TABLE I

RELATIVE BIOLOGICAL ACTIVITIES OF PEPTIDES

No.	Compound	Guinea pig ileum, %	Rat pressor, %
1	Asn-Arg-Val-Tyr-Val-His-Pro-Phe[a]	100	100
2	Val-Tyr-Ile-His-Pro-Phe	0.1	
3	*cyclo*-(-Val-Tyr-Ile-His-Pro-Phe-)	0.1	0.03
4	*cyclo*-(-Val-Tyr-Gly-Gly-His-Gly-)[b]	0.005	
5	*cyclo*-(-Gly-Tyr-Gly-Gly-Gly-His-)[b]	1.5	<0.01
6	*cyclo*-(-Gly-Tyr-Gly-Gly-His-Gly-)[b]	0.005	
7	*cyclo*-(-Gly-DTyr-Gly-Gly-His-Gly-)[b]	0.003	
8	*cyclo*-(-Tyr-His-)[b]	0.003	

[a] [Asn[1],Val[5]]-angiotensin II, provided by CIBA Pharmaceuticals, Inc. [b] Provided by Dr. K. D. Kopple, see ref 8.

ponent, no starting material, and four minor components. A 170-mg portion was dissolved in MeOH–H_2O (1:1), applied in bands on five sheets of Whatman No. 3MM filter paper, and subjected to electrophoresis at pH 3.5. The major band at E_H 0.50 was eluted with water and lyophilized to yield 63 mg of white powder: single spot on paper electrophoresis at pH 3.5 (E_H 0.53) and pH 6.5 (E_H 0.51); on paper chromatography, R_f 0.74; ninhydrin and Pauly +; amino acid analysis; Val 1.00, Tyr 0.57, Ile 0.91, His 1.02, Pro 0.98, Phe 0.94.

cyclo-(**-Val-Tyr-Ile-His-Pro-Phe-**).—To a stirred solution of 16 mg (0.084 mmole) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride in 2 ml of DMF was added dropwise over 14 hr 32 mg (0.04 mmole) of Val-Tyr-Ile-His-Pro-Phe dissolved in 14 ml of DMF. After 24 hr at room temperature in the dark, paper electrophoresis showed no starting material at E_H 0.50 (pH 3.5), and in addition to several minor spots, a single major component at E_H 0.40 (pH 3.5); Pauly +, ninhydrin −. The solvent was removed *in vacuo* and the residue was dissolved in MeOH, applied in bands on sheets of Whatman No. 3MM filter paper. Following electrophoresis, the band at E_H 0.40 was eluted with water and lyophilized to yield 15 mg (47%) of a white powder: single spot on paper electrophoresis at pH 3.5, E_H 0.43; Pauly +, ninhydrin −; amino acid analysis, Val 1.07, Tyr 0.91, Ile 0.89, His 1.01, Pro 1.04, Phe 1.08.

Acknowledgments.—We are grateful to Dr. Kenneth D. Kopple for samples of cyclic peptides, Drs. P. A. Lehman, T. C. Lee, and G. Windridge for assistance with the bioassays, Drs. B. Katzung and S. J. Feinglass for assistance with computer programming, and Dr. D. Nitecki for her helpful discussions and a sample of the soluble carbodiimide derivative used in the cyclization reaction.

Hypotensive, Antiadrenergic, and Antihistaminic 3-Substituted 2-Methyl- (or 2-Phenyl-) 4(3H)-quinazolones

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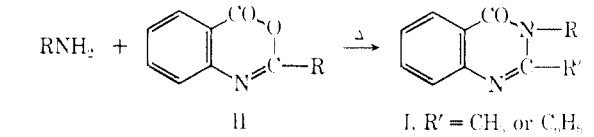
3-Aryl-2-methyl-4(3H)-quinazolones[2] are known to possess hypnotic, sedative, and anticonvulsant activities. Also, 3-ω-dialkylaminoalkyl-2-methyl-4(3H)-quinazolones[3] are reported to have similar activities. Our previous experience with N-arylpiperazine derivatives[4] having sedative, hypotensive, and antiadrenergic activities led us to study certain 3-ω-(4-aryl-1-piperazinyl)alkyl-2-methyl- (or 2-phenyl-) 4(3H)-quinazolones (I) (Tables I and II).

