this case the alkylated 6- or 7-hydroxy-5,8-quinolinequinones were generally purified by crystn from Et_2O–hexane. Purification by salt formation was not necessary. The melting points and yields of the new quinolinequinone derivatives are listed in Table I and II along with their corresponding antimalarial activity. Pmr spectra for these new derivatives were consistent with the proposed structures.

1,2,3,4-Tetrahydro-7-*n*-tetradecyl-6-hydroxy-5,8-quinolinequinone.—7-*n*-Tetradecyl-6-hydroxy-5,8-quinolinequinone (500 mg) in EtOH (100 ml) was reduced (PtO_2) with the Parr hydrogenator at an initial pressure of 3.1 kg/cm^2. After 6 hr, the reaction mixt was filtered (Celite); the filtrate was air oxidized for several hr and then evapd *in vacuo* to a purple solid. Repeated recrystn from Et_2O–$CHCl_3$–EtOH yielded purple crystals (400 mg, 79% yield): mp 136–137°; R_f 0.16 (Et_2O–hexane, 1:1), 0.65 (Et_2O); pmr absorptions 6.27 (m, 1 H), 6.61 (t, 2 H), 7.60 (m, 4 H), 8.17 (t, 3 H), 8.75 (s, ≅24 H), and 9.12 (m, 3 H).

1,2,3,4-Tetrahydro-7-ω-cyclohexyloctyl-6-hydroxy-5,8-quinolinequinone.—7-ω-Cyclohexyloctyl-6-hydroxy-5,8-quinolinequinone (1 g) in EtOH (100 ml) was reduced (PtO_2) with the Parr hydrogenator. After 4 hr the reaction mixt was filtered (Celite); the filtrate was air oxidized for several hr and then evapd *in vacuo*. The purple solid was repeatedly recrystd from EtOH–$CHCl_3$ to yield purple crystals (750 mg, 74% yield): mp 158–159°; R_f 0.18 (Et_2O), 0.83 (ether–ethanol, 1:1); pmr absorptions 6.58 (t, 2 H), 7.58 (q, 4 H), and 8.0–9.0 (m, ≅27 H).

Acknowledgments.—Appreciation is expressed to the U.S. Army Medical Research and Development Command. Their contract No. DADA 17-69-C-9067 contributed to the support of this research. This is Contribution No. 924 from the Army Research Program on Malaria.

Schistosomicides. 1.[1] Derivatives of 2-Aminomethyl-1,2,3,4-tetrahydroquinoline

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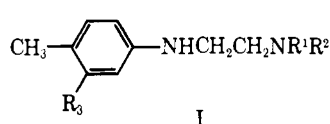
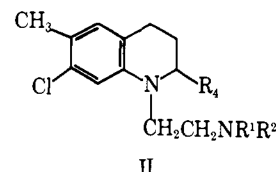
Received February 3, 1971

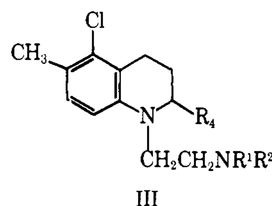
The synthesis and structure–activity relationships of a novel series of schistosomicidal 2-aminomethyl-1,2,3,4-tetrahydroquinoline derivatives (V) are described. The activity pattern of these conformationally constrained compounds is compared with that of the mirasan series of schistosomicides (I). Thus, in mice, for I decreasing activity is in the order R^3 = halogen, CN, and NO_2, whereas in V the reverse is the case, and an explanation based on lipophilicity considerations is proposed. The isomeric series VI is devoid of activity whereas members of series V display marked activity in single oral doses against *Schistosoma mansoni*, especially **10**, 2-*N*-isopropylaminomethyl-6-methyl-7-nitro-1,2,3,4-tetrahydroquinoline [V; R^1 = H; R^2 = $CH(CH_3)_2$; R^3 = NO_2]; the dextro form of **10** was the more active enantiomer. Members of series V show a distinct advantage over the mirasan series in that they display activity against *S. mansoni* in monkeys; thus, **10** is active in a single oral dose of 50 mg/kg. It is metabolized in mouse and monkey to the corresponding 6-hydroxymethyl derivative, 6-hydroxymethyl-2-*N*-isopropylaminomethyl-7-nitro-1,2,3,4-tetrahydroquinoline [XX&III; R^1 = H; R^2 = $CH(CH_3)_2$; R^3 = NO_2], which has been shown to be curative in monkeys in single im doses of 5–7.5 mg/kg.

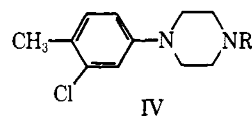
Several examples are known in which structural modification of a biologically active compound has yielded analogs of constrained molecular conformation without consequent loss of biological activity, and a study of such compounds has provided useful information regarding structure–activity relationships.[2] 1-Substituted tetrahydroquinolines[3,4] (II and III) and 1-phenylpiperazines[5] (IV), may be regarded as examples of constrained molecules which retain the schistosomicidal activity displayed by the prototype mirasan series[3] (I), of which mirasan (I; $R^1 = R^2 = C_2H_5$; R^3 = Cl) is the parent member.

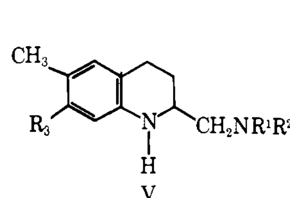
As an extension of this principle, we have synthesized 2-aminomethyltetrahydroquinolines of type V and VI which represent a new class of cyclic analogs of series I. A prime objective was the development of novel agents that would display worthwhile activity against schistosome infections in primates, since this is a property which is lacking in the earlier series I–IV.[4,6]

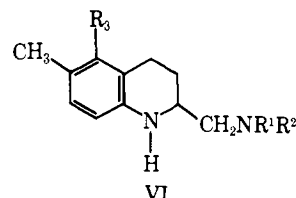












Chemistry.—The following general account describes the main methods of synthesis; the particular synthesis employed for each individual compound is indicated in the appropriate table.

(1) **Nitro Compounds.**—Three synthetic routes that have been used to prepare the key precursor XIII are

(1) A preliminary paper describing these compds has appeared: H. C. Richards and R. Foster, *Nature (London)*, **222**, 581 (1969).

(2) R. B. Barlow, "Introduction to Chemical Pharmacology," 2nd ed, Wiley, New York, N. Y., 1964.

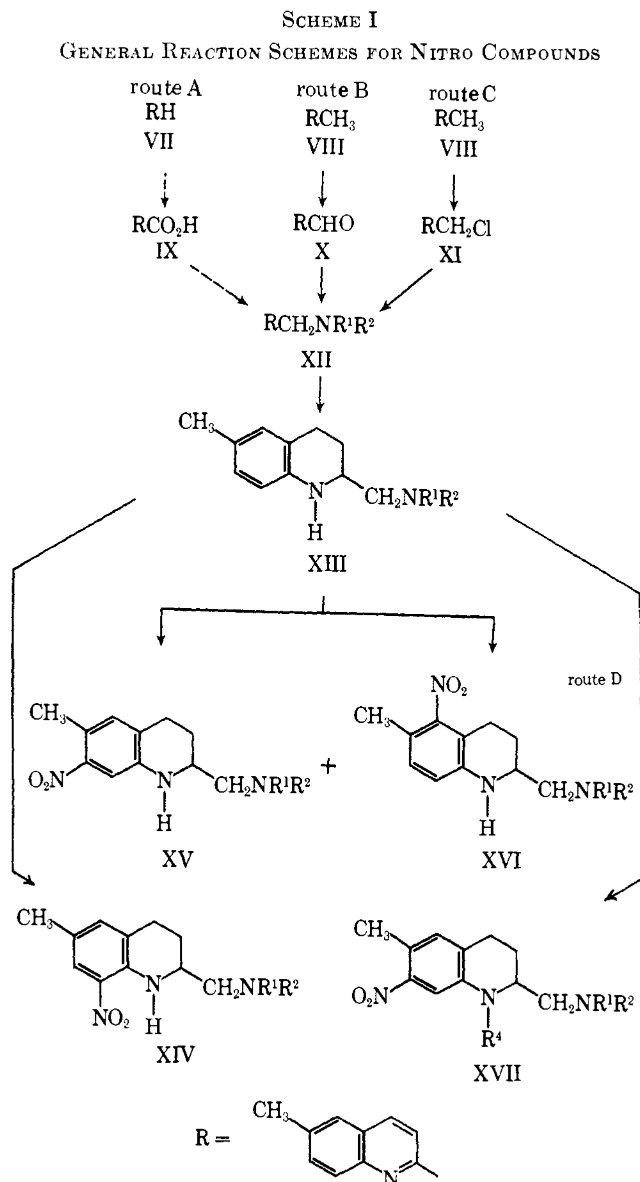
(3) H. Mauss, H. Kölling, and R. Gönnert, *Med. Chem., Abhandl. Med. Chem. Forschungsstaetten Farbenfabriken Bayer*, **5**, 185 (1956).

(4) R. Gönnert, *Bull. W. H. O.*, **25**, 702 (1961).

(5) Hoechst, U. S. Patent, 2,830,056 (1958); *Chem. Abstr.*, **53**, 3253d (1959).

(6) O. D. Standen in "Experimental Chemotherapy," R. J. Schnitzer and F. Hawking, Ed., Vol. I, Academic Press, London, p 773 1963.

SCHEME I
GENERAL REACTION SCHEMES FOR NITRO COMPOUNDS



outlined in Scheme I. Following the initially used route A, 6-methylquinoline (VII) was converted to the Reissert derivative[7] which on hydrolysis with HBr in AcOH gave 6-methylquinoline-2-carboxylic acid[8] (IX). The acid chloride of IX, prepared with PCl_5 in PhMe, was treated *in situ* with the appropriate amine to give the corresponding amide, and subsequent reduction with LAH gave the desired quinoline amine contaminated with ring-reduced material.[9] Hydrogenation of the crude mixture over Raney Ni to the 1,2,3,4-tetrahydroquinoline derivative XIII, followed by nitration in concd H_2SO_4 gave the expected[10] 7 isomer XV plus a minor proportion of the 5 isomer XVI. Separation of the isomers was achieved by fractional distillation, column chromatography, or, more conveniently, by fractional crystallization of the free base or a suitable salt derivative, *e.g.*, hydrochloride or hydrogen maleate. The biologically inactive 5-nitro isomer was always the minor isomer and was frequently discarded with the crystallization mother liquors. Each isomer was identified by means of its nmr spectrum, that of XV showing 2 apparent singlets and that of XVI showing an AB quartet in the aromatic region.

