[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF IRWIN, NEISLER & CO.]

Bis-ammonium Salts. Unsymmetric Derivatives of Decahydroquinoline and of Decahydroisoquinoline

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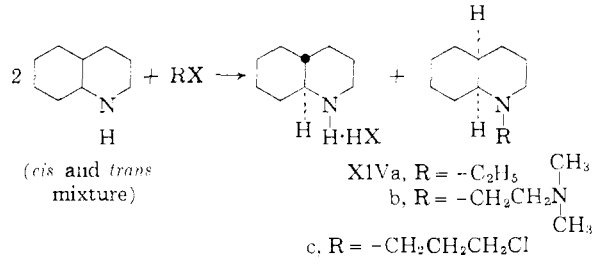
Unsymmetric bis-quaternary salts derived from decahydroquinoline and from decahydroisoquinoline have been prepared. Indirect evidence has been obtained showing that *cis*-decahydroquinoline reacts more rapidly with alkyl halides than does the *trans* isomer. A number of the derivatives displayed marked hypotensive activity accompanied by weak peripheral blocking action. The steric environment of the cationic nitrogen of the large head markedly influences the biological properties of these salts.

This report continues an investigation of unsymmetric bis-quaternary ammonium salts.[1] Earlier work[1] has served to define in some detail the structural features necessary for high hypotensive activity with, comparatively, minimal peripheral blocking action. In essence these are: a large cationic head of a lipophilic bulk which may be varied rather widely but which must lie within certain specified limits; a small cationic head of severely restricted size and with the cationic charge concentrated on the nitrogen; and a C_{2-3} linking chain. Both hypotensive and ganglionic blocking activities are usually enhanced, albeit not to the same degree or even in consistent proportion, by concentration of the charge on, and by decrease in the steric hindrance to approach to, the ammonium nitrogen of the large head (for convenience, hereinafter designated N^+_L). These features are, obviously, interdependent and fit with the previously outlined concept[1] of the mode of action of these salts.

The object of the present investigation was to examine more fully the effect on activity of the environment of N^+_L. To this end a series of decahydro-isoquinoline and -quinoline unsymmetric bis-salts, listed in Table I, have been prepared for comparison with the earlier reported tetrahydroisoquinoline derivatives.[2] Thereby, it was hoped to learn more concerning the effect of the steric environment[3] of N^+_L, and also concerning the effect, if any, of electrostatic interaction between N^+_L and the benzenoid ring (*i.e.*, in the tetrahydroisoquinoline derivatives).[4]

Most of the bis-quaternary salts were conveniently prepared by the general method described earlier.[1] Yields were comparable although the decahydroquinoline products were particularly hygroscopic and difficult to purify. Those salts designated in Table I as *trans* were prepared by quaternization of N-methyl-*trans*-decahydro-quinoline or -isoquinoline. Needless to say, the *cis–trans*-salt mixtures were similarly derived from the corresponding mixed tertiary bases. Compound VII and VIII represent two apparently stereoisomeric, or mixtures of stereoisomeric, salts which were obtained from the reaction of 3-bromopropyl-N-methylpyrrolidinium bromide with the *cis–trans* mixed N-methyldecahydroisoquinolines. The two preparations were different and neither corresponded to the salt X, obtained by quaternization of the pure *trans* base. Since the salts have three asymmetric centers, no stereochemical conclusions can be drawn at this time.

The routes to the decahydroquinoline derivatives IV and V involved, as the first step, the reaction in benzene solution of two equivalents of a mixture of *cis*- and *trans*-decahydroquinoline with one equivalent of an alkyl halide. The precipitate of decahydroquinoline hydrohalide formed in this process was found to be the salt of the *trans* isomer (identified by the melting point and mixed melting point of the base). On the basis of this indirect evidence, the alkylated product is presumed to be at least predominantly derived from the *cis* isomer, *i.e.*



This implies the process is sterically controlled, the *cis* base reacting faster with alkyl halide than the *trans*. Further, it might be noted that by this means pure *trans*-decahydroquinoline can be conveniently obtained from a mixture of the isomers.