These compounds were readily prepared by heating 2-methyl- (or 2-phenyl-) 4-oxo-4H-3,1-benzoxazine (II) with appropriate primary amines (method A) or by treating isatoic anhydride (III) with the amines to give *o*-amino-N-substituted benzamides (IV) which were then benzoylated and cyclized with Ac_2O (method B) (Scheme I). I (R′ = CH_3) is also prepared by heating IV in Ac_2O. The details of the preparative chemistry have been described in a recent patent.[5]

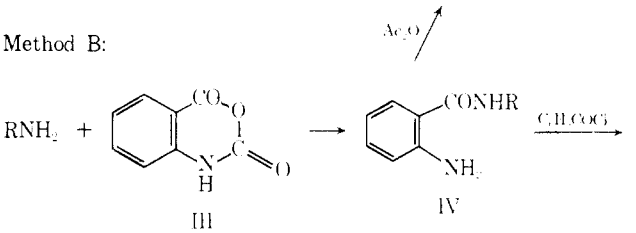
SCHEME I

Method A:

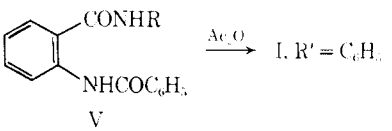


II I, R′ = CH_3 or C_6H_5

Method B:



III IV



V

Pharmacology.—The activity of compounds of this series was evaluated as follows: antiadrenergic action

(1) To whom inquiries should be addressed.

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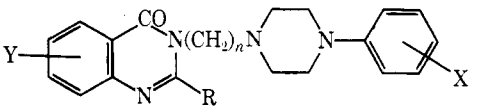
(5) S. Hayao, U. S. Patent 3,231,572 (Jan 25, 1966).

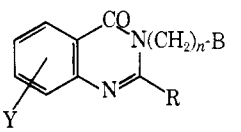
TABLE I

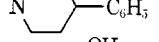
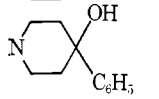
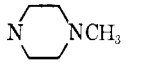


No.	n	R	X	Y	Formula	Mp, °C	Analyses
1	0	CH_3	H	H	$C_{19}H_{20}N_4O$	135–136	N
					$C_{19}H_{20}N_4O \cdot 2HCl$	251–252 dec	HCl
2	3	CH_3	H	H	$C_{22}H_{26}N_4O$	104–105	N
					$C_{22}H_{26}N_4O \cdot CH_3OH \cdot 3HCl$	250–251 dec	HCl
3	3	CH_3	4-CH_3	H	$C_{23}H_{28}N_4O$	132–133	N
					$C_{23}H_{28}N_4O \cdot 3HCl \cdot CH_3OH$	228–229 dec	HCl
					$C_{23}H_{28}N_4O \cdot CH_3I$	252–253	N
4	3	CH_3	2-Cl	H	$C_{22}H_{25}ClN_4O \cdot C_2H_2O_4$[a]	187–189 dec	N
5	3	CH_3	3-Cl	H	$C_{22}H_{25}ClN_4O \cdot 3HCl$	249–250 dec	HCl
6	3	CH_3	H	6-Cl	$C_{22}H_{25}ClN_4O \cdot 3HCl \cdot CH_3OH$	195–196 dec	N, HCl
7	3	CH_3	H	7-Cl	$C_{22}H_{25}ClN_4O \cdot C_2H_2O_4 \cdot H_2O$	210–212	C, H, N
8	3	CH_3	4-Cl	7-Cl	$C_{22}H_{25}Cl_2N_4O \cdot C_4H_4O_4$[b]	216–218	N
9	5	CH_3	H	H	$C_{24}H_{30}N_4O \cdot 3HCl$	170–172	HCl
10	6	CH_3	H	H	$C_{25}H_{32}N_4O \cdot 2HCl$	265–268 dec	HCl
11	7	CH_3	H	H	$C_{26}H_{34}N_4O$	*Ca.* 75	N
12	3	C_2H_5	H	H	$C_{23}H_{28}N_4O \cdot 3HCl \cdot CH_3OH$	167–170 dec	
13	2	C_6H_5	H	H	$C_{26}H_{26}N_4O$	147–148.5	N, N(basic)[c]
					$C_{26}H_{26}N_4O \cdot C_4H_4O_4$	207–208 dec	N
14	3	C_6H_5	H	H	$C_{27}H_{28}N_4O$	141–149	N
					$C_{27}H_{28}N_4O \cdot C_2H_2O_4$	203–204 dec	N
					$C_{27}H_{28}N_4O \cdot C_4H_4O_4$	115.5–117	N
15	3	C_6H_5	4-Cl	H	$C_{27}H_{27}ClN_4O$	193–194	N
					$C_{27}H_{27}ClN_4O \cdot C_4H_4O_4$	189–191 dec	N
16	3	C_6H_5	H	6-Cl	$C_{27}H_{27}ClN_4O \cdot C_4H_4O_4$	204–205.5 dec	C, H, N
17	4	C_6H_5	H	H	$C_{28}H_{30}N_4O \cdot C_2H_2O_4$	200–201.5 dec	N, N(basic)[c]
18	5	C_6H_5	H	H	$C_{29}H_{32}N_4O \cdot C_2H_2O_4$	186–188 dec	N, N(basic)[c]

[a] Oxalate. [b] Maleate. [c] Basic N with $HClO_4$ titration.

