temperature overnight. The product was extracted from the reaction mixture with CH_2Cl_2; yield 45%, mp 191–192° after two recrystallizations from aqueous acetone (lit.[8a] mp 191–192°).

5,5-Diphenyl-3-methyl-4-methyleneoxazolidone (XII).—1,1-Diphenyl-2-propynyl N-methylcarbamate (10 g, 0.04 mole) and 0.22 mole of NaOEt in 150 ml of ethanol were refluxed for 2 hr. After cooling, the reaction mixture was diluted with H_2O and extracted with ether. After drying ($MgSO_4$), the ether was distilled. A fraction, bp 148–158° (0.05 mm), was recrystallized from petroleum ether (bp 60–71°) giving 7.7 g (66%) of white solid: mp 92–94°; nmr, 181 (3 H, singlet, NCH_3), 250 (1 H, doublet, J = 3 cps), 269 (1 H, doublet, J = 3 cps), 441 cps (10 H, multiplet).

Anal. Calcd for $C_{17}H_{15}NO_2$: N, 5.28. Found: N, 5.13.

Treatment of Ia with NaOH in Aqueous Ethanol.—An ethanolic solution of 5 g (0.02 mole) of Ia and 20 ml of 20% NaOH was refluxed 3.5 hr. After diluting with H_2O, the mixture was extracted with ether, and the ether was dried and distilled. The product, bp 117–118° (0.3 mm), 2.7 g (68%), was identical with an authentic sample of 1,1-diphenyl-2-propyn-1-ol (infrared, nmr).

Treatment of Ia with Sodium Methoxide in Ethanol.—An ethanolic solution of 0.04 mole of Ia and 0.02 mole of NaOEt was stirred 16 hr at 20°. After isolation as described above, 7 g of distillate, identified as 1,1-diphenyl-2-propyn-1-ol, was obtained.

Reaction of Ia with Sodium.—A xylene dispersion of Na (1.4 g, 0.06 mole) and 5 g (0.02 mole) of Ia were stirred at 25° for 16 hr. The excess Na was decomposed with ethanol (25 ml), and H_2O was added. The organic layer was separated and dried, and the solvent was removed at reduced pressure. An oily residue (4 g) remained (infrared and nmr spectra identical with those of 1,1-diphenyl-2-propyn-1-ol). Water was removed from the aqueous layer; the residue was a mixture of NaOH and NaCNO (strong band at 4.5 μ in the infrared spectrum).

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Some 2,3,6,8-Tetrasubstituted Quinazolone Hydrazides as Monoamine Oxidase Inhibitors[1a]

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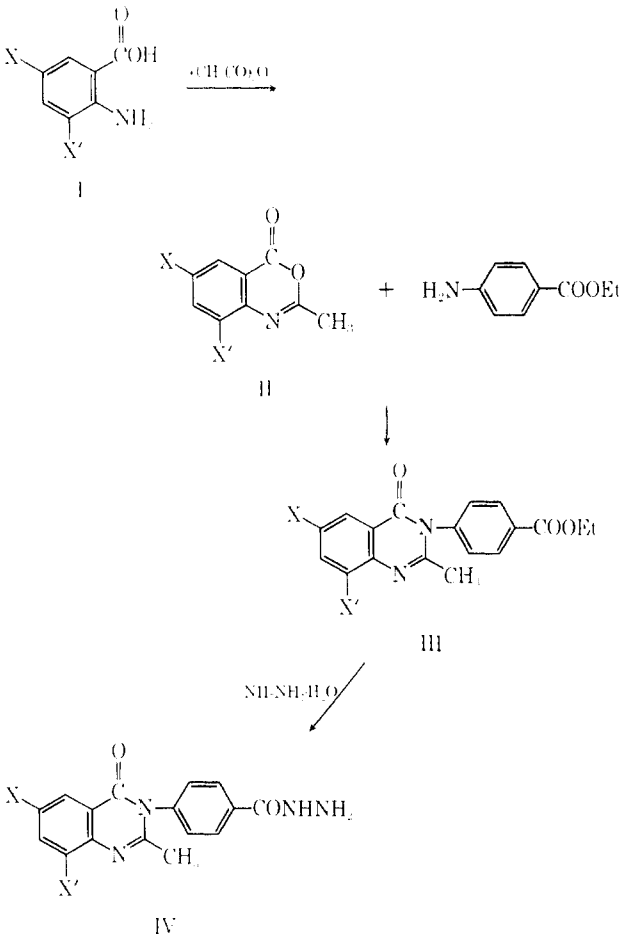
Inhibitors of monoamine oxidase (MAO) have been shown to possess pronounced anticonvulsant properties.[2] The effectiveness of 2-methyl-3-(4-benzhydrazide)-4-quinazolone in inhibiting this enzyme was found to be significantly increased by the introduction of a substituent at position 6 of the quinazolone nucleus.[3] For that reason, corresponding 2-methyl-3-(4-benzhydrazide)-4-quinazolones with substituents at positions 6 and 8 have now been synthesized as potential hypnotics and anticonvulsants.[4,5] In the present study, attempts have also been made to investigate the role of such substituents on the ability of quinazolone hydrazides to inhibit rat liver MAO. The quinazolone hydrazides have been synthesized according to Scheme I (X or X′ = H, Cl, Br, or I).