Compound XIVa was obtained by alkylating the base with ethyl iodide, XIVb with dimethylaminoethyl chloride and XIVc with trimethylene chlorobromide. Quaternization of XIVb with methyl bromide provided IV. Reaction of XIVc with trimethylamine afforded decahydroquinolinopropyltrimethylammonium chloride. This could not be

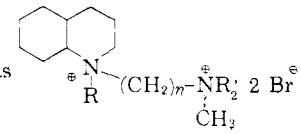
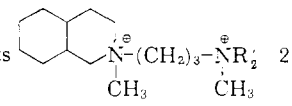
(1) See the preceding paper in this series, A. P. Gray, W. L. Archer, E. E. Spinner and C. J. Cavallito, THIS JOURNAL, **79**, 3805 (1957), and references cited therein; T. B. O'Dell and M. D. Napoli, *J. Pharmacol. Exptl. Therap.*, **120**, 438 (1957).

(2) A. P. Gray, W. L. Archer, D. C. Schlieper, E. E. Spinner and C. J. Cavallito, THIS JOURNAL, **77**, 3536 (1955).

(3) Since the last paper from these laboratories a number of reports have appeared, particularly by Rice and Grogan, describing other series of unsymmetrics that have a closely related bearing on the steric problem. Unfortunately, the dearth of detailed biological data precludes any attempt at correlation of these at this time. See L. M. Rice and C. H. Grogan, *J. Org. Chem.*, **23**, 844 (1958), and references cited therein; J. H. Biel and A. E. Drukker, U. S. Patent 2,834,770 (1958).

(4) Ultraviolet spectral evidence has recently been reported that demonstrates the existence of interaction between a quaternary nitrogen and an α,β-unsaturated ketone system. This effect has been interpreted as a transannular electrostatic interaction by V. Georgian, *Chemistry & Industry*, 1480 (1957), or, less likely, as an inductive effect by C. B. Clarke and A. R. Pinder, *J. Chem. Soc.*, 1967 (1958). It seems reasonable that there should be similar, although weaker, interaction with a benzenoid ring.

TABLE I

	Isomer	R	NR_2'	n	M.p., °C.[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Bromine, %[b] Calcd.	Bromine, %[b] Found	Hypotensive activity[c,d]	Ganglionic blockade[c,e]
	A. Decahydroquinoline salts 													
I	*cis–trans* mixt.	CH_3	$N(CH_3)_2$	3	108–110	$C_{16}H_{34}Br_2N_2$	46.38	46.11	8.29	8.10	38.58	38.15	30	3
II	*trans*	CH_3	$N(CH_3)_2$	3	130–136	$C_{16}H_{34}Br_2N_2$	46.38	45.56	8.29	8.27	38.58	38.33	80	4
III	*trans*	CH_3	C_4H_8N[f]	3	83–86	$C_{18}H_{36}Br_2N_2$	49.09	48.50	8.24	8.08	36.30	35.72	200	4
IV	*cis*[j]	CH_3	$N(CH_3)_2$	2	142	$C_{15}H_{32}Br_2N_2$	45.00	44.75	8.06	7.78	39.93	40.08	2	2
V	*cis*[j]	H	$N(CH_3)_2$	3	238–241	$C_{15}H_{32}Cl_2N_2$	57.86	57.58	10.36	10.36	22.78[i]	22.51[i]	4	...
	B. Decahydroisoquinoline salts 													
VI	*cis–trans* mixt.		$N(CH_3)_2$		238–241	$C_{16}H_{34}Br_2N_2$	46.38	46.12	8.29	7.97	38.58	38.73	40	4
VII	*cis–trans* mixt.		C_4H_8N[f]		218–220	$C_{18}H_{36}Br_2N_2$	49.09	49.45	8.24	8.64	36.30	36.22	50	...
VIII	*cis–trans* mixt.[g]		C_4H_8N[f]		188–189	$C_{18}H_{36}Br_2N_2$	49.09	49.32	8.24	8.29	36.30	36.48	50	4
IX	*trans*		$N(CH_3)_2$		231–233	$C_{16}H_{34}Br_2N_2$	46.38	46.66	8.29	8.43	38.58	38.19	10	...
X	*trans*		C_4H_8N[f]		238–240	$C_{18}H_{36}Br_2N_2$	49.09	49.58	8.24	8.14	36.30	36.43	10	...
	C. $AN-(CH_2)_3-\overset{\ominus}{N}(CH_3)_3\ 2Br^{\ominus}$													
XI	AN = N-Methyltetrahydroisoquinoline				[h]								20	1
XII	AN = Phenethyldimethylamine				187–188	$C_{16}H_{30}Br_2N_2$	46.83	46.54	7.38	7.40	38.96	39.22	40	0.5