Nitration of XIII in glacial AcOH gave the 8 isomer XIV, a consequence of nonprotonation of the heterocyclic N.

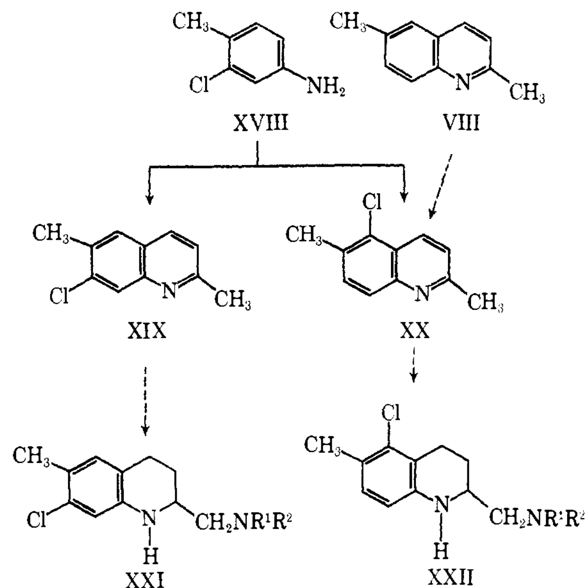
Route B was also employed but was restricted to providing XV and XVI in which R^1 = H since a primary amine was required[11] in the reductive amination step from the aldehyde[12] X, produced by SeO_2 oxidation of VIII.

The most versatile and convenient route was route C in which 2,6-dimethylquinoline (VIII) was selectively monochlorinated[13] with Cl_2 in CCl_4 containing Na_2CO_3, and the chloromethyl product XI was aminated to give XII. In this last step, it was necessary to use a large excess of amine when this was a *primary* amine, in order to prevent formation of bis(quinolinyl) product.

A number of 1-alkyl derivatives of type XVII were prepared by acylation of XIII, followed by LAH reduction and subsequent nitration in H_2SO_4, (route D).

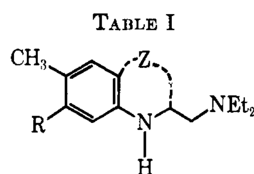
(2) **Chloro Compounds.**—The synthetic routes for preparing members of the 5- and 7-chloro series XXI and XXII, resp, are indicated in Scheme II. 3-Chloro-4-methylaniline (XVIII) underwent the Doebner-Miller reaction[14] to give a mixture of the quinaldines XIX and XX. Fractional distillation gave pure XIX but the isomer XX was difficult to purify; it was prepared better[15] from 2,6-dimethylquinoline (VIII) by nitration, which occurs exclusively in the 5 position, followed by reduction with $SnCl_2$, diazotization of the

SCHEME II
GENERAL REACTION SCHEMES FOR CHLORO COMPOUNDS



(7) F. D. Popp, W. Blount, and P. Melvin, *J. Org. Chem.*, **26**, 4930 (1961).
(8) J. W. Davis, *ibid.*, **24**, 1691 (1959).
(9) C. E. Kaslow and W. R. Clark, *ibid.*, **18**, 55 (1953), suggested that reduction of the hetero ring occurred during LAH reduction of ethyl quinoline-2-carboxylate.
(10) M. Kulka and R. H. F. Manske, *Can. J. Chem.*, **30**, 720 (1952), showed that nitration of 1,2,3,4-tetrahydroquinoline gave the 7-nitro isomer exclusively.
(11) F. Zymalkowski, *Arch. Pharm. (Weinheim)*, **292**, 682 (1959).
(12) M. Seyhan and W. C. Fernelius, *J. Org. Chem.*, **22**, 217 (1957).
(13) W. Mathes and H. Schüly, *Angew. Chem., Int. Ed. Engl.*, **2**, 144 (1963).
(14) Bayer, British Patent, 758,570 (1956); *Chem. Abstr.*, **51**, 18009*f* (1957).
(15) D. M. Bowen, R. W. Belfit, and R. A. Walser, *J. Amer. Chem. Soc.*, **75**, 4307 (1953).

TABLE I



Compd[a]	R	πR^b	Z	πZ^c	$\Sigma\pi$	ED_{50}, mmoles/kg	Log $1/ED_{50}$ Obsd	Log $1/ED_{50}$ Estd form eq
A	Cl	0.98			0.98	71.2	−1.8525	−1.8258
B	NO_2	0.47			0.47	113.5	−2.0550	−2.0576
C	Cl	0.98	CH_2CH_2	0.62	1.60	261.0	−2.4166	−2.4140
D	NO_2	0.47	CH_2CH_2	0.62	1.09	68.2	−1.8338	−1.8605

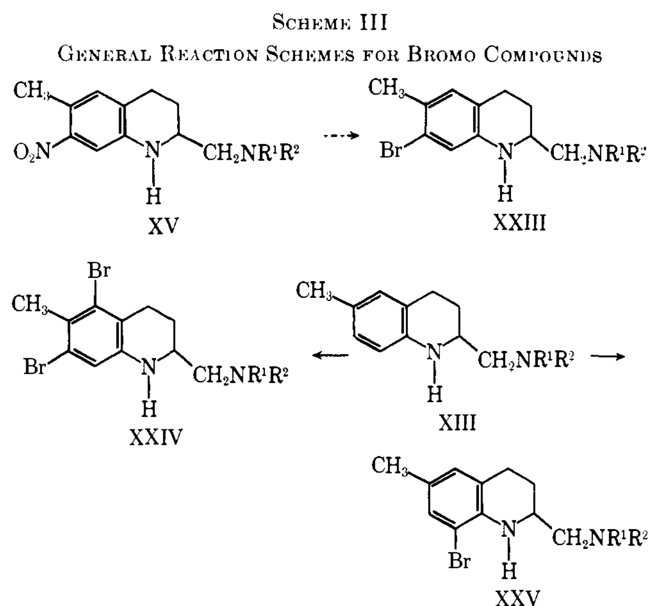
[a] Compds C and D are **32** and **3** in Tables III and II, resp. [b] πR values were taken from the aniline system; T. Fujita, J. Iwasa, and C. Hansch, *J. Amer. Chem. Soc.*, **86**, 5175 (1964). [c] πZ values were calcd using $\pi = 0.41$ for each cyclic CH_2 and deducting 0.20 to allow for a branch in the chain; C. Hansch, J. E. Quinlan, and G. L. Lawrence, *J. Org. Chem.*, **33**, 347 (1968).

5-amino compound, and Sandmeyer reaction. The quinaldines XIX and XX were converted to the corresponding tetrahydroquinolines XXI and XXII *via* the derived aldehyde as indicated in Scheme I (route B) or the 2-bromomethyl compound, obtained by $SnBr_2$ reduction of the corresponding 2-tribromomethyl compound.[16] Hydrogenolysis of the 5- or 7-chloro atom during hydrogenation of the hetero ring was an initial problem which was overcome by using dilute acidic solutions with a minimum of Pt catalyst.[17]

(3) **Bromo Compounds.**—7-Bromo compounds (XXIII) were prepared as indicated in Scheme III

SCHEME III

GENERAL REACTION SCHEMES FOR BROMO COMPOUNDS



from the corresponding 7-nitro compound XV by N-acylation (for protection during diazotization), catalytic reduction with Pd, Sandmeyer reaction, and hydrolysis of the *N*-Ac group(s). An attempt to prepare these compounds by bromination of XIII with "positive Br" ions[18] gave a mixture from which only the dibromo compound XXIV was isolated whereas bromination of XIII with Br_2 in CCl_4 gave the 8-bromo derivative XXV.

(4) **Miscellaneous compounds** were prepared by methods indicated in Tables I–IV.

(16) B. R. Brown, D. Ll. Hammick, and B. H. Thewlis, *J. Chem. Soc.*, 1145, (1951).

(17) M. Freifelder, W. B. Martin, G. R. Stone, and E. F. Coffin, *J. Org. Chem.*, **26**, 383 (1961).

(18) D. H. Derbyshire and W. A. Waters, *J. Chem. Soc.*, 573 (1950).

Screening Methods. Primary Screening.—Primary screening was undertaken in mice infected with an East African strain of *Schistosoma mansoni* and compounds in the form of their free bases or a salt derivative (*e.g.*, hydrochloride, *p*-toluenesulfonate, or hydrogen maleate) were administered orally either in a single dose or one dose daily for 4 consecutive days (see dose schedules in tables). Activity was assessed[19] by the hepatic shift method (the movement of adult worms from the mesenteric plexus to the intrahepatic vessels) 24 hr after the final dose. For some compounds, a dose-response curve was obtained to assess the ED_{50}, *i.e.*, the dose required to shift 50% of the mesenteric population to the liver.

Secondary Screening.—Secondary evaluation was undertaken in vervet monkeys (*Cercopithecus aethiops*) infected with the same strain of *S. mansoni* employed for rodents. Fecal egg output (initially 5000–10,000/24 hr) was determined[20] daily before and after treatment, and efficacy was judged by the reduction in egg load. Treatment was claimed as curative when the count fell to zero and remained so for several weeks.

Schistosomicidal Activity in Mice. Structure–Activity Relationships.—In the following discussion on structure–activity relationships, the biological effect produced by chemical modification at 3 regions of the tetrahydroquinoline molecule will be considered, *i.e.*, the benzene ring, the heterocyclic ring, and the side chain. Activity relates to assessments in mice against *S. mansoni* and is indicated in a qualitative manner in Tables II–V.

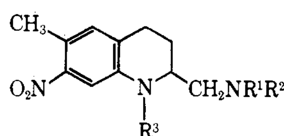
(1) **Substitution in the Benzene Ring.**—In the mirasan series (I), the electronegative substituent must be ortho to the Me group and, in keeping with this requirement,[3,4] 8-substituted derivatives of type XIV and XXV were inactive. Furthermore, the 5-substituted derivatives of type VI, listed in Table IV, were inactive, which contrasted with the usually high activity displayed by the 7 isomers, listed in Tables II and III, and these results indicate that in this region of the molecule a critical steric factor is operative. The positional specificity of the electronegative substituent in series II and III will be considered in a later paper.

