reaction mixture heated on the steam-bath for an additional 3 hours. The cold mixture was treated cautiously with water, the xylene layer separated and extracted with dilute sulfuric acid. The aqueous layer was brought to a *p*H of about 8 with potassium carbonate and extracted with ether. The ether solution was water-washed, dried over sodium sulfate, evaporated, and the residue distilled to yield 7.0 g. (60%) of the product as a thick oil, b.p. 167–170° (0.1 mm.).

On making the remaining alkaline layer strongly basic with 20% sodium hydroxide, a small amount of dark, green fluorescent oil was obtained. This could not be purified.

The dihydrochlorides and dimethiodides of the Ind-N-(dialkylaminoalkyl)-carbolines were prepared by the usual procedures. The dihydrochlorides generally were recrystallized from ethanol or propanol, and the dimethiodides from methanol.

Py-N-substituted Carboline Salts.—The examples that follow will serve to illustrate the methods used for the preparation of the salts listed in Table I. Yields ranged from a low of 20% for the α-carboline derivative up to about 70%. The β-carboline salts were as a rule obtained in yields of 50–70%.

A. Reaction of 1-Methyl-9-pyrid-3,4b-indole with 3-Bromopropylmethyldiethylammonium Bromide. Compound VI.—A solution of 12.0 g. (0.037 mole) of crude (90% pure) 3-bromopropylmethyldiethylammonium bromide and 3.6 g. (0.02 mole) of harman in 75 ml. of acetonitrile was refluxed on the steam-bath for 15 hours. The precipitate was collected and recrystallized from ethanol to yield 6.4 g. (69%) of VI, m.p. 252–254° dec.

B. Reaction of 1,9-Dimethyl-9-pyrid-3,4b-indole with 3-Bromopropylmethylpyrrolidinium Bromide. Compound XI.—Refluxing a solution of 2.7 g. (0.014 mole) of Ind-N-methylharman and 5.7 g. (0.021 mole) of 3-bromopropylmethylpyrrolidinium bromide in 30 ml. of acetonitrile for 18 hours afforded 5.1 g. of crystalline precipitate, m.p. 250–253°. After two recrystallizations from ethanol, there was obtained 3.5 g. (52% yield) of XI, m.p. 254–257° with gas evolution.

C. Reaction of 1,2-Dimethyl-1,2,3,4-tetrahydro-9-pyrid-3,4b-indole with 3-Bromopropyltrimethylammonium Bromide. Compound XII.—A solution of 2.8 g. (0.015 mole) of Py-N-methyltetrahydroharman and 3.9 g. (0.015 mole) of bromopropyltrimethylammonium bromide in 50 ml. of isopropyl alcohol was refluxed on the steam-bath for 24 hr. On refrigeration a crystalline precipitate formed. Two recrystallizations from *n*-propyl alcohol and ethyl acetate yielded 2.0 g. (29%) of XII, m.p. 220–222°.

D. Reaction of 9-Pyrid-2,3b-indole with 3-Bromopropyltrimethylammonium Bromide. Compound XIV.—A solution of 3.4 g. (0.02 mole) of α-carboline and 10.4 g. (0.04 mole) of bromopropyltrimethylammonium bromide in 100 ml. of a 1-to-1 mixture of dioxane and isopropyl alcohol was refluxed (oil-bath) for 50 hours. Addition of ether to the cooled solution precipitated the crude product which was recrystallized several times from ethanol and ethyl acetate and finally from absolute ethanol to yield 1.8 g. (21%) of XIV, m.p. 226–230°.

Acknowledgment.—The authors wish to express their appreciation to Mr. Donald L. Miller for performing the ionic halogen and basic nitrogen determinations.

