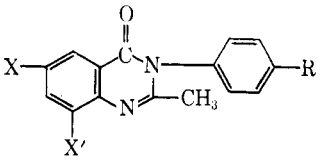
TABLE I

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.

(11) S. S. Parmar, *Biochem. Pharmacol.*, **15**, 1497 (1966).
(12) N. H. Creasey, *Biochem. J.*, **64**, 178 (1956).
(13) S. S. Parmar, R. C. Arora, and S. Gabay, in preparation.

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.

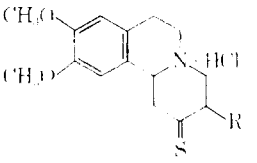
Experimental Section[4]

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-

(1) A. Brossi, H. Lindlar, M. Walter, and O. Schnider, *Helv. Chim. Acta*, **41**, 119 (1958).
(2) J. R. Tretter, Belgian Patent 618,741 (1962).
(3) S. K. Mitra, *J. Indian Chem. Soc.*, **10**, 71 (1933).
(4) Melting points were taken on a Thomas–Hoover capillary melting point apparatus and are corrected. Elemental analyses were performed by Mr. O. Kolsto and his associates in the analytical department of Abbott Laboratories.

TABLE I

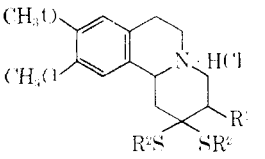
2-THIO-1,3,4,6,7,11b-HEXAHYDRO-9,10-DIMETHOXY-2H-BENZO[*a*]QUINOLIZINE HYDROCHLORIDES



No.	R	Mp, °C	Yield, %	Formula	Calcd, % C	H	N	S	Found, % C	H	N	S
1	$CH_2CH(CH_3)_2$	216–217	73.3	$C_{19}H_{27}NO_2S \cdot HCl$	61.7	7.6	3.8	8.7	61.5	7.5	3.8	8.8
2	$CON(C_2H_5)_2$	176–178	35.8	$C_{20}H_{28}N_2O_3S \cdot HCl$	58.2	7.1	6.8	7.9	58.4	7.0	6.9	7.8

TABLE II

2,2-BIS(ALKYLTHIO)- AND 2,2-BIS(ARYLTHIO)-1,3,4,6,7,11b-HEXAHYDRO-9,10-DIMETHOXY-2H-BENZO[*a*]QUINOLIZINE HYDROCHLORIDES



No.	R^1	R^2	Mp, °C	Yield, %	Formula	Calcd, % C	H	N	S	Found, % C	H	N	S
3	$CH_2CH(CH_3)_2$	CH_3	226–227	86.4	$C_{21}H_{33}NO_2S_2 \cdot HCl$	58.4	7.9	3.2	14.8	58.2	8.2	3.3	15.0
4	$CON(C_2H_5)_2$	CH_3	197–200	99.4	$C_{22}H_{34}N_2O_3S_2 \cdot HCl$	55.6	7.4	5.9	13.5	55.8	7.4	5.9	13.4
5	$CH_2CH(CH_3)_2$	C_2H_5	222–224	98.0	$C_{23}H_{37}NO_2S_2 \cdot HCl$	60.0	8.3	3.0	13.9	60.2	8.4	3.1	14.1
6	$CON(C_2H_5)_2$	C_2H_5	177–179	85.9	$C_{24}H_{38}N_2O_3S_2 \cdot HCl$	57.3	7.8	5.6	12.7	57.1	8.0	5.3	12.8
7	$CH_2CH(CH_3)_2$	$(CH_2)_3CH_3$	171–173	78.1	$C_{27}H_{45}NO_2S_2 \cdot HCl$	62.8	9.0	2.7	12.4	62.8	9.3	2.5	12.2
8	$CH_2CH(CH_3)_2$	$CH_2CH{=}CH_2$	142–145	74.0	$C_{25}H_{37}NO_2S_2 \cdot HCl$	62.0	7.9	2.9	13.3	62.2	8.0	2.7	13.4
9	$CH_2CH(CH_3)_2$	C_6H_5	216–218	46.3	$C_{31}H_{37}NO_2S_2 \cdot HCl$	66.9	6.9	2.5	11.5	66.9	7.1	2.6	11.5
10	$CH_2CH(CH_3)_2$	CH_2CH_2OH	217–219	30.4	$C_{28}H_{37}NO_4S_2 \cdot HCl$	56.1	7.8	2.9	13.0	56.3	8.0	3.0	13.2