As previously indicated,[1] a feature of interest regarding the 7 substituent in series V is that the order of decreasing activity is $NO_2 > CN > F > Cl > Br$ (*cf.*

(19) R. Foster, B. L. Cheetham, and E. T. Mesmer, *J. Trop. Med. Hyg.*, **71**, 139 (1968).

(20) D. R. Bell, *Bull. W. H. O.*, **29**, 525 (1963).

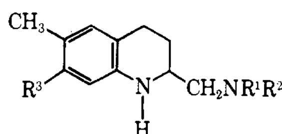
TABLE II



Compd	NR^1R^2	R^3	Oral activity[a] at 25 mg/kg (base equiv) × 4	Salt	Mp, °C	Formula	Analyses	Method of synthesis[b]
1	NH_2	H	−	Free base	133–135	$C_{11}H_{15}N_3O_2$	C, H[h]	E
2	$N(CH_3)_2$	H	−	HCl	246–248	$C_{13}H_{19}N_3O_2 \cdot HCl$	C, H, N	A
3	$N(C_2H_5)_2$	H	++	Free base	49–51	$C_{15}H_{23}N_3O_2$	C, H, N	C
4	$N(C_3H_7)_2$	H	−	2HCl	110 dec	$C_{17}H_{27}N_3O_2 \cdot 2HCl$	C, H	A
5	$N(CH_3)CH(CH_3)_2$	H	++	HCl	216–218	$C_{15}H_{23}N_3O_2 \cdot HCl$	C, H, N	C
6	$NHCH_3$	H	−	HCl	200–202	$C_{12}H_{17}N_3O_2 \cdot HCl$	C, H, N	A
7	NHC_2H_5	H	+++	HCl	244–248	$C_{13}H_{19}N_3O_2 \cdot HCl$	N	A
8	NHC_3H_7	H	++	HCl	232–235	$C_{14}H_{21}N_3O_2 \cdot HCl$	C, H[i]	A
9	NHC_4H_9	H	−	HCl	199–203	$C_{15}H_{23}N_3O_2 \cdot HCl$	C, H	A
10	$NHCH(CH_3)_2$	H	++++	Maleate	187–189	$C_{14}H_{21}N_3O_2 \cdot C_4H_4O_4$	C, H, N	A, B, or C
11	$NHC(CH_3)_3$	H	+++	Free base	63–68	$C_{15}H_{23}N_3O_2$	C, H, N	B
12	$NHCH(CH_3)C_2H_5$	H	++	HCl	226	$C_{15}H_{23}N_3O_2 \cdot HCl$	C, H, N	B
13	$NHCH_2CH(CH_3)_2$	H	+	HCl	244–246	$C_{15}H_{23}N_3O_2 \cdot HCl$	C, H, N	B
14	$NHCH_2C(CH_3)_3$	H	−	1.5HCl	192–194	$C_{16}H_{25}N_3O_2 \cdot 1.5HCl$	C, H, N	B
15	$NHCH_2CH_2N(C_2H_5)_2$	H	−	3HCl	172–175	$C_{17}H_{28}N_4O_2 \cdot 3HCl$	C, H,	A
16	$NHCH_2C_6H_5$	H	−	HCl	199–201	$C_{18}H_{21}N_3O_2 \cdot HCl$	C, H	F
17	NHC_3H_5[c]	H	+++	Maleate	172–173	$C_{14}H_{19}N_3O_2 \cdot C_4H_4O_4$	C, H, N	C
18	NHC_6H_{11}[d]	H	−	Free base	84–86	$C_{17}H_{25}N_3O_2$	C, H, N	C
19	$C_5H_{10}N$[e]	H	−	Free base	102–104	$C_{16}H_{23}N_3O_2$	C, H, N	A
20	C_4H_8NO[f]	H	−	Free base	134–135	$C_{15}H_{21}N_3O_3$	C, H, N	A
21	C_4H_8N[g]	H	−	Free base	97–98	$C_{15}H_{21}N_3O_2$	C, H, N	A
22	NHC_2H_5	C_2H_5	++++	TsOH	172–174	$C_{15}H_{23}N_3O_2 \cdot C_7H_8O_3S$	C, H, N	D
23	$N(C_2H_5)_2$	C_2H_5	+	1.5HCl	180–185	$C_{17}H_{27}N_3O_2 \cdot 1.5HCl$	N	D
24	$N(C_2H_5)CH(CH_3)_2$	C_2H_5	+	TsOH	150	$C_{18}H_{29}N_3O_2 \cdot C_7H_8O_3S$	C, H, N	D
25	$N(C_2H_5)_2$	CH_3	+	HCl	200–202	$C_{16}H_{25}N_3O_2 \cdot HCl$	C, H, N	D
26	$NHCOCH_3$	$COCH_3$	−		191–193	$C_{15}H_{19}N_3O_4$	C, H, N	G
27	$N(C_2H_5)_2$	$COCH_3$	−		74–77	$C_{17}H_{25}N_3O_3$	C, H, N	H
28	$NCH(CH_3)_2COCH_3$	H	−		115–116	$C_{16}H_{23}N_3O_3$	N	I
29	$NCH(CH_3)_2COCH_3$	$COCH_3$	−		110	$C_{18}H_{25}N_3O_4$	C, H, N	J

[a] Activity rating ++++, hepatic shift >95%; +++, 75–95%; ++, 50–75%; +, <50%; −, 0, against *S. mansoni* in mice; in the case of inactive compounds activity was often displayed at higher dose levels. [b] A, B, C, and D refer to appropriate routes in Scheme I; E, by nitration of 2-aminomethyl-6-methyl-1,2,3,4-tetrahydroquinoline, obtained from 1-benzoyl-2-cyano-1,2-dihydro-6-methylquinoline (*cf.* ref 34). F, $NaBH_4$ redn of Schiff base of 1 with PhCHO. G, diacetylation of 1. H, acetylation of **3**. I, monoacetylation of **10**. J, diacetylation of **10**. [c] Cyclopropyl. [d] Cyclohexyl. [e] Piperidino. [f] Morpholino. [g] Pyrrolidinyl. [h] C: calcd, 59.73; found 59.24. [i] C: calcd, 56.05; found 56.70.

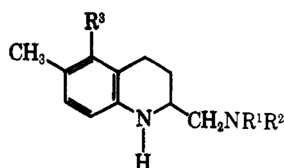
TABLE III



Compd	NR^1R^2	R^3	Oral activity[a] at 25 mg/kg (base equiv) × 4	Salt	Mp, °C	Formula	Analyses	Method of synthesis[b]
30	NHC_4H_9	Cl	+	HCl	233–234	$C_{15}H_{23}ClN_2 \cdot HCl$	C, H, N	A
31	$NHCH(CH_3)_2$	Cl	+	HCl	252–255	$C_{14}H_{21}ClN_2 \cdot HCl$	C, H, N[c]	A
33	$N(C_2H_5)_2$	Cl	−	HCl	172–173	$C_{15}H_{23}ClN_2 \cdot HCl$	C, H, N	B
33	$NHCH(CH_3)_2$	F	++	HCl	225–228	$C_{14}H_{21}FN_2 \cdot HCl$	C, H, N	C
34	$N(C_2H_5)_2$	F	−	2HCl	172	$C_{15}H_{23}FN_2 \cdot 2HCl$	C, H, N	D
35	$NHCH_2CH_2OH$	F	−	Free base	91–92	$C_{13}H_{19}FN_2O$	C, H, N	C
36	$NHCH(CH_3)_2$	Br	+	HCl	240–241	$C_{14}H_{21}BrN_2 \cdot HCl$	C, H, N	E
37	$NHCH(CH_3)_2$	H	−	HCl	222–224	$C_{14}H_{22}N_2 \cdot HCl$	C, H, N	F
38	$NHCH(CH_3)_2$	CN	++	Maleate	190	$C_{15}H_{21}N_3 \cdot C_4H_4O_4$	C, H, N	E
39	$NHCH(CH_3)_2$	$CONH_2$	−	Free base	133	$C_{15}H_{23}N_3O$	C, H, N[d]	G
40	$NHCH(CH_3)_2$	NH_2	−	3HCl	190 dec	$C_{14}H_{23}N_3 \cdot 3HCl$	C, H	H

[a] Symbols as in Table II. [b] A, from 7-chloro-2-formyl-6-methylquinoline. B, from 2-bromomethyl-7-chloro-6-methylquinoline. C, from 7-fluoro-2-formyl-6-methylquinoline. D, from 2-chloromethyl-7-fluoro-6-methylquinoline. E, from **10** by acylation, reduction. Sandmeyer reaction, and hydrolysis. F, precursor to **10**. G, hydrolysis of **38** with 80% aq H_2SO_4. H, catalytic reduction of **10**. [c] C: calcd, 58.10; found, 58.71. [d] C: calcd, 68.93; found, 68.35.

TABLE IV



Compd	NR^1R^2	R^3	Salt	Mp, °C	Formula	Analyses	Method of synthesis[a]
41	$NHCH(CH_3)_2$	NO_2	Maleate	193–194	$C_{14}H_{21}N_3O_2 \cdot C_4H_4O_4$	C, H N	C
42	$N(C_2H_5)_2$	NO_2	2HCl	220 dec	$C_{15}H_{23}N_3O_2 \cdot 2HCl$	C, H	C
43	C_4H_8NO[b]	NO_2	Free base	175–177	$C_{15}H_{21}N_3O_3$	C, H, N	A
44	$NHCH(CH_3)_2$	Cl	Maleate	205–206	$C_{14}H_{21}ClN_2 \cdot C_4H_4O_4$	C, H, N	D
45	NH_2	Cl	HCl	231–232	$C_{11}H_{15}ClN_2 \cdot HCl$	C, H, N	B
46	$NHCH_2CH_2OH$	Cl	Free base	119–122	$C_{13}H_{19}ClN_2O$	C, H, N	D

[a] A, route A, Scheme I. B, as for **1**, Table II, but beginning with 5-chloro-6-methylquinoline. C, route C, Scheme I. D, employing 5-chloro-2-formyl-6-methylquinoline with appropriate amine during reductive amination step, as per route B, Scheme I. [b] Morpholino.