TABLE II



No.	n	R	Y	B	Formula	Mp, °C	Analyses
19	2	CH_3	H	C_6H_5	$C_{17}H_{16}N_2O \cdot HCl$	220–222 dec	HCl
20	2	CH_3	7-Cl	C_6H_5	$C_{17}H_{15}ClN_2O$	127–128	N
					$C_{17}H_{15}ClN_2O \cdot HCl$	238–241	N
21	3	C_6H_5	H		$C_{28}H_{29}N_3O \cdot C_4H_4O_4$	205–206 dec	N
22	3	C_6H_5	H		$C_{28}H_{29}N_3O_2 \cdot C_2H_2O_4$	112.5–115 dec	N
23	3	CH_3	H		$C_{17}H_{24}N_4O \cdot 2C_4H_4O_4$	198–200	N

was assessed on the rabbit aortic strip, the cat nictitating membrane, and the dog blood pressure; hypotensive action on the blood pressure of anesthetized rats and dogs; antihistaminic action on the guinea pig ileum; sedative activity by gross observation of unanesthetized rats.

Most compounds displayed parallel antiadrenergic and hypotensive actions, the most potent being **9**, **13**, and **14**. Compound **10**, which was studied in more detail, blocked aortic strip and nictitating membrane responses to epinephrine and reversed the vasopressor response to epinephrine in the dog. This compound produced an intense and long-lasting blood pressure fall in rats and dogs, at doses as low as 0.1 mg/kg iv. Cross circulation experiments in dogs revealed lack of a central component in the vascular action of the compound. In a mecamylamine-hypertensive dog, daily oral doses of 10.0 mg/dog produce a sustained decrease of blood pressure during 2 months of continued administration.

Compounds **3**, **5**, **8–10**, **17**, and **18** displayed moderate antihistaminic effect. Compound **10** was the most potent of the group; however, it was slightly less active than diphenhydramine. None of the members of this series elicited sedative action in the rat, at doses up to 31.0 mg/kg po.

Experimental Section[6]

The preparative method A is represented in an experiment as follows.

2-Methyl-3-[3-(4-phenyl-1-piperazinyl)propyl]-4(3H)-quinazolone (2).—A mixture of 2-methyl-4-oxo-4H-3,1-benzoxazine (16.1 g, 0.1 mole) and 4-(3-aminopropyl)-1-phenylpiperazine (21.9 g, 0.1 mole) was heated at 175–180° in a wax bath for 1 hr and dissolved in MeOH. The MeOH solution was treated with dry HCl to give a salt, yield 36.8 g. The salt was recrystallized (aqueous MeOH–HCl), yield 32.9 g, mp 250–251°. A 5-g sample of the salt was converted to the free base, yield 3.9 g. The free base was recrystallized (aqueous AcMe), mp 104–105°.

Method B is exemplified in the following experiment.

4-[3-(2-Amino-5-chlorobenzamido)propyl]-1-phenylpiperazine.—To 1-(3-aminopropyl)-4-phenylpiperazine (87.6 g, 0.4 mole) in 100 ml of C_6H_6 was added 6-chloroisatoic anhydride (79.0 g, 0.4 mole); the mixture was heated on a steam bath for 1 hr after CO_2 evolution had subsided. About 250 ml of Et_2O was added to the mixture and the insoluble solid was collected, yield 132.9 g (92.8%), mp 184–150°. A sample was recrystallized (aqueous DMF), mp 152–155°.

6-Chloro-2-phenyl-3-[3-(4-phenyl-1-piperazinyl)propyl]-4(3H)-quinazolone (16).—A suspension of 4-[3-(2-amino-5-chlorobenzamido)propyl]-1-phenylpiperazine (52 g, 0.14 mole) in 500 ml of $CHCl_3$ was treated with C_6H_5COCl (19.8 g, 0.14 mole) as usual to give the corresponding benzamide of mp 199.5–200.5°, yield 43.8 g. The above benzamide (43.8 g, 0.092 mole) in 250 ml of Ac_2O was refluxed for 16 hr. The solvent was removed *in vacuo* and the residue was crystallized (aqueous AcMe), mp 126–131°.