[a] Most of the salts melt with decomposition. Melting points are corrected for stem exposure. [b] Titrimetric determination of ionic halogen. [c] Relative activities on a scale on which hexamethonium = 1. Although this device is recognized to be an approximation, for convenience in this discussion the compounds are rated at doses equivalent (in potency) to 2 mg./kg. of hexamethonium bromide. [d] Intravenously in anesthetized dogs; relative activities are primarily weighted on the basis of duration at about the same percentage maximum fall. [e] Superior cervical ganglion in the cat; the relative activities are primarily weighted on the basis of duration of about the same degree of block. [f] Pyrrolidino group. [g] Apparently a stereoisomer of VII. [h] See Gray *et al.*, ref. 2. [i] Ionic chlorine. [j] Predominantly *cis;* see text.

isolated as the free amino substituted quaternary salt and was converted to its hydrochloride V.

Structure–Activity Relationships.—In attempting to interpret the relative hypotensive and ganglionic blocking activities reported in Table I, it must be kept in mind that the measured biological responses to a given quantity of drug are the resultant of at least two primary factors: drug distribution and drug–site interaction. Further, structural variations produce interrelated effects which are difficult to separate and evaluate individually. With these reservations it is worth noting that changes in the steric environment of N^+_L can have striking effects on activity. Thus, the *trans*-decahydroquinoline derivative II evidences 2–3 times the hypotensive activity of the *cis–trans* mixture I and must be many times more active than the pure *cis* material (note also the low hypotensive activity of the C_2-*cis* compound IV). On the other hand, in the decahydroisoquinoline series, the *cis–trans* mixed salts are 4–5 times as active as the pure *trans* derivatives (VI *vs.* IX; VII and VIII *vs.* X). In view of these differences it is perhaps not surprising that the *trans*-decahydroquinoline derivatives have 10–20 times the hypotensive activity of the corresponding isoquinoline salts (II and III *vs.* IX and X). There is hardly any difference, however, in the activities of the analogous mixed salts (I *vs.* VI). Ganglionic blocking action appears to vary in the same direction as hypotensive effect with steric changes in the group I–VIII but the variations are of almost negligible magnitude.

Inspection of models suggests a possible approach to correlation of these effects. The ability of the molecule to approach close to a surface *when* N^+_L *is within bonding distance of that surface* decreases in the order: *trans*- decahydroquinoline > *cis*-decahydroquinoline ≅ *cis*-decahydroisoquinoline > *trans*-decahydroisoquinoline. This order is in fair accord with the relative hypotensive activities.

Of the compounds tabulated the tetrahydroisoquinoline derivative XI is the most capable of close approach to a surface. On this basis, XI should be the most potent agent in Table I, whereas it has, in fact, hypotensive activity within the range of the decahydroisoquinoline analogs. Explanation may lie in transannular electrostatic interaction between N^+_L and the benzene ring of XI (*vide supra*). Such interaction would polarize the molecule and serve to decrease the electrostatic energy of bonding to a site. Alternative explanations (*e.g.*, one based on distribution) are not, however, ruled out. The phenethyldimethylamine salt (XII) is included in Table I for comparison as a ring-opened analog of XI.

As has been remarked with other series,[2] substitution of N-methylpyrrolidinium for the trimethylammonium of the small head does not have a consistent effect upon activity. It is of some interest that in the decahydroquinoline series a compound, V, in which N^+_L is *tertiary* is a quite active agent, although a comparable tetrahydroisoquinoline analog was almost inert.[2] Active monoquaternary salts have previously been reported by Rice and Grogan.[5] Since the tertiary nitrogen of V, and of the azabicycloöctane derivatives of Rice and Grogan, is considerably more basic than that of the

(5) L. M. Rice and C. H. Grogan, *J. Org. Chem.*, **22**, 185 (1957).

corresponding tetrahydroisoquinoline derivative, the relative activities are explicable in terms of the concentration of di-cation at physiological *p*H.