TABLE V

Compd	Structure	Oral activity[a] at 100 mg/kg (Base equiv) × 4	Salt	Mp, °C	Formula	Analyses	Method of synthesis[b]
	(general structure: R^1, R^2 as below)						
47	R_1 = H, R_2 = C_4H_9	++	Maleate	191–192	$C_{16}H_{25}N_3O_2 \cdot C_4H_4O_4$	C, H, N	C
48	R_1 = C_2H_5, R_2 = C_2H_6	+++	Maleate	131–132	$C_{16}H_{25}N_3O_2 \cdot C_4H_4O_4$	C, H, N	C
49		+	HCl	139 dec	$C_{15}H_{23}N_3O_2 \cdot HCl$	C, H	B
50		++	2HCl	150–155	$C_{16}H_{25}N_3O_2 \cdot 2HCl$	C, H, N	D
51		–	TsOH	158–160	$C_{16}H_{25}N_3O_2 \cdot C_7H_8O_3S$	N	A
52		–	TsOH	181–183	$C_{14}H_{21}N_3O_2 \cdot C_7H_8O_3S$	C, H	A

[a] Symbols as in Table II; note that in Table V dose level four times that in Tables II and III. [b] A, following route A in Scheme I, but utilizing 6-ethylquinoline [R. A. Glen and J. R. Bailey, *J. Amer. Chem. Soc.*, **68**, 1840 (1946)] in the case of **51** and quinoline in the case of **52**. B, as for route B in Scheme I but using 2-acetyl-6-methylquinoline [K. N. Campell, C. H. Helbing, and J. F. Kerwin, *J. Amer. Chem. Soc.*, **63**, 639 (1941)] for the reductive amination step. C, refers to route C in Scheme I, but beginning from 2,4,6-trimethylquinoline [E. Roberts and E. E. Turner, *J. Chem. Soc.*, 1837 (1927)]. D, Mannich reaction of 2,6-dimethylquinoline with $HN(C_2H_5)_2$ and HCHO, followed by reduction and nitration.

10, **38**, **33**, **31**, and **36**) whereas in the mirasan series I the order is reversed,[3] *i.e.*, halogen > CN > NO_2. This particular difference between series I and V could well be explained in terms of lipophilicity, a property that can be correlated with a compounds partition coefficient or summation of substituent π values.[21,22] In Table I, 4 compounds have been considered, two (A and B) from the mirasan series I and the corresponding pair (C and D) from the tetrahydroquinoline series V, and $\Sigma\pi$, the summation of π values for the substituent R and the linkage **Z**, has been listed with the molar ED_{50}. A Hansch equation[23] fitting these particular values very closely ($r = 0.997$, $s = 0.038$) is

$$\log 1/ED_{50} = 2.255\pi - 1.242\pi^2 - 2.843$$

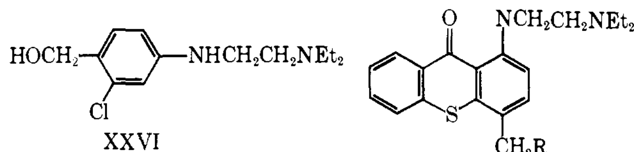
$$\text{Optimum } \Sigma\pi = \pi_0 = \frac{2.255}{2 \times 1.1242} = 0.91$$

Comparing π_0 with the $\Sigma\pi$ values in Table I may explain why: (a) the Cl compound A is more active than the corresponding (insufficiently lipophilic) NO_2 compound B, (b) the NO_2 compound D is more active than the corresponding (too lipophilic) Cl compound C, and why (c) the Cl compound A of the mirasan series

(21) C. Hansch and T. Fujita, *J. Amer. Chem. Soc.*, **86**, 1616 (1964).
(22) T. Fujita, J. Iwasa, and C. Hansch, *ibid.*, **86**, 5175 (1964).
(23) The authors thank Dr. M. S. Tute for this calcn; with only 4 compds the *statistical* significance is not high ($p = 0.1$ on π and π^2 by Student's *t* test) but a later correlation, using 8 compds within this series, showed both π and π^2 terms to be significant at the $p = 0.01$ level with $\pi_0 = 0.87$.

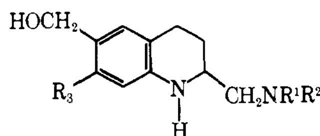
and the NO_2 compound D of the tetrahydroquinoline series are of similar activity (optimum lipophilicity).

The presence of a 6-Me group is essential for activity (note the inactivity of the 6-de-Me compound **52** and 6-Et compound **51**) which is in harmony with the requirement[3] for a Me group para to the basic side chain in series I. Recent work by Rosi, *et al.*,[24] has demonstrated that mirasan (I, $R^1 = R^2 = Et$; $R^3 = Cl$) undergoes hydroxylation *in vivo* to give the active metabolite XXVI and that lucanthone (XXVIIa), from which series the mirasans were developed,[3,4] undergoes similar metabolism[25] to give hycanthone (XXVIIb), whish is showing promise as a schistosomicidal drug suitable for mass treatment.[26]



XXVI

XVII
a, R = H
b, R = OH



XXVIII

For certain members of series V, it has been demonstrated[27] that a similar metabolic hydroxylation of the 6-Me group occurs in mice (and other species) to give compounds of type XXVIII, several of which have been prepared[28] by an oxidative fermentation technique,[24,25,29] using a strain of *Aspergillus sclerotiorum* Huber obtained from the Centralbureau voor Schimmelcultures, Baarn, Holland (No. 549. 65). These hydroxylated derivatives are highly schistosomicidal, a compound of particular interest, as previously reported,[1] being 6-hydroxymethyl-2-*N*-isopropylaminomethyl-7-nitro-1,2,3,4-tetrahydroquinoline [XXVIII; $R^1 = H$; $R^2 = i\text{-Pr}$; $R^3 = NO_2$]. In mice, it has been shown[30] that *per os*, its schistosomicidal activity is similar to that of the parent 6-Me compound, 2-*N*-isopropylaminomethyl-6-methyl-7-nitro-1,2,3,4-tetrahydroquinoline (**10**), but by the intramuscular route its activity is very much superior.

In series V, the effect of a Me group in the 8 position (XXX) was to lower activity markedly which was unexpected since the activity of XXIX, is reported[6] to be superior to that of mirasan (I, $R^1 = R^2 = Et$; $R^3 = Cl$).

(24) D. Rosi, T. R. Lewis, R. Lorenz, H. Freele, D. A. Berberian, and S. Archer, *J. Med. Chem.*, **10**, 877 (1967).

(25) D. Rosi, G. Peruzzotti, E. W. Dennis, D. A. Berberian, H. Freele, B. F. Tullar, and S. Archer, *ibid.*, **10**, 867 (1967).

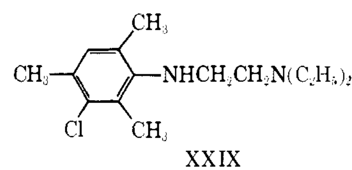
(26) R. Foster and H. C. Richards, *Chim. Ther.*, **5**, 293 (1970).

(27) These studies were conducted by Dr. B. Kaye and Mr. N. M. Woolhouse of the Department of Drug Metabolism, Research Division of Pfizer Ltd.

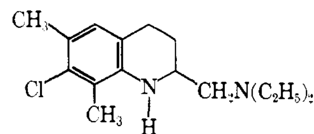
(28) The authors thank Mr. G. F. Parker of Fermentation Development, Chemicals Division of Pfizer Ltd., for this aspect of the work.

(29) Pfizer, South African Patent, 68,03636 (1968); *Chem. Abstr.*, **71**, 30369*k* (1969).

(30) R. Foster and B. L. Cheetham, manuscripts in preparation.

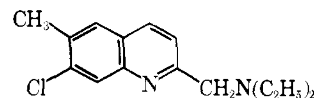


XXIX



XXX

(2) **The Heterocyclic Ring.**—Inclusion on the heterocyclic N of an alkyl group such as Me (**25**) or Et (**22**, **23**, and **24**) produced compounds in which activity was retained or slightly enhanced (*cf.* **7** and **22**) whereas destruction of the basicity of the heterocyclic N by acylation (**26**, **27**, and **29**) resulted in a complete loss of activity. The activity of **47** and **48** shows that incorporation of a Me in the 4 position is "allowed" and suggests that this region of the molecule is not critical in drug–receptor interaction. However, the inactivity of the nonreduced chloroquinoline XXXI highlights the importance of the stereochemical and/or electronic nature of the hetero ring.



XXXI

(3) **The Side Chain.**—Table II illustrates the effect of different terminal N substituents on activity in the 7-NO_2 series. Of the tertiary amines, **3** and **5** were the most active, and of the secondary amines bearing a straight alkyl chain, maximum activity was displayed by **7**. However, highest activity was possessed by compounds bearing an α-branched alkyl group, *i.e.*, **10**, **11**, and **17**, which may be a reflection of their expected resistance to *in vivo* dealkylation to produce **1**. The size of the terminal substituent seems to be an important factor and possibly those compounds possessing a bulky group, *e.g.*, **14**, **18**, **19**, **20**, and **21** are incapable of being accommodated in a receptor "pocket" at this region. Activity of 7-Cl compounds (XXI) given in Table III, appeared to follow the same pattern regarding the effects of terminal N substitution displayed by the 7-NO_2 series (XV).

The most effective compound was the *N*-*i*-Pr derivative, **10**, 2-*N*-isopropylaminomethyl-6-methyl-7-nitro-1,2,3,4-tetrahydroquinoline [V; $R^1 = H$; $R^2 = i\text{-Pr}$; $R^3 = NO_2$], administered as the hydrogen maleate salt. It has been shown[31] to be curative against *S. mansoni* infections in mice treated with 17 mg/kg po once daily for 5 consecutive days, or with a single dose of 65 mg/kg; the corresponding figures obtained for a Puerto Rican strain of *S. mansoni* were 11 mg/kg for 5 consecutive days and 33 mg/kg (all doses correspond to weight of free base).

Destruction of the basic nature of the terminal N by acylation (*e.g.*, **28**) resulted in a complete loss of activity.

(31) R. Foster, B. L. Cheetham, D. F. King, and E. T. Mesmer, *Ann. Trop. Med. Parasitol.*, **65**, 59 (1971).

