds were those that produced a reduction in mean arterial blood pressure of 20% or more after 2 hr.

Hypoglycemic Test.[15] Compds (0.2–0.8 mmole/kg) were administered by gavage to normal mice. Blood glucose was detd 4 and 6 hr after dosing; active compds in this study produced a 25–88% reduction in this factor.

Analgetic Test.[16] Compds that produced a reduction in the number of phenylquinone-induced writhes by 50% or more in treated mice as compared with untreated mice were considered active.

Antiinflammatory Test.[17] Carrageenin (2%) was injected in the sacral area of the rat and the resultant abscesses were removed

#D. A. Blickens and S. Riggi, private communication.

**Fatty infiltration of liver or derangement of lipid metabolism has been reported following treatment of experimental animals with the hypoglycemic agents hypoglycin A,[9,10] synthalin,[11,12] or 4-pentenoic acid.[13]

and weighed after 24 hr. Five rats were tested per compd and active compds were those that produced a mean decrease in abscess weight of 30% or greater, as compared with controls.

General Methods for Preparation of Diazirine-Containing Acyl Derivatives. Method 1A. 4,4-Azopentanoic Acid *m*-Methoxybenzylidenehydrazide (37). A soln of 1.0 g of 4,4-azopentanoyl hydrazide[1] and 0.43 g of HOAc in 5 ml of EtOH and 3 ml of H_2O was treated at room temp with 0.96 g of *m*-methoxybenzaldehyde in 4 ml of EtOH. The product sepd within 1 hr as long needles. Recrystn from EtOH–H_2O afforded 0.91 g of product, mp 98–100°. A second crop (0.52 g) of mp 96–98° was obtained upon partial evapn of the mother liquor.

Method 1B. *N,N'*-Diphenyl-4,4-azopentanoyl Hydrazide (38). To a well-stirred, water-cooled mixt of 5 ml of 5 *N* NaOH and 2.6 g of 1,2-diphenylhydrazine in 30 ml of dry C_6H_6 was added dropwise a soln of 1.8 g of 4,4-azopentanoyl chloride[1] in 15 ml of C_6H_6. The mixt was stirred 30 min and the ppt was removed by filtration and dissolved in CH_2Cl_2. After decolorization of the soln with activated charcoal and drying, the CH_2Cl_2 was evapd to afford 1.44 g of cryst solid. Recryst from CH_2Cl_2–hexane afforded 1.16 g of product as yellow platelets, mp 126–128°.

Method 2A. *N*-Benzyl-4,4-azopentanamide (25). To a soln of 1.37 g (24 mmoles) of cyclopropylamine and 4 ml of Et_3N in 30 ml of C_6H_6 at 20° was added dropwise with ice cooling a soln of 3.3 g (24 mmoles) of 4,4-azopentanoyl chloride[1] in 20 ml of C_6H_6. The mixt was stirred 1 hr, then washed consecutively with H_2O, 5% HCl, and 10% $NaHCO_3$, and dried. Evapn of the soln afforded an oil which crystd on trituration with hexane. Recrystn from Et_2O–hexane at 0° afforded 1.21 g colorless platelets, mp 39–41°. For the prepn of bisamides, 2.1 equiv of the acid chloride was used.

Method 2B. *N*-(Pyridyl-2)-4,4-azopentanamide (29). A soln of 0.94 g of 3-aminopyridine and 2 ml of Et_3N in 50 ml of dry C_6H_6 was cooled to 6° and treated with 1.28 g of 4,4-azopentanoyl chloride[1] in 10 ml of C_6H_6, maintaining a temp of 6–10° with external cooling. The resulting soln was stirred at 25° for 2 hr, washed with two 20-ml portions of H_2O, and extd with two 15-ml portions of 2 *N* HCl. The aqueous exts were combined, washed with C_6H_6, made basic with 10% $NaHCO_3$, and extd with CH_2Cl_2. The combined organic exts were washed once each with H_2O and brine and then dried. The cryst residue (1.14 g), remaining after evapn of the CH_2Cl_2 at reduced pressure, was recrystd from acetone–hexane to give 0.80 g of pale yellow crystals, mp 78.5–80°.

In several instances purification of the free base was difficult. When it was, the HCl salt was prepd by passing dry HCl into an ethereal soln of the free base, collecting the cryst ppt, and recrystg from EtOH.