Acknowledgments.—The authors are indebted to Dr. T. B. O'Dell and his associates for the pharmacological data. Mr. D. F. Cortright and Miss Mary Unroe of these laboratories performed the ionic halogen and basic nitrogen determinations.

Experimental[6]

Intermediates.—The preparation of pure *trans*-N-methyldecahydroisoquinoline and of a *cis–trans* mixture was described earlier.[7] *trans*-Decahydroquinoline and a *cis–trans* mixture of decahydroquinolines were Eastman (White Label) Chemicals, and were methylated by the Eschweiler–Clarke method[8] to give, respectively, *trans*-*N*-methyldecahydroquinoline, b.p. 51–52° (3.5 mm.), $n^{25}D$ 1.4787, and N-methyldecahydroquinoline (*cis–trans* mixture), b.p. 117–118° (50 mm.), $n^{25}D$ 1.4833.

1-(3-Chloropropyl)-decahydroquinoline (XIVc).—A solution of 38 g. (0.27 mole) of decahydroquinoline (*cis–trans* mixture) and 21.4 g. (0.13 mole) of trimethylene chlorobromide in 75 ml. of benzene was allowed to stand at room temperature for three days. The precipitate was collected and washed with ether to give 19.5 g. (65%) of *trans*-decahydroquinoline hydrobromide, m.p. 280–281° (lit.[9] m.p. 277–279°). Decomposition of the salt provided *trans*-decahydroquinoline, m.p. 47–49°, no melting point depression on admixture with authentic material (lit.[9] m.p. 48°).

The filtrate and ether washings from the hydrobromide salt were combined and extracted with 10% hydrochloric acid. The acid extract was made alkaline and extracted with ether. After drying and removal of the ether the residue was distilled to yield 12.6 g. (43%) of XIVc as a colorless, relatively unstable oil, b.p. 94–96° (0.3 mm.). Presumably the *cis* isomer predominates in the product.

The hydrochloride salt of XIVc, recrystallized from isopropyl alcohol–ether, showed m.p. 162–164°.

Anal. Calcd. for $C_{12}H_{23}Cl_2N$: C, 57.15; H, 9.19; Cl (ionic), 14.06. Found: C, 57.02; H, 9.39; Cl, 14.01.

1-Ethyldecahydroquinoline (XIVa).—To a solution of 20.0 g. (0.14 mole) of the mixture of decahydroquinoline isomers in 100 ml. of benzene was added 11.2 g. (0.07 mole) of ethyl iodide. After the initial reaction had subsided the mixture was refluxed on the steam-bath for 1 hr. The precipitate of 16.0 g. (83%) of *trans*-decahydroquinoline hydriodide (identified on the basis of the melting point of the free base) was separated and the filtrate was distilled to yield 8.0 g. (67%) of 1-ethyldecahydroquinoline, assumed to be largely the *cis* isomer, b.p. 65–67° (2.5 mm.),[10] $n^{20}D$ 1.4830.

1-(Dimethylaminoethyl)-decahydroquinoline (XIVb).—Similarly, a solution of 30 g. (0.22 mole) of the mixed decahydroquinolines and 11.6 g. (0.11 mole) of dimethylaminoethyl chloride in 75 ml. of benzene was refluxed on the steam-bath for 80 hr. Filtering off the precipitate of 13.6 g. (72%) of *trans*-decahydroquinoline hydrochloride (identified as before) and distilling the filtrate afforded 9.0 g. (40% yield) of XIVb, probably mainly *cis*, b.p. 104–106° (1.5 mm.), $n^{25}D$ 1.4862.

The dihydrochloride salt of XIVb, recrystallized from ethanol, melted with decomposition at 272°.

Anal. Calcd. for $C_{13}H_{28}Cl_2N_2$: C, 55.10; H, 9.96; Cl, 25.03. Found: C, 55.24; H, 10.21; Cl (ionic), 24.48.