(6) All melting points are corrected and were determined with a Büchi melting point apparatus. Ir spectra were determined with a Perkin-Elmer Model 237 spectrophotometer. Titrations were carried out with a Sargent Model D recording titrator. All analytical samples had ir spectra compatible with their assigned structures. The analytical samples gave values for C, H, N, and HCl within 0.4% of the theoretical values.

meta-Substituted Benzenesulfonylureas as Hypoglycemic Agents

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The literature during the past decade on the synthesis and hypoglycemic activity of substituted benzenesulfonylureas is very extensive but contains very few *meta*-(mono)substituted derivatives.[2,3] The present note describes the synthesis and screening for hypoglycemic activity of such *meta*-substituted benzenesulfonylureas wherein the substituents are Cl, F, Me, or CF_3. These have been obtained by the treatment of the corresponding *meta*-substituted benzenesulfonylthioureas with H_2O_2 under alkaline conditions.[4] The sulfonylthioureas were synthesized by the interaction of the benzenesulfonamides and appropriate isothiocyanates in Me_2CO under alkaline conditions.[5] The requisite benzenesulfonamides were prepared from the benzenesulfonyl chlorides which in turn were obtained by diazotization of the corresponding anilines followed by the action of SO_2 in glacial AcOH.[6]

The relevant data for new *meta*-substituted benzenesulfonylthioureas and the sulfonylureas are given in Tables I and II, respectively.

Pharmacology.—All the benzenesulfonylureas have been evaluated for their hypoglycemic activity in normal healthy rabbits. The animals were fasted 18–20 hr prior to the oral administration of 50 mg/kg of the test compounds. Blood sugar was estimated by Somogyi's method[7] using Nelson's reagent[8] and the activity at different intervals up to 7 hr is given in Table II as per cent change in blood sugar.

Twelve out of 21 compounds were almost inactive. Significant activity was shown by three compounds (**34**, **41**, and **45**), and in all these three compounds R′ was *n*-propyl. The order of activity in relation to the substituent R was $CH_3 > Cl > F > CF_3$ while that with regard to the alkyl group R′ was $n\text{-}C_3H_7 > i\text{-}C_3H_7 > C_6H_{11} > n\text{-}C_4H_9 > i\text{-}C_4H_9 > C_2H_5 > CH_2CH{=}CH_2$.

N-*m*-Tolylsulfonyl-N′-*n*-propylurea (**41**) was found to be the most potent in the series, showing blood sugar reduction of 22.0% in rabbits and of 30.4% in rats after 5 hr. It was also tested along with tolbutamide at 25 and at 100 mg/kg in both species and was found to be slightly less potent than tolbutamide. Crossover tests confirmed this. The LD_{50} (oral) in albino mice for **41** was 2.0 g/kg (for tolbutamide 2.6 g/kg).

Experimental Section[9]

***m*-Chlorobenzenesulfonamide.**—*m*-Chloroaniline (25.5 g, 0.2 mole) in 80 ml of concentrated HCl and 200 ml of H_2O was diazotized with $NaNO_2$ (18 g in H_2O, 50 ml) at 0–5°. This diazotized solution was slowly added with stirring to 200 ml of saturated (30%) SO_2 solution in glacial AcOH containing $CuCl_2$ (4 g) and concentrated HCl (15 ml) at 5–10°. The mixture was stirred for 30 min and was allowed to stand for 3 hr at room temperature. The oily layer of *m*-chlorobenzenesulfonyl chloride was then separated and added to 200 ml of 25% NH_4OH. It was stirred for 3 hr and left overnight. Excess NH_3 was then removed by heating on a water bath. The solid that separated on cooling was filtered off and crystallized (H_2O), 12.6 g (33%), mp 145–146° (lit.[10] mp 148°). *Anal.* ($C_6H_6ClNO_2S$) N.

Similarly prepared were *m*-fluorobenzenesulfonamide in 22.3% yield, mp 131–133° (lit.[11] mp 129–130°); *m*-tolylsulfonamide in 33.4% yield, mp 111–112° (lit.[12] mp 108°); and *m*-(α,α,α-trifluoromethyl)benzenesulfonamide in 49% yield, mp 123° (lit.[13] mp 121–122°).

N-*m*-Fluorobenzenesulfonyl-N′-*n*-propylthiourea (10).—*m*-Fluorobenzenesulfonamide (3.5 g, 0.02 mole) was dissolved in Me_2CO (35 ml). To this solution were added aqueous NaOH (0.8 g in 5 ml) and *n*-propyl isothiocyanate (2.45 ml, 0.024 mole) and the mixture was refluxed for 3 hr. The solvent was then removed and the residue was diluted with H_2O (50 ml). The solution was decolorized, filtered, acidified with HCl, and crystallized to obtain the desired compound.

All the benzenesulfonylthioureas were prepared by the above procedure and are listed in Table I.

(1) To whom communications regarding this publication should be addressed.

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