Method 2C. *N*-(Pyrimidinyl-2)-4,4-azopentanamide (30). A soln of 2.8 g (29 mmoles) of 2-aminopyrimidine in 40 ml of pyridine was cooled in solid H_2O and 4.1 g (29 mmoles) of 4,4-azopentanoyl chloride[1] was added in portions with vigorous stirring. The pyridine was evapd, the residue was washed with 50 ml of H_2O, and recrystd from C_6H_6–hexane to afford 2.0 g of crystals, mp 97–99°.

Method 2D. 6,6-Azoheptanamide (34). To 30 ml of concd NH_4OH (cooled by addn of an equal wt of ice) was added dropwise with stirring 0.8 g of 6,6-azoheptanoyl chloride.[1] The resulting mixt was extd with three 20-ml portions of CH_2Cl_2, and the solvent was evapd from the combined exts. The residue was recrystd from CH_2Cl_2–hexane to afford 0.62 g of 6,6-azoheptanamide, mp 94–96°.

Method 2E. *N*-[1-(4,4-Azopentanoyl)-2(1*H*)-pyrimidinylidene]-4,4-azopentanamide (47). To a well-stirred soln of 1.70 g of 2-aminopyrimidine and 7 ml of Et_3N in 50 ml of $CHCl_3$ was added dropwise a soln of 2.60 g of 4,4-azopentanoyl chloride[1] in 20 ml of $CHCl_3$. The mixt was stirred 15 min and washed consecutively with 20-ml portions each of 5 *N* NaOH, H_2O, and brine. The organic portion was dried ($MgSO_4$), and the soln was evapd. The cryst residue was recrystd from EtOAc–hexane to yield 0.80 g of product with mp 62–63°.

Method 3. Methyl 5,5-Azohexanoate (41). A soln of 8.0 g of 4,4-azohexanoic acid[1] in 50 ml of CH_3OH contg a small amt of HCl gas was allowed to stand for 16 hr. The soln was dild with H_2O (contg some $NaHCO_3$) and extd with Et_2O. The combined exts were washed with brine and dried. The soln was evapd and the residual oil was distd, yielding 6.3 g of product, bp 50° (3 mm).

***N*-(3-Ketobutyl)phenothiazine (2a).** A well-stirred mixt of 2.52 g (9.2 mmoles) of phenothiazine-*N*-propionic acid[4] **(1a)** in 100 ml of dry Et_2O was treated dropwise with 25 ml of 1 *N* MeLi in THF. The soln was stirred 30 min and then poured over 300 g of solid H_2O. The layers were sepd, and the aqueous layer was extd with Et_2O. The combined organic exts were washed with H_2O to neutrality, and then with brine, and dried. Et_2O was evapd and the oily residue was chromatogd on 100 g of silica gel. After washing the column with 1 l. of C_6H_6; from which was recovered 92 mg of phenothiazine, the fraction eluted with 2 l. of 3% (v:v) ether-in-benzene was collected, the soln was evapd at reduced pressure, and the oily residue was then chromatogd on 80 g of alumina. Elution with C_6H_6 afforded 1.54 g of **2a**. Recrystn from Et_2O–petr ether afforded 1.31 g (62%) of highly cryst product, mp 55–58°. *Anal.* ($C_{16}H_{15}NOS$), C: 71.33; found, 70.80; H, N, S.

3-(2-Chlorophenothiazinyl)propionic acid **(1b)** (2.14 g, 7 mmoles) treated as described above afforded 568 mg (26.4%) of ***N*-(3-ketobutyl)-2-chlorophenothiazine (2b),** recrystd from CH_2Cl_2–petr ether, mp 114–115.5°. *Anal.* ($C_{16}H_{14}ClNOS$), C, H, N, S.

***N*-(3,3-Azobutyl)phenothiazine (4a).** A soln of 3.02 g of *N*-(3-ketobutyl)phenothiazine **(2a)** in 150 ml of MeOH and 300 ml of liq NH_3 was allowed to stir at reflux for 3.5 hr. The soln was cooled in Dry Ice–acetone and then treated with 7.5 g of hydroxylamine-*O*-sulfonic acid over a 2-hr period. The resulting soln was then allowed to warm to room temp with evapn of excess NH_3. The mixt was filtered and the soln was evapd. The noncryst residue was dissolved in 100 ml of MeOH, and 9.5 g of $AgNO_3$ was added. The mixt was stirred for 40 min, and 20 ml of 10% NaOH was added dropwise over a period of 1 hr. The black mixt was stirred 2 hr at room temp and filtered through Celite.†† The soln was partially evapd at reduced pressure and the residue was dild with H_2O. The aqueous soln was extd with three 40-ml portions of CH_2Cl_2, and the combined exts were dried. The residue, after evapn of the soln, was chromatogd on 100 g of silica gel. The product (442 mg) was eluted with C_6H_6 and was recrystd from Et_2O–hexane to yield 416 mg (13%) of fine needles, mp 77–79°. *Anal.* ($C_{16}H_{15}N_3S$), C, H, N, S.