Extension of the side chain by one CH_2 (**50**) reduced activity, a result which is in harmony with the finding[3] that in the mirasan series (I), the N–N distance of the basic side chain is critical and that activity is at a maximum with an ethylene linkage; inclusion of a Me on the CH_2 side chain (**49**) also led to a reduction in activity.

Each compound listed in Tables II–V was tested as the racemic mixture, optical isomerism arising from the presence of the asymmetric C at position 2 of the molecule. Resolution of **10**, has been achieved using *d*-α-bromocamphor-π-sulfonic acid, and the dextro form of **10** has been shown to be the more active isomer. Thus, at single oral dosages of 36 mg/kg of the hydrogen maleate salts, the hepatic shifts recorded for *dl*, *d*, and *l* forms of **10** were 33, 56, and 11%, resp. The isomers are likely to assume a half-chair conformation, with the side chain equatorially oriented[32] although conformational changes might well occur during drug–receptor interaction.

Schistosomicidal Activity in the Monkey.—At an early stage of the program we wished to establish whether the new series displayed schistosomicidal activity in infected monkeys (which would serve as an indication of their likely activity in man) since it is known[4,6] that members of series I–IV, despite their high activity in mice, lack convincing activity in primates.

Several compounds of type V were evaluated in monkeys and it was established that structure–activity patterns roughly parallelled those in mice. Compd **10**, was again one of the most promising members,[31] complete cures being obtained with a single oral dose of 50 mg/kg (corresponding to 72 mg/kg of the hydrogen maleate salt).

The work of Rosi, *et al.*,[24] suggested that the inactivity of mirasan (I, $R^1 = R^2 = Et$; $R^3 = Cl$) in the monkey is due to the inability of the host's enzymes to convert the compound into the hydroxylated metabolite, XXVI. In the case of certain compounds of type V, it has been shown[27] that hydroxylation occurs in this species to give the corresponding 6-hydroxymethyl derivatives (XXVIII). The 6-hydroxymethyl derivative of **10**, proved to be extremely active in the monkey, particularly im, curative doses being in the range of 5–7.5 mg/kg, administered as a single dose.[30]

This difference in ease of hydroxylation between series I and V may be a consequence of stereochemical factors, and it is evident that the type of molecular constraint imposed on the mirasan skeleton is critical since compounds II, III, and IV do not appear to possess the same high activity in the monkey as members of type V. The marked activity of compounds V in this higher species is very encouraging as this finding prognosticates useful activity against *S. mansoni* infections in man.

Experimental Section

Melting points were obtained on an Electrothermal melting point apparatus and are corrected. Pmr spectra were recorded on a Varian A60 spectrometer (TMS as internal standard) as solns in $CDCl_3$ unless otherwise indicated. Where analyses are indicated only by symbols of the elements, anal. results obtd for those elements were within ±0.4% of the theor values.

(32) H. Booth, *J. Chem. Soc.*, 1841 (1964).

2-*N*-Isopropylaminomethyl-6-methyl-7-nitro-1,2,3,4-tetrahydroquinoline (10).—The following syntheses typify routes A, B, and C in Scheme I.

Route A.—(1) A soln of 6-methylquinoline-2-carboxylic acid[7,8] (24.0 g) and PCl_5 (23.5 g) in dry PhMe (685 ml) was refluxed for 2 hr. The red soln was treated with decolorizing charcoal, filtered, cooled in ice, and added slowly to an ice-cooled soln of *i*-$PrNH_2$ (38.4 g) in dry PhMe (180 ml). After 0.5 hr the soln was washed with H_2O (3 × 150 ml), dried (Na_2SO_4), and evapd *in vacuo* to yield 2-*N*-isopropylcarbamoyl-6-methylquinoline as a brown mobile oil which solidified. A sample was recrystd from petr ether (bp 60–80°) as white needles, mp 108–109° (26 g; 88%). *Anal.* ($C_{14}H_{16}N_2O$) C, H, N.

(2) A soln of the above compd (26.4 g) in dry dioxane (350 ml) was slowly added to a stirred warm suspension of LAH (17.5 g) in dry dioxane (550 ml) and when addn was complete the mixt was refluxed for 3 hr. After cooling, excess LAH was carefully decompd with H_2O and the whole was extd with Et_2O (6 × 300 ml). The dried ($MgSO_4$) Et_2O ext was evapd *in vacuo* to yield a dark red mobile oil (22.0 g) which was dissolved in EtOH (400 ml) and hydrogd over Raney Ni (5.7 ml) at 75° and an initial H_2 pressure of 52.73 kg/cm² for 4 hr. The catalyst was removed by filtn, and the solvent was evapd *in vacuo*. Fractional distn of the crude oil yielded 2-*N*-isopropylaminomethyl-6-methyl-1,2,3,4-tetrahydroquinoline as a yellow viscous oil, bp 111–113° (0.1 mm) (13.6 g; 55%). *Anal.* ($C_{14}H_{26}N_2$) C, H, N.

(3) A soln of HNO_3 (d = 1.5), (41.1 g) in H_2SO_4 (250 ml) was added over 0.5 hr to a stirred ice-cold soln of 2-*N*-isopropylaminomethyl-6-methyl-1,2,3,4-tetrahydroquinoline sulfate (200 g) (obtd as a solid by adding 1 equiv of H_2SO_4 to a soln of the base in EtOH) in H_2SO_4 (2 l.). The reaction mixt was stirred for a further 4 hr, then poured onto crushed ice and basified with 10 *N* NaOH, the temp being kept at 0–10°. The soln was extd with CH_2Cl_2, and the dried ($MgSO_4$) org layer was evapd *in vacuo* to yield a red oil (175 g). The oil was treated with 1 equiv of maleic acid (87.5 g) in EtOAc, the crude maleate salt was then dissolved in hot EtOH (2.5 l.), and sufficient EtOAc was added to start sepn of the hydrogen maleate salt of **10**. The yellow cryst solid of mp 187–189° (140 g; 40%) was found to contain <1% 5-NO_2 isomer by glc (5% SE 52, 12.5 × 0.31 cm glass column at 220°).

The free base (obtd by basification of the salt with 5 *N* NaOH soln and extg with Et_2O) exhibited singlets at τ 2.73 (sharp) and 3.04 (broad, due to coupling to the 6-CH_3) for the 8-H and 5-H resp. *Anal.* ($C_{14}H_{21}N_3O_2 \cdot C_4H_4O_4$) C, H, N.

Route B.—(1) A soln of 2-formyl-6-methylquinoline[12] (10.25 g), with *i*-$PrNH_2$ (25 ml) in EtOH (200 ml) was hydrogd over 5% Pd/$BaSO_4$ catalyst (10 g) at an initial H_2 pressure of 3.5 kg/cm² for 1 hr. The catalyst was removed by filtn and evapn of the solvent *in vacuo* yielded a brown mobile oil which was fractionally distd. 2-*N*-Isopropylaminomethyl-6-methylquinoline was isolated as its HCl salt, mp 210–212° (14.3 g; 96%). *Anal.* ($C_{14}H_{22}N_2 \cdot HCl$) C, H, N.

(2) A soln of the above base (72 g) in EtOH (1500 ml) was hydrogd over Raney Ni (12 ml) at 75° and an initial H_2 pressure of 52.73 kg/cm² until the theoretical amt of H_2 had been taken up. The catalyst was removed by filtn, and evapn of the solvent *in vacuo* yielded a pale brown mobile oil (54 g; 73%). Treatment with HCl in Et_2O yielded 2-*N*-isopropylaminomethyl-6-methyl-1,2,3,4-tetrahydroquinoline as the HCl salt, mp 222–224°. *Anal.* ($C_{14}H_{26}N_2 \cdot HCl$) C, H, N. Nitration as above gave **10**.

Route C.—(1) A mixt of 2,6-dimethylquinoline (314 g) and Na_2CO_3 (200 g) in CCl_4 (1 l.) was stirred and heated at 60°. The source of heat was removed and Cl_2 passed in at 300–400 ml/min, the temp being controlled at about 60°. When the reaction was complete (*ca.* 5.5 hr as judged by tlc) the mixt was cooled and poured into 1 l. of 2 *N* HCl. The org layer was sepd and extd with 2 *N* HCl (3 × 1 l.) and the combined aq exts were washed with CH_2Cl_2 (500 ml); basification of the acid ext with Na_2CO_3 gave 2-chloromethyl-6-methylquinoline as a tan solid, mp 108–110° (348 g; 91%). *Anal.* ($C_{11}H_{10}ClN$) C, H, N.

(2) The above compd (250 g) was added during 0.5 hr to a stirred soln of *i*-$PrNH_2$ (1250 ml) in EtOH (1250 ml), and stirring was contd for 1 hr. After standing overnight the reaction mixt was treated with decolorizing charcoal and filtered. The solvent was removed *in vacuo*, and the thick slurry was treated with H_2O (1 l.) and extd with CH_2Cl_2 (3 × 750 ml); the dried ($MgSO_4$) CH_2Cl_2 layer was evapd *in vacuo* to yield 2-*N*-isopropylaminomethyl-6-methylquinoline as a dark oil (249 g; 73%),

identical with a sample prepd by route B. Reduction and nitration as above gave **10**.

6-Hydroxymethyl-2-*N*-isopropylaminomethyl-7-nitro-1,2,3,4-tetrahydroquinoline [XXVIII; $R^1 = H$, $R^2 = i$-Pr; $R^5 = NO_2$] was prepared from **10** as described in ref 29.

Optical Resolution of 2-*N*-Isopropylaminomethyl-6-methyl-7-nitro-1,2,3,4-tetrahydroquinoline (10).—The method used was essentially that described by Pope and Peachey,[33] except that the H_2O-sol MsO^- salt of the racemate was used.