DECATUR, ILLINOIS

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

Bis-ammonium Salts. Unsymmetrical Derivatives of Some Isoquinolines and Related Heterocyclic Bases[1]

BY ALLAN P. GRAY, WESLEY L. ARCHER, DOROTHY C. SCHLIEPER, ERNEST E. SPINNER AND CHESTER J. CAVALLITO

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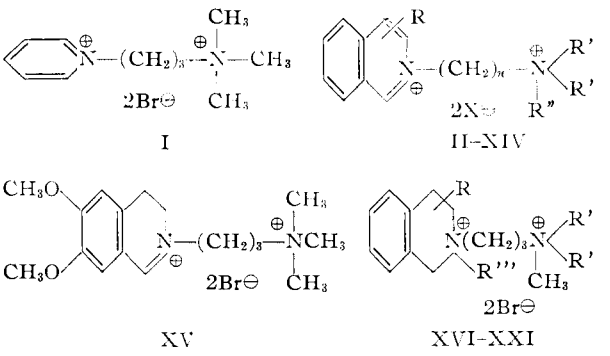
Investigations of unsymmetrical bis ammonium salts have been extended to include derivatives of isoquinoline, tetrahydroisoquinoline and various substituted relatives, 2,3-dihydro-1-benz[de]isoquinoline, some substituted quinolines, benzo[f]quinoline and phenanthridine. As in the carboline series, each of these salts comprises a small cationic head attached through an alkyl chain to the ring nitrogen of a heterocyclic base. Many of these salts possess potent hypotensive activity not necessarily associated with strong ganglionic blockade. Structure–activity relationships are discussed.

Some carboline unsymmetrical bis-ammonium salts with high hypotensive activity were described in the preceding paper.[2] On the basis of that investigation, requirements for pharmacological activity in regard to size of the small cationic head and distance between the two charged nitrogens were fairly well delineated, and tentative conclusions were drawn concerning the effects of changes in charge distribution and degree of ionization. These studies have been continued in order to probe further the problem of the relationship of chemical to biological properties and, in particular, to ascertain the structural and size limitations imposed on the large, charged heterocyclic nucleus.

That the β-carboline ring system was not unique in imparting activity soon became evident as a wide variety of heterocyclic bases has afforded potent unsymmetrical bis salt derivatives.[3] The present series comprises derivatives of pyridine, isoquinoline, tetrahydroisoquinoline, 2,3-dihydro-1-benz[de]isoquinoline, quinoline, benzo[f]quinoline and phenanthridine, *viz.*



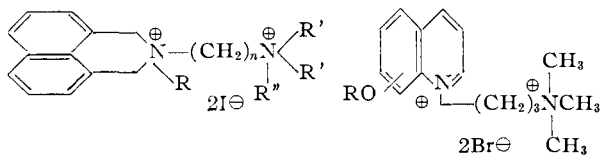
I II–XIV

XV XVI–XXI

(1) Presented in part before the Division of Medicinal Chemistry at the 127th National Meeting of the American Chemical Society, Cincinnati, Ohio, March 29–April 7, 1955.

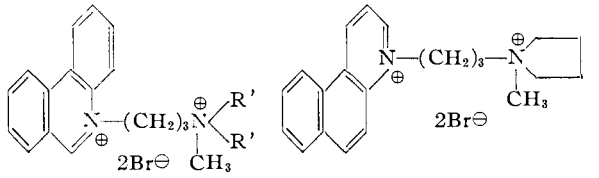
(2) A. P. Gray, E. E. Spinner, D. C. Schlieper and C. J. Cavallito, THIS JOURNAL, **77**, 3533 (1955).

(3) Subsequent to the initation of this work, L. M. Rice, C. H. Grogan and E. E. Reid (*ibid.*, **75**, 4911 (1953)), reported on the marked hypotensive activity of various isoindoline bisquaternary derivatives. These were considered by the authors to be structurally related to the Ergot alkaloids. One of these isoindole derivatives, obtained through the courtesy of Dr. Rice, showed intense ganglionic blocking activity. It remains to be determined whether the isoindoles also have a central component of action (see Biological section).



XXII–XXV

XXVI–XXVIII



XXIX, XXX

XXXI

With the exception of X and XIX, which are monoquaternary-tertiary amine analogs, all of the compounds listed in Tables I and II are bisquaternary ammonium salts. Except for the dihydrobenz[de]isoquinoline derivatives (XXII–XXV) all of the bisquaternaries were prepared by alkylation of the tertiary nitrogen of the appropriate heterocyclic base with the desired ω-bromoalkyl quaternary ammonium bromide.[4] As previously noted in other series (*cf.* ref. 2), acetonitrile was found to be a highly useful solvent for the quaternization of all but the tetrahydro bases, which were more satisfactorily treated in an alcoholic solvent. If