SCHEME I



Experimental Section[6]

Anthranilic Acids (I).—Substituted anthranilic acids were synthesized according to the methods reported in the literature. The anthranilic acids used were 3,5-dichloro-,[7] 3,5-dibromo-,[8] and 3,5-diiodoanthranilic acids.[9]

Acetanthranils (II).—Appropriate anthranilic acids (1 mole) were refluxed with Ac_2O (2 moles) for 1 hr. After excess Ac_2O was distilled, the acetanthranils separated as solid masses and were used without further purification. 3,5-Dibromoacetanthranil had been reported earlier.[10] **3,5-Dichloroacetanthranil,** mp 145–146°, and **3,5-diiodoacetanthranil,** mp 185–187°, were obtained in 80 and 70% yields, respectively.

Anal. Calcd for $C_9H_5Cl_2NO_2$: C, 46.9; H, 2.2; N, 6.1. Found: C, 46.7; H, 2.0; N, 5.9.

Anal. Calcd for $C_9H_5I_2NO_2$: C, 26.2; H, 1.2; N, 3.4. Found: C, 25.9; H, 1.5; N, 3.2.

(1) (a) The authors wish to express their thanks to Dr. Sabit Gabay and Dr. J. P. Barthwal for their advice and encouragement and to Dr. M. L. Dhar and Dr. Nitya Anand from Central Drug Research Institute, Lucknow, for providing facilities for microanalysis. Grateful acknowledgment is made to the Council of Scientific and Industrial Research, New Delhi, for providing financial assistance. (b) Visiting Scientist, Biochemical Reseach Laboratory, Boston University, Veterans Administration Hospital, Brockton, Mass. (May–Aug 1965). (c) Senior Research Fellow of the Council of Scientific and Industrial Research, New Delhi.

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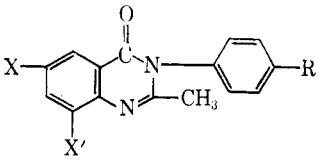
TABLE I

2,3,6,8-TETRASUBSTITUTED QUINAZOLONES AND QUINAZOLONE HYDRAZIDES



X	X′	R	Mp, °C	Yield, %	Formula	Nitrogen, % Calcd	Nitrogen, % Found	MAO inhib,[a] %
Cl	Cl	$COOC_2H_5$	235	45	$C_{18}H_{14}Cl_2N_2O_3$	7.4	7.1	...
Br	Br	$COOC_2H_5$	250–252	55	$C_{18}H_{14}Br_2N_2O_3$	6.0	6.1	...
I	I	$COOC_2H_5$	175	40	$C_{18}H_{14}I_2N_2O_3$	5.0	5.5	...
Cl	Cl	$CONHNH_2$	220	50	$C_{16}H_{12}Cl_2N_4O_2$	15.4	15.3	31.4
Br	Br	$CONHNH_2$	238–240	55	$C_{16}H_{12}Br_2N_4O_2$	12.3	12.5	27.4
I	I	$CONHNH_2$	180	50	$C_{16}H_{12}I_2N_4O_2$	10.2	10.0	23.7

[a] The per cent inhibition was calculated from the decrease in the oxygen uptake during a 1-hr period. Assay procedure and the vessel contents are as described earlier.[3] Rat liver mitochondria, equivalent to 250 mg of fresh tissue, were used in each Warburg vessel. Quinazolone hydrazides were used at a final concentration of 3×10^{-4} *M*. Each experiment was done in duplicate, and the values are the mean of three separate experiments. The quinazolone hydrazides present in the side arm were incubated with enzyme preparation for 10 min before tyramine (10 m*M*) was added from the other side arm. The enzyme system was further incubated at 37° for 1 hr under O_2.