(a) ***d*-Isomer.**—A soln of ammonium *d*-α-bromocamphorsulfonate (125 g) in H_2O (1.25 l.) was added with stirring to a soln of the MsO^- salt of **10** (275 g) in H_2O (1.25 l.). The red oil which sepd soon crystd to a yellow solid which was filtered, washed with H_2O, and azeotroped with C_6H_6 until dry. The C_6H_6 soln was evapd *in vacuo*, the residual bromocamphorsulfonate salt recrystd from Me_2CO (1.5 l.) to give a yellow solid (130 g) and this further recrystd from EtOAc to yield yellow needles (90 g) (crop A). This procedure was repeated with slight modification: a soln of ammonium *d*-α-bromocamphorsulfonate (150 g) in H_2O (2.5 l.) was added with stirring to a soln of the MsO^- salt of **10** (300 g) in H_2O (2 l.), and the pptd yellow salt was filtered and recrystd with drying ($MgSO_4$) from EtOAc (2.5 l.) to yield yellow needles of the bromocamphorsulfonate salt (160 g) (crop B). Crops A and B were combined and recrystd from EtOAc (3.5 l.) to give yellow needles (220 g), $[\alpha]^{25}_{546}$ + 82.9°; $[\alpha]^{25}_{578}$ + 70.0° (MeOH). A further recrystn from EtOAc produced no change in the rotation. The above salt was added to 50% (v/v) 0.880 sp gr NH_4OH–H_2O (2 l.), and the soln was extd with Et_2O (3 × 1 l.), dried ($MgSO_4$), and evapd *in vacuo* to yield a red oil (97 g) which was dissolved in Me_2CO (500 ml) and treated with a soln of MsOH (36 g) in Me_2CO (350 ml). On standing, the MsO^- salt sepd as orange needles, which were filtered, washed with cold Me_2CO and Et_2O, and dried *in vacuo* at 50° to give the monohydrate (yield 118 g), $[\alpha]^{25}_{546}$ + 20.5°; $[\alpha]^{25}_{578}$ + 17.0° (MeOH). The anhyd salt (which rapidly hydrated on exposure to the atm) gave rotations of $[\alpha]^{25}_{546}$ + 22.0°; $[\alpha]^{25}_{578}$ + 18.7° (MeOH). *Anal.* ($C_{14}H_{21}N_3O_2 \cdot CH_4O_3S$) C, H, N.

(b) ***l*-Isomer.**—The org mother liquors from the above resoln were combined and evapd to dryness; the residue was partitioned between 2 *N* NaOH and EtOAc, and the residue obtd on evapn of the EtOAc was dissolved in CH_2Cl_2. The aq mother liquors from the above resoln were combined, basified with 2 *N* NaOH soln, and extd with CH_2Cl_2. The combined CH_2Cl_2 exts were dried ($MgSO_4$) and evapd *in vacuo* to give an oily mixt of *l* and racemic **10**, which was dissolved in Me_2CO (1 *l.*) and treated with a soln of MsOH (83 g) in Me_2CO (250 ml). The yellow salt was filtered, washed with cold Me_2CO, dissolved in H_2O (1 l.), and treated with a soln of ammonium *l*-α-bromocamphorsulfonate (100 g) in H_2O (750 ml); the pptd salt was filtered, washed with H_2O, and recrystd with drying ($MgSO_4$) from EtOAc (1.2 l.) (yield 135 g). The salt was basified with 50% (v/v) 0.880 sp gr NH_4OH–H_2O, and the free base was extd with Et_2O. The Et_2O ext was evapd and the red oil (57 g) was dissolved in Me_2CO (500 ml) and treated with a soln of MsOH (21 g) in Me_2CO (250 ml). The methanesulfonate salt crystd on cooling as orange needles (74 g) which were filtered and dried *in vacuo* at 50°. This salt was the monohydrate, $[\alpha]^{25}_{546}$ − 20.8°; $[\alpha]^{25}_{578}$ − 17.3° (MeOH). A sample was dried at 120° *in vacuo* to give the anhyd salt, $[\alpha]^{25}_{546}$ − 22.1°, $[\alpha]^{25}_{578}$ − 18.7° (MeOH). *Anal.* ($C_{14}H_{21}N_3O_2 \cdot CH_4O_3S$) C, H, N.

2-*N*-Isopropylaminomethyl-6-methyl-5-nitro-1,2,3,4-tetrahydroquinoline (41).—The mother liquors from the prepn of **10** were found to contain by glc a mixt of 5- and 7-nitro isomers in the ratio 55:45. This mixt of isomers was suspended in H_2O, 5 *N* NaOH was added until basic, the mixt was extd several times with Et_2O, and the dried ($MgSO_4$) Et_2O ext was evapd *in vacuo* to yield a dark red viscous oil. A 15-g sample of this free base mixt was distd and the first fraction, bp 178° (0.2 mm), solidified in the condenser as a yellow solid. Recrystn from *n*-C_6H_{14} gave a golden yellow solid, mp 64–66°, which was identified as the 5-NO_2 isomer (yield 15%). *Anal.* ($C_{14}H_{21}N_3O_2$) C, H, N.

In the pmr spectrum, 41 showed 2 doublets centered at τ 2.83 (broad, J = 8.5 cps) and 3.30 (sharp, J = 8.5 cps) for the 7-H and 8-H resp.

The hydrogen maleate salt prepd in the usual way recrystd from EtOH as a yellow solid, mp 193–194°. *Anal.* ($C_{14}H_{21}N_3O_2 \cdot C_4H_4O_4$) C, H, N.

2-*N*-Isopropylaminomethyl-6-methyl-8-nitro-1,2,3,4-tetrahydroquinoline [XIV; $R^1 = H$; $R^2 = i$-Pr].—A stirred soln of 2-*N*-isopropylaminomethyl-6-methyl-1,2,3,4-tetrahydroquinoline (11 g) in AcOH (150 ml) was cooled to 5° and treated over 0.5 hr with a soln of HNO_3 (d = 1.5, 3.2 g) in H_2SO_4 (4.3 g). The reaction mixt was stirred for a further 0.5 hr, quenched into H_2O, basified with K_2CO_3, and extd with CH_2Cl_2. The dried ($MgSO_4$) CH_2Cl_2 ext was evapd *in vacuo* to yield a red oil which was dissolved in EtOAc, and a large vol of petr ether (bp 30–40°) added. The yellow solid was recrystd once more from EtOAc–petr ether, mp 92–93° (yield 8 g; 60%). The material was shown to be XIV (R^1 = H, R^2 = *i*-Pr); the pmr spectrum showed two broad singlets, due to meta coupling, at τ 1.96 and 2.78 for the 7-H and 5-H, resp. *Anal.* ($C_{14}H_{21}N_3O_2$) C, H, N.

2-Benzamidomethyl-6-methyl-1,2,3,4-tetrahydroquinoline was prepd from the Reissert deriv[7] of 6-methylquinoline by the method of Rupe, *et al.*[34] The crude product was recrystd from C_6H_6 as a white solid, mp 130–132° (99%). *Anal.* ($C_{18}H_{20}N_2O$) C, H.

2-Aminomethyl-6-methyl-1,2,3,4-tetrahydroquinoline was prepd by hydrolysis of the above amide by the method of Rupe, *et al.*[34] The amine, bp 130° (0.7 mm) (66%), was treated with Et_2O–HCl, and the crude HCl salt was recrystd from EtOH as a white solid, mp 291–293°. *Anal.* ($C_{11}H_{16}N_2 \cdot HCl$) C, H, N.

2-Aminomethyl-6-methyl-7-nitro-1,2,3,4-tetrahydroquinoline (1).—2-Aminomethyl-6-methyl-1,2,3,4-tetrahydroquinoline (5.5 g) was nitrated as described for **10**. The crude ext was recrystd from MeOH to yield an orange solid, mp 133–135° (1.1 g; 16%). *Anal.* ($C_{11}H_{15}N_3O_2$) C, H.

2-*N*-Benzylaminomethyl-6-methyl-7-nitro-1,2,3,4-tetrahydroquinoline (16).—An equimolar mixt of 1 (1.1 g) and PhCHO (0.55 g) in EtOH (30 ml) was refluxed on a steam bath for 30 min; the solvent was removed *in vacuo* and the resulting oil (1.6 g) was dissolved in MeOH (25 ml) and treated with $NaBH_4$ (1.0 g) dissolved in the minimum amount of H_2O–MeOH. The reaction mixt was stood at room temp for 20 hr after which time excess hydride was decompd with 5 *N* HCl, the soln was rebasified with 5 *N* NaOH, and the product then was extd with $CHCl_3$. The dried ($MgSO_4$) $CHCl_3$ ext was evapd *in vacuo* to yield a red oil which could not be crystd; the oil was chromatogd on neutral Al_2O_3, elution with benzene removing an unidentified impurity. The main band was eluted with C_6H_6–$CHCl_3$ (50:50 v/v) and the solvents were removed *in vacuo;* the resulting red oil was treated with HCl–EtOH, and the HCl salt was recrystd from EtOH to give a yellow solid, mp 199–201° (300 mg; 17.5%). *Anal.* ($C_{18}H_{21}N_3O_2 \cdot HCl$) C, H.

2-*N*,*N*-Diethylaminomethyl-1-formyl-6-methyl-1,2,3,4-tetrahydroquinoline (Route D).—2-*N*,*N*-Diethylaminomethyl-6-methyl-1,2,3,4-tetrahydroquinoline (6 g) was dissolved in a mixt of C_6H_6 (50 ml) and PhMe (50 ml) contg 98% HCO_2H (4 ml), and the mixt was refluxed for 18 hr, the H_2O formed being collected in a Dean–Stark trap. A further 4 ml of HCO_2H was added and refluxing contd for 24 hr, when a total vol of 6.7 ml of H_2O was collected. The mixt was cooled and extd with 2 *N* HCl (2 × 50 ml), and the acid ext was basified with 5 *N* NaOH. The basic soln was then extd with Et_2O (2 × 100 ml), dried ($MgSO_4$), and evapd *in vacuo* to yield a colorless oil (5.6 g). The pure compd obtained by fractional distn had bp 133–134° (0.45 mm) (4.82 g; 71%). *Anal.* ($C_{16}H_{24}N_2O$) C, H, N.

2-*N*,*N*-Diethylaminomethyl-1,6-dimethyl-1,2,3,4-tetrahydroquinoline.—A soln of 2-*N*,*N*-diethylaminomethyl-1-formyl-6-methyl-1,2,3,4-tetrahydroquinoline (4.2 g) in dry dioxane (70 ml) was added over 20 min to a stirred suspension of LAH (3 g) in dry dioxane (100 ml). The mixt was stirred and refluxed for 6 hr, and the excess LAH was cautiously decompd with 50% aq dioxane. The mixt was filtd, the residue washed with dioxane, and the filtrate evapd to dryness *in vacuo*. Vacuum distn of the crude product yielded pure material, bp 116–118° (0.5 mm) (2.84 g; 72%). *Anal.* ($C_{16}H_{26}N_2$) N.