Reaction of XIVc with Trimethylamine. Preparation of V.—Into a solution of 10.0 g. (0.04 mole) of XIVc in 75 ml. of ethanol was bubbled 12.0 g. (0.2 mole) of anhydrous trimethylamine. After being heated in a pressure bottle at 50° for 16 hr., the solution was evaporated *in vacuo* to yield 12 g. of a thick oil residue. This material rapidly liberated trimethylamine on standing. It was, therefore, redissolved in ethanol and treated with ethereal hydrogen chloride. Removal of the ethanol under reduced pressure left an oil which was crystallized and several times recrystallized from isopropyl alcohol-ether to yield 4.3 g. of V, m.p. 238–241°.

Reaction of 2-Methyldecahydroisoquinoline (*cis–trans* Mixture) with 3-Bromopropyl-N-methylpyrrolidinium Bromide. Preparation of VII and VIII.—A solution of 11.0 g. (0.07 mole) of the N-methyldecahydroisoquinoline mixture and 20.7 g. (0.07 mole) of 3-bromopropyl-N-methylpyrrolidinium bromide[11] in 50 ml. of acetonitrile was refluxed on the steam-bath for 7 hr. The solid which precipitated from the cooled solution was recrystallized from isopropyl alcohol to give 9.6 g. of white powder, m.p. 188–193°. Two further recrystallizations afforded 2.0 g. of VII, m.p. 218–220°.

Recrystallization of a mother liquor fraction from isopropyl alcohol provided VIII, m.p. 188–189°.

(6) Microanalyses were performed by the Clark Microanalytical Laboratories, Urbana, Ill., and by the Micro-Tech Laboratories, Skokie, Ill.

(7) A. P. Gray and D. E. Heitmeier, THIS JOURNAL, **80**, 6274 (1958).

(8) M. Ehrenstein and W. Bunge, *Ber.*, **67**, 1728 (1934).

(9) I. M. Heilbron, "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1953.

(10) Y. Sawa, K. Inouye and T. Kitamura, *J. Pharm. Soc. Japan*, **63**, 401 (1943); *C. A.*, **44**, 7323g (1950), report b.p. 71–75° (3.5 mm.) for 1-ethyldecahydroquinoline of unspecified configuration, prepared in another way.

(11) A. P. Gray, D. C. Schlieper, E. E. Spinner and C. J. Cavallito, THIS JOURNAL, **77**, 3648 (1955).

DECATUR, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CARNEGIE INSTITUTE OF TECHNOLOGY]

2,4,6-Tri-*p*-chlorophenylpyridine—a By-product of a Fischer Indole Transformation[1]

BY ROBERT B. CARLIN AND LUIS AMOROS-MARIN[2]

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A by-product previously isolated from the Fischer reaction of *p*-chloroacetophenone 2,6-dichlorophenylhydrazone with molten stannous chloride at 260° has now been shown to be 2,4,6-tri-*p*-chlorophenylpyridine. The chief product of this reaction was 2-*p*-chlorophenyl-7-chloroindole, but a small amount of 2-*p*-chlorophenyl-5,7-dichloroindole has also been isolated. A relatively larger amount of the latter compound and a better conversion of the hydrazone to products was observed when stannous chloride–hydrogen chloride replaced stannous chloride as the promoter and when the reaction temperature was 160°, but no triarylpyridine was formed under these conditions. 2,4,6-Tri-*p*-chlorophenylpyridine was also formed, along with 2-*p*-chlorophenyl-7-chloroindole, when *p*-chloroacetophenone *o*-chlorophenylhydrazone was fused with stannous chloride at 300°. The same hydrazone, when heated to 300° with zinc chloride, gave 2-phenylindole as the only crystalline product. *p*-Chloroacetophenone phenylhydrazone gave only 2-*p*-chlorophenylindole and no triarylpyridine when fused with stannous chloride at 260°. An unexpected stability of *p*-chloroacetophenone *o*-chlorophenylhydrazone was demonstrated when 33% of it was recovered unchanged after an hour's treatment with stannous chloride at 260°.

An investigation of the action of molten stannous chloride on the 2,6-dichlorophenylhydrazones of five ketones disclosed that each reaction yielded a 7-chloroindole but that a by-product could be isolated in only one instance; *p*-chloroacetophenone

(1) Submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the Carnegie Institute of Technology.

(2) American Viscose Corp. Fellow, 1954–1955.