TABLE III[a]

Compd	Min dose (mg/kg) causing signif CNS depres[b] ip	Oral	Approx LD_{50}, mg/kg ip	Oral
1	100	100	500	1000
2	200	200	500	>1000
3	50	50	300	1000
4	200	200	200	500
5	100	100	500	>1000
6	50	200	300	500
7	100	100	500	500
8	300	1000	500	>1000
9	300	>1000	300	>1000
10	200	500	500	>1000
Tetrabenazine	50	300	500	750

[a] We are grateful to Mrs. I. M. Cole for biological data. [b] The minimum dose causing the same degree of loss of the spontaneous motor activity as an intraperitoneal dose of 20 mg/kg of pentobarbital.

centrated at reduced pressure. The 2-thio-3-isobutyl derivative was purified by trituration of the residue with water (50 ml) and reprecipitation of the solid thus obtained from MeOH with ether. The 2-thio-3-(N,N-diethylcarboxamido) compound (**2**) was obtained as a yellow solid on treatment of the residue with ether (50 ml) and recrystallized from EtOH.

2,2-Bis(alkylthio)- and 2,2-Bis(arylthio)-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2H-benzo[*a*]quinolizine Hydrochlorides.—A solution of the ketone hydrochloride (5.0 g) and the appropriate thiol (50 ml) in saturated EtOH–HCl (250 ml) was allowed to stand at room temperature for 2 days and then concentrated at reduced pressure. The water-insoluble 3-isobutyl derivatives (**3**, **5**, and **7**–**10**) were purified by trituration of the residue with water (50 ml) and recrystallization of the solid thus obtained from benzene or benzene–ether mixtures. 3-(N,N-Diethylcarboxamido) compounds (**4** and **6**) were recrystallized from EtOH.

Infrared Data.—The infrared absorption spectra[5] were in full accordance with the proposed structures. The ketone C=O stretching bands present at 1720 cm^{-1} in the spectrum of tetrabenazine hydrochloride and at 1730 cm^{-1} in that of 1,3,4,6,7,11b-hexahydro-3-(N,N-diethylcarboxamido)-9,10-dimethoxy-2H-benzo[*a*]quinolizin-2-one hydrochloride were not present in the spectra of the products **1**–**10**. The amide C=O stretching band at about 1640 cm^{-1} was, however, present in the spectra of the compounds with the carboxamido substituent (**2**, **4**, **6**).

Biological Data.—The compounds were administered as 2% suspensions in 3% tragacanth to albino Swiss–Webster mice by both intraperitoneal and oral routes.

(5) Determined as Nujol mulls by Mr. W. Washburn.

Some 2,6-Methanonaphth[1,2-*d*]azocines

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The development by May and co-workers of a convenient synthesis of the benzomorphan or, more properly, the 2,6-methano-3-benzazocine ring system[1] has made possible the synthesis of compounds exhibiting a variety of biological activities. In an attempt to improve certain parameters, some 2,6-methanonaphth[1,2-*d*]azocines were prepared by the same route.

Both the *cis* isomer **3** with 6-quasi-equatorial (with respect to the hydroaromatic ring) and 13-axial methyl groups and the *trans* isomer **4** with 6-quasi-equatorial and 13-equatorial methyl groups were obtained. These could be separated by recrystallization or chromatography on silica. Addition of the dihydropyridine **1**

(1) E. L. May and E. M. Fry, *J. Org. Chem.*, **22**, 1366 (1957); N. B. Eddy, J. G. Murphy, and E. L. May, *ibid.*, **22**, 1370 (1957). The synthetic route was originally developed by R. Grewe and A. Mondon [*Chem. Ber.*, **81**, 279 (1948)] for the morphinans.