2-*N*,*N*-Diethylaminomethyl-1,6-dimethyl-7-nitro-1,2,3,4-tetrahydroquinoline (25).—2-*N*,*N*-Diethylaminomethyl-1,6-dimethyl-1,2,3,4-tetrahydroquinoline was nitrated as described for **10**. The product, isolated as the HCl salt, had mp 200–202° (28% yield). *Anal.* ($C_{16}H_{25}N_3O_2 \cdot HCl$) C, H, N.

2-(β-Diethylaminoethyl)-6-methylquinoline.—$Et_2NH \cdot HCl$ (5.5 g) dissolved in formalin (10 ml) was added dropwise to a soln of 2,6-dimethylquinoline (15.7 g) in EtOH (10 ml), and the mixt was homogenized by warming to 50° for 30 min. The mixt

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(34) H. von Rupe, R. Paltzer, and K. Engel, *Helv. Chim. Acta*, **20**, 209 (1937).

was cooled, H_2O was added, and the unreacted quinoline which pptd was extd with Et_2O (2 × 50 ml); the aq portion was basified with 5 *N* NaOH, extd with Et_2O (2 × 50 ml), dried ($MgSO_4$), and evapd *in vacuo* to give a yellow oil. Fractionation of the oil yielded the product as a yellow oil, bp 119–120° (0.1 mm) (4.0 g; 16.5%). *Anal.* ($C_{16}H_{22}N_2$) N.

2-(β-Diethylaminoethyl)-6-methyl-1,2,3,4-tetrahydroquinoline.—2-(β-Diethylaminoethyl)-6-methylquinoline (6.9 g) in EtOH (100 ml) was hydrogd over Raney Ni (2 g) at 75° and an initial H_2 pressure of 52.73 kg/cm². The catalyst was filtered, the EtOH was removed *in vacuo*, and the oil was fractionated to yield the product, bp 120–122° (0.2 mm) (4.7 g; 67%). *Anal.* ($C_{16}H_{26}N_2$) N.

2-(β-Diethylaminoethyl)-6-methyl-7-nitro-1,2,3,4-tetrahydroquioline (50).—2-(β-Diethylaminoethyl)-6-methyl-1,2,3,4-tetrahydroquinoline (4 g) was nitrated as described for **10**. The product was isolated by chromatography on neutral Al_2O_3 using $CHCl_3$ as eluent and converted to its 2HCl salt by treatment with HCl–Et_2O. The yellow solid had mp 150–151° (1.0 g; 16.5%). *Anal.* ($C_{16}H_{25}N_3O_2 \cdot 2HCl$) C, H, N.

7-Chloro-2-formyl-6-methylquinoline.—A soln of 7-chloro-2,6-dimethylquinoline[14] (27.2 g) and SeO_2 (22.3 g) in dioxane (250 ml) contg H_2O (20 ml) was stirred and refluxed for 2.5 hr. The dioxane was evapd *in vacuo*, and the residue was treated with H_2O and steam distd; the steam dist was extd with Et_2O and evapn of the dried ($MgSO_4$) combined Et_2O exts yielded a white solid recrystd from petr ether, bp 80–100°. The product (18 g; 61.5%) had mp 128–129°. *Anal.* ($C_{11}H_8ClNO$) C, H.

7-Chloro-2-(N-isopropylaminomethyl)-6-methylquinoline.—A soln of 7-chloro-2-formyl-6-methylquinoline (25 g) with *i*-$PrNH_2$ (35 ml) in EtOH (400 ml) was refluxed on the steam bath for 3 hr. After 18 hr at room temp the solvent was removed *in vacuo* and replaced with MeOH (600 ml). The soln was warmed while a soln of $NaBH_4$ (30 g) in H_2O (50 ml) contg a pellet of NaOH was added over 2 hr. After final addn of the $NaBH_4$ the reaction was refluxed for 2 hr on a steam bath. The soln was cooled, excess $NaBH_4$ was decompd by careful addn of 5 *N* HCl, the mixt was basified with 5 *N* NaOH and extd with Et_2O. Evapn of the dried ($MgSO_4$) Et_2O ext yielded 17 g of crude oil which was treated with Et_2O–HCl gas; the salt recrystd from *i*-PrOH–Et_2O as an off-white solid, mp 210–215° dec (12.3 g; 31.5%). *Anal.* ($C_{14}H_{17}ClN_2 \cdot 2HCl$) C, H, N.

7-Chloro-2-(N-isopropylaminomethyl)-6-methyl-1,2,3,4-tetrahydroquinoline (31).—A soln of 7-chloro-2-(N-isopropylaminomethyl)-6-methylquinoline (8.0 g) in H_2O (350 ml) contg 2 mole equiv of HCl (12.87 ml of 5 *N* HCl) was hydrogd over PtO_2 (1.0 g) at an initial H_2 pressure of 3.2 kg/cm² for 3 hr. During the hydrogn much solid was pptd; EtOH was added to the mixt to dissolve the solid product, and the catalyst was removed by filtration. The filtrate was evapd to dryness *in vacuo*, and the semisolid was treated with 5 *N* NaOH and extd with Et_2O. The dried ($MgSO_4$) Et_2O ext was evapd *in vacuo*, the mobile yellow oil (7.0 g) was dissolved in dry Et_2O, and the soln was satd with HCl gas. The white fluffy solid was recrystd from H_2O, mp 252–255° (9.2 g; 99%). *Anal.* ($C_{14}H_{21}ClN_2 \cdot HCl$) C, H, N.

2-Bromomethyl-7-chloro-6-methylquinoline.—7-Chloro-6-methyl-2-tribromomethylquinoline was prepd in theoretical yield from 7-chloro-2,6-dimethylquinoline by the method of Brown, *et al.*,[16] as an unstable off-white solid, mp 145–148°, which was immediately reduced[16] with $SnBr_2$ to yield the product which was recrystd from H_2O–EtOH, mp 139–142° (68%). *Anal.* ($C_{11}H_9BrClN$) N.

7-Chloro-2-diethylaminomethyl-6-methylquinoline (XXXI).—A soln of 2-bromomethyl-7-chloro-6-methylquinoline (10 g) in EtOH (100 ml) contg $CHCl_3$ (200 ml) was added slowly to a soln of Et_2NH (8.1 g) in EtOH (100 ml). After 2 days at 25° the solvent was removed *in vacuo*, H_2O was added, and the org material was extd into $CHCl_3$. The dried ($MgSO_4$) $CHCl_3$ ext was evapd, and the oil was dissolved in Et_2O and treated with HCl gas. The crude salt was recrystd from EtOH–Et_2O to yield pure HCl salt, mp 196–202° dec (6.6 g; 60%). *Anal.* ($C_{15}H_{19}ClN_2 \cdot HCl$) C, H, N.

7-Chloro-2-diethylaminomethyl-6-methyl-1,2,3,4-tetrahydroquinoline (32).—7-Chloro-2-diethylaminomethyl-6-methylquinoline·HCl (0.5 g) was hydrogd over W1 Raney Ni as described for **31**. The product was isolated from the reaction mixt as the HCl salt and recrystd from *i*-PrOH–Et_2O, mp 172–173° (0.1 g; 20%). *Anal.* ($C_{15}H_{23}ClN_2 \cdot HCl$) C, H, N.

7-Chloro-6,8-dimethyl-2-isopropylaminomethyl-1,2,3,4-tetrahydroquinoline (XXX) was obtained in 16% overall yield from 7-chloro-2,6,8-trimethylquinoline by the method described for the prepn of **31**. The maleate salt recrystd from EtOAc as yellow plates, mp 190–191°. *Anal.* ($C_{15}H_{23}ClN_2 \cdot C_4H_4O_4$) C, H, N.

5-Chloro-2-formyl-6-methylquinoline.—5-Chloro-2,6-dimethylquinoline[15] (70 g) was oxidized with SeO_2 (60 g) in dioxane (500 ml) as described above for the 7-Cl isomer to give the 2-aldehyde as orange needles (EtOAc), mp 172–173° (55 g; 73%). *Anal.* ($C_{11}H_8ClNO$) C, H, N.

5-Chloro-2-(N-isopropylaminomethyl)-6-methylquinoline.—5-Chloro-2-formyl-6-methylquinoline (3 g) was treated with *i*-$PrNH_2$ (10 ml), and the crude product was treated with $NaBH_4$ as described for the 7-Cl isomer. The HCl salt recrystd from EtOH as colorless needles, mp 219–221° (2.9 g; 83%). *Anal.* ($C_{14}H_{17}ClN_2 \cdot HCl$) C, H, N.

5-Chloro-2-(N-isopropylaminomethyl)-6-methyl-1,2,3,4-tetrahydroquinoline (44).—The above amine·HCl salt (2.5 g) was hydrogd as described for **31**. The hydrogen maleate deriv recrystd from EtOH–EtOAc (1:1 vv) as a pale yellow powder, mp 205–206° (1.2 g; 37%). *Anal.* ($C_{14}H_{21}ClN_2 \cdot C_4H_4O_4$) C, H, N.

1-Acetyl-2-(N-acetyl-N-isopropylaminomethyl)-6-methyl-7-nitro-1,2,3,4-tetrahydroquinoline (29).—A soln of 2-(N-isopropylaminomethyl)-6-methyl-7-nitro-1,2,3,4-tetrahydroquinoline (24.3 g) in Ac_2O (100 ml) was refluxed for 2.5 hr. The hot soln was poured into a large excess of H_2O and stirred for 2 hr to hydrolyze excess Ac_2O. The soln was then extd with Et_2O and the dried ($MgSO_4$) Et_2O ext evapd *in vacuo* to yield an oil which was basified with K_2CO_3 and extd with $CHCl_3$. Evapn of the dried ($MgSO_4$) ext yielded a red oil which on trituration with Et_2O gave a yellow solid, mp 107° (28 g; 87.5%). *Anal.* ($C_{18}H_{25}N_3O_4$) C, H, N.