N-(3,3-Ketobutyl)-2-chlorophenothiazine **(2b)** treated as described above failed to yield any characterizable diazirine-containing material.

***N*-(2,2-Azopropyl)-1,2-diphenyl-3,5-pyrazolidinedione (11).** A soln of 770 mg of *N,N'*-diphenyl-4,4-azopentanoyl hydrazide **(38)** in 10 ml of C_6H_6 was treated with 1 ml of freshly distd diethyl carbonate and 200 mg of NaH (as a 54% dispersion in mineral oil) and the mixt was refluxed for 16 hr. After cooling, it was dissolved in a mixt of 50 ml of C_6H_6 and 50 ml of H_2O with stirring. The layers were sepd and the C_6H_6 layer was extd with two 5-ml portions of 5% NaOH. The aqueous exts were combined with the aqueous layer previously obtained and washed once with C_6H_6, then made acidic to Congo Red with HCl and extd with C_6H_6 and CH_2Cl_2. The combined exts were dried and the soln was evapd. The residual red oil crystd slowly to afford 302 mg of product. Recrystn from EtOH–H_2O afforded 156 mg of yellow platelets with mp 134–135.5°. *Anal.* ($C_{18}H_{16}N_4O_2$), C, H, N.

***N*-(4,4-Azobutyl)-*N'*-(*p*-tolylsulfonyl)urea (12).** A soln of 0.67 g (6.7 mmoles) of 3,3-azobutylamine (**8**, $n = 1$) in about 40 ml of Et_2O (prepd by drying thoroughly an Et_2O ext of an aqueous soln of NaOH and 3,3-azobutylamine·HCl[1]) was treated dropwise with 1.32 g of *p*-toluenesulfonyl isocyanate. The product pptd within about 5 min. It was removed by filtration and recrystd from acetone–hexane, then from MeOH–H_2O to afford 1.19 g of product, mp 139–140° dec. *Anal.* ($C_{12}H_{16}N_4SO_3$), C, H, N, S.

1-(3,3-Azobutyl)biguanide·HCl (13). A soln of 1.07 g (10 mmoles) of 3,3-azobutylamine·HCl[1] and 2.0 ml of 5 *N* NaOH in 2 ml of H_2O–CH_3OH soln (1:1) was treated with 1.52 g (10 mmoles) of *N*-guanyl-*O*-methylisourea[6] and the resulting soln was allowed to stand 22 hr. The soln was evapd and the residual oily solid was triturated with about 10 ml of EtOH and filtered. The filtrate was allowed to stand several days at −10° and then dild with Et_2O to the cloud point. After a further week at −10° 138 mg of material was filtered and discarded. The filtrate was dild with 10 ml of Et_2O and allowed to stand 24 hr. A mixt of oil and cryst solid sepd. The supernatant liquid was decanted, the soln was concd to about 5 ml, treated with 3 ml of EtOH and 5 ml of acetone, and allowed to stand at −10° for 24 hr. The resulting very fine needle-like crystals were removed by filtration and recrystd from EtOH–acetone to afford 340 mg of white crystals, mp 129–133° dec. *Anal.* ($C_6H_{14}ClN_7$), C: 32.80; found: 30.70; H, N.

2-(3,3-Azobutyl)-7-chloro-1,2,3,4-tetrahydro-4-oxo-6-quinazolinesulfonamide (16). A mixt of 465 mg of 4,4-azo-1,1-diethoxypentane,[1] 624 mg of 2-amino-4-chloro-5-sulfamoylbenzamide **(15)**,[18] 1 drop of concd HCl, and 50 ml of abs EtOH was stirred and refluxed for 1.5 hr. Soln was complete after about 30 min. The soln was evapd and the residue was recrystd from acetone–H_2O to afford 656 mg of white solid with mp 154.5° dec. One further recrystn

††Celite is the trademark of the Johns Manville Company for diatomaceous earth silica products.

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-