Quinazolones (III).—Equimolar proportions of the appropriate acetanthranils and *p*-aminoethyl benzoate (benzocaine) were heated for the synthesis of quinazolones.[3] The quinazolones shown in Table I are characterized by their sharp melting points and by analyses.

Quinazolone Hydrazides (IV).—A mixture of 1 mole of the appropriate quinazolone, 2 moles of hydrazine hydrate (99–100%), and absolute ethanol was refluxed for 6–8 hr for the synthesis of quinazolone hydrazides.[3] On distilling the ethanol, the hydrazides separated as solid masses and were recrystallized from ethanol. The physical constants are given in Table I.

Determination of Monoamine Oxidase Activity.—The MAO activity of rat liver mitochondria was determined by the conventional Warburg manometric method described earlier.[11] Mitochondria were isolated by differential centrifugation of rat liver homogenate in ice-cold 0.25 *M* sucrose (10% w/v), and the enzyme activity was determined by measuring the oxygen uptake using tyramine as the substrate.

The inhibitory effects of the 4-quinazolone hydrazides on rat liver mitochondrial MAO during oxidative deamination of tyramine are shown in Table I. Oxygen uptake, as an index of MAO activity, has been shown to reveal true activity of the enzyme in washed mitochondrial preparations.[11] The use of cyanide and semicarbazide as suggested earlier[12] was, therefore, not necessary in the present experiments. All 2-methyl-3-(4-benzhydrazide)-4-quinazolones, used at a final concentration of 3×10^{-4} *M* to determine relative percentage of enzyme inhibition, were found to inhibit MAO. Maximum inhibition was observed with the hydrazide derived from 3,5-dichloroanthranilic acid. Inhibition of 2,3,6,8-tetrasubstituted quinazolone hydrazides, although found to be greater than 2-methyl-3-(4-benzhydrazide)-4-quinazolone (11.3%), was significantly lower than that reported for 2,3,6-trisubstituted derivatives (6-chloro-, 60.3%; 6-bromo-, 52.6%; 6-iodo-, 75%) under similar experimental conditions.[3] These results are felt to provide further evidence of the existence of primary and secondary sites on the enzyme molecule which are essentially involved in the formation of an enzyme–substrate and enzyme–inhibitor complex.[11] At present, it is difficult to provide a suitable explanation for decrease in the inhibitory effects of 2,3,6-trisubstituted quinazolone hydrazides on the introduction of an additional substituent at position 8 of the quinazolone nucleus. The competition between the substituents at positions 6 and 8 for the active site(s) on the enzyme molecule may presumably account for the lowering of their inhibitory effects. However, our further detailed biochemical investigation on purified, soluble enzyme preparations[13] and the synthesis of other related structures carrying substituents at different positions may provide a suitable explanation for the inhibitory effects of quinazolone hydrazides.

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2-Thio-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2H-benzo[*a*]quinolizines

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As part of an investigation of sulfur-containing derivatives of biologically active ketones, several 2-thio-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2H-benzo[*a*]quinolizines have been prepared (Tables I and II). The thio derivatives were isolated as their hydrochloride salts by reaction of either 1,3,4,6,7,11b-hexahydro-3-isobutyl-9,10-dimethoxy-2H-benzo[*a*]quinolizin-2-one hydrochloride[1] (tetrabenazine hydrochloride) or 1,3,4,6,7,11b-hexahydro-3-(N,N-diethylcarboxamido)-9,10-dimethoxy-2H-benzo[*a*]quinolizin-2-one hydrochloride[2] with hydrogen sulfide (Table I, **1** and **2**) or with the appropriate thiol (Table II, **3**–**10**) in ethanolic HCl.[3]

Pharmacology.—The compounds were tested for CNS depressant properties (Table III). The most active member of the series is 2,2-bis(methylthio)-1,3,4,6,7,11b-hexahydro-3-isobutyl-9,10-dimethoxy-2H-benzo[*a*]quinolizine hydrochloride (**3**), the therapeutic index of which compares very favorably with that of tetrabenazine.

Experimental Section[4]

2-Thio-3-isobutyl- and 2-Thio-3-(N,N-diethylcarboxamido)-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2H-benzo[*a*]quinolizine Hydrochloride.—The ketone hydrochloride (6.0 g) was dissolved in saturated EtOH–HCl (300 ml) and H_2S was bubbled through the stirred solution at 0° for 5 hr. The reaction mixture was allowed to stand at room temperature for 2 days and con-

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