1-Acetyl-2-(N-acetyl-N-isopropylaminomethyl)-7-amino-6-methyl-1,2,3,4-tetrahydroquinoline.—A soln of 1-acetyl-2-(N-acetyl-N-isopropylaminomethyl)-6-methyl-7-nitro-1,2,3,4-tetrahydroquinoline (25 g) in EtOH (600 ml) was hydrogd over Pd/C (2.7 g) for 7 hr at an initial H_2 pressure of 7 kg/cm². The catalyst was removed by filtration and the EtOH evapd *in vacuo* to yield a dark yellow gum. Treatment of this with Et_2O–HCl gave the product as the HCl·$2H_2O$ salt, mp 165–170° dec (26 g; 92.5%). *Anal.* ($C_{18}H_{27}N_3O_2 \cdot HCl \cdot 2H_2O$) N.

1-Acetyl-2-(N-acetyl-N-isopropylaminomethyl)-7-bromo-6-methyl-1,2,3,4-tetrahydroquinoline.—A soln of 1-acetyl-2-(N-acetyl-N-isopropylaminomethyl)-7-amino-6-methyl-1,2,3,4-tetrahydroquinoline (5.07 g) in 40% HBr (9.9 ml) was cooled to 5–10°, and powdered $NaNO_2$ (1.23 g) was added portionwise; during each addn the flask was stoppered and shaken vigorously. The soln was allowed to reach room temp when Cu-bronze (0.053 g) was added, and then it was finally warmed on a steam bath for 0.5 hr. The purple soln was cooled, H_2O (20 ml) was added, and the mixt was basified by addn of 5 *N* NaOH. The soln was extd with $CHCl_3$ and the dried ($MgSO_4$) ext was evapd *in vacuo*; trituration of the residue with Et_2O yielded a light brown solid, mp 96° (2.2 g; 36.5%). *Anal.* ($C_{18}H_{25}BrN_2O_2$) N.

7-Bromo-2-(N-isopropylaminomethyl)-6-methyl-1,2,3,4-tetrahydroquinoline (36).—The above product (2.0 g) dissolved in 5 *N* HCl (20 ml) was refluxed for 1 hr. The cooled soln was poured into H_2O and basified with 5 *N* NaOH, and the soln was extd with $CHCl_3$. The dried ($MgSO_4$) ext was evapd *in vacuo* to yield a red oil and the product was isolated by chromatog on a neutral Al_2O_3 column using $CHCl_3$ as eluent. Evapn of the $CHCl_3$ eluent gave an oil which was dissolved in Et_2O and satd with dry HCl. The crude HCl salt crystd from H_2O, mp 240–241° (185 mg; 10.5%). *Anal.* ($C_{14}H_{21}BrN_2 \cdot HCl$) C, H, N.

2-(N-Butylaminomethyl)-5,7-dibromo-6-methyl-1,2,3,4-tetrahydroquinoline.—Br_2 (3.2 g) was added to a stirred mixt of 2-(N-butylaminomethyl)-6-methyl-1,2,3,4-tetrahydroquinoline (2.32 g) and Ag_2SO_4 (6.24 g) in H_2SO_4 (20 ml) over 0.5 hr, and the reaction mixt was stirred for a further 3 hr. During the addn AgBr was pptd. The mixt was poured onto crushed ice, basified with K_2CO_3, and extd with Et_2O. Evapn of the dried ($MgSO_4$) Et_2O exts yielded a white solid which recrystd from petr ether (bp 80–100°) as a white fluffy solid, mp 226–227° (1.5 g; 38.5%), and analyzing as the dihydrate. *Anal.* ($C_{15}H_{22}Br_2N_2 \cdot 2H_2O$) C, H, N.

8-Bromo-2-(N,N-diethylaminomethyl)-6-methyl-1,2,3,4-tetrahydroquinoline.—A soln of Br_2 (1.6 g) in dry CCl_4 (15 ml) was added dropwise to a stirred soln of 2-(N,N-diethylaminomethyl)-6-methyl-1,2,3,4-tetrahydroquinoline (2.78 g) in dry CCl_4 (30 ml) over 1 hr. After 18 hr at room temp the CCl_4 was removed *in vacuo*, and the brown oil was triturated with dry Et_2O when it crystd to a brown solid. This HBr salt was shown by tlc to be

a mixt of product and unreacted starting material, and the free base was chromatogd on a neutral alumina column, the first 150 ml of petr ether yielding the product as a pale yellow oil (1.3 g). Treatment of the oil with Et_2O–HCl gave the 2-HCl salt as a white solid, mp 198–200° (1.4 g; 30.5%). *Anal.* ($C_{15}H_{23}BrN_2 \cdot 2HCl$) C, H, N.

1-Acetyl-2-(*N*-acetyl-*N*-isopropylaminomethyl)-7-cyano-6-methyl-1,2,3,4-tetrahydroquinoline.—A 30% soln of $NaNO_2$ in H_2O at 0° was added until just in excess to a stirred ice-cold soln of 1-acetyl-2-(*N*-acetyl-*N*-isopropylaminomethyl)-7-amino-6-methyl-1,2,3,4-tetrahydroquinoline·HCl (6.0 g) in HCl (4.3 ml) and crushed ice (17 g). This soln of the diazonium salt was neutralized by the addn of K_2CO_3 and then added to a stirred CuCN soln[35] [prepd from Cu_2SO_4 (5.28 g)] covered with a layer of PhMe, care being taken to keep the temp at 0–3°. After 0.5 hr at this temp the reaction mixt was allowed to warm up to room temp and kept overnight. The soln was then heated at 50° for 0.5 hr and cooled, and the PhMe was sepd and evapd *in vacuo*. The crude product recrystd from Et_2O–petr ether as a tan powder, mp 120° (2.9 g; 57.5%). *Anal.* ($C_{19}H_{25}N_3O_2$) N.

7-Cyano-2-(*N*-isopropylaminomethyl)-6-methyl-1,2,3,4-tetrahydroquinoline (38).—A soln of 1-acetyl-2-(*N*-acetyl-*N*-isopropylaminomethyl)-7-cyano-6-methyl-1,2,3,4-tetrahydroquinoline (1.5 g) in 5 *N* HCl (20 ml) was refluxed for 1 hr; after this time an ir anal. indicated absence of C=O absorpn but the C≡N group still remained. The reaction mixt was cooled, poured into H_2O, basified with K_2CO_3, and extd into $CHCl_3$. Evapn of the dried ($MgSO_4$) ext gave a red oil which was dissolved in EtOAc (5 ml) and treated with a soln of maleic acid (315 mg) in EtOAc (2 ml). The maleate salt had mp 190° (950 mg; 57%). *Anal.* ($C_{15}H_{21}N_3 \cdot C_4H_4O_4$) C, H, N.

7-Carbamoyl-2-(*N*-isopropylaminomethyl)-6-methyl-1,2,3,4-tetrahydroquinoline (39).—A soln of **38** (2.0 g) in 80% H_2SO_4 (15 ml) was heated on the steam bath for 1 hr. The mixt was cooled, poured onto ice, basified with K_2CO_3, and extd with $CHCl_3$. The dried ($MgSO_4$) $CHCl_3$ ext was evapd and the crude solid recrystd from C_6H_6–petr ether (bp 40–60°) to yield a brown solid, mp 133° (1.6 g; 74%). *Anal.* ($C_{11}H_{23}N_3O$) C, H, N.

7-Amino-2-(*N*-isopropylaminomethyl)-6-methyl-1,2,3,4-tetrahydroquinoline (40).—A soln of **10** (0.6 g) in EtOH (150 ml) was hydrogd over Pd/C (60 mg) at an initial H_2 pressure of 7.03 kg/cm² for 3.5 hr. The catalyst was removed by filtn, and the EtOH was evapd to yield a viscous oil (0.4 g) which was dissolved in Et_2O and treated with dry HCl. The product was dried *in vacuo* over KOH and P_2O_5 for 2 days to yield a white hygroscopic powder, mp 160° dec (0.5 g; 64.5%) which analyzed as the 3-HCl salt. *Anal.* ($C_{14}H_{23}N_3 \cdot 3HCl$) C, H.

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Synthesis of Aminoethyl Derivatives of α,ω-Alkylenediamines and Structure–Activity Relationships for the Polyamine–Bovine Plasma Amine Oxidase System[1,2]

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Growth-inhibitory activity in mammalian cell and bacterial systems, as well as phagocidal action on T-uneven phages, of the naturally occurring polyamines, spermine and spermidine, is known to be the result of conversion of the polyamine to a cytotoxic derivative by means of the enzyme bovine plasma amine oxidase (BPAO). In an attempt to define the geometry of the substrate molecule required for this conversion, a number of polyamine structural variants were examined for growth-inhibitory activity against KB cells (human epidermoid carcinoma) in culture in media supplemented with calf serum (contains BPAO). During these studies, it became necessary to assay some polyamines, other than diethylenetriamine and triethylenetetramine, with 2-aminoethylamino terminal groupings. Such compounds were prepared expeditiously by direct mono- and diaminoethylation of α,ω-alkylenediamines; the diaddition products from these reactions, however, are not of unequivocal structure and it required X-ray diffraction powder analysis to characterize the products as the desired bis-substituted derivatives. Correlation of ID_{50} values with molecular structure indicates that the terminal grouping $H_2N(CH_2)_3$-NH is essential for inhibitory activity and that the secondary amino group must be at least 3 carbon atoms removed from the next basic center. These findings suggest the existence of a hydrophobic region adjacent to the active site of BPAO. We believe that the failure of certain amines to undergo oxidative deamination in the presence of BPAO is related to their inability to bond at this hydrophobic region.

For some time, we have been engaged in a program of synthesis of analogs of the biogenetic amines spermidine (**1**, $x = 4$) and spermine (**2**, $x = 4$) as a source of potential antitumor substances. In connection with this program, we previously reported the synthesis of some homologs of spermidine and spermine;[3] these products retained the 3-aminopropyl terminal function which is present in the naturally occurring polyamines, but showed variation of the putrescine portion of the molecule from 2 through 12 methylene units. A number of these substances were found to inhibit the growth of transplantable mouse tumors *in vivo*.[3,4] The tetrahydrochloride salt of **2**, $x = 9$, was particularly effective against a broad spectrum of experimental tumor systems in mice, rats, and hamsters.[4,5] Against the murine C1498 myeloid leukemia, this agent significantly inhibited tumor growth at the implant site and prevented leukemic infiltration in distant organs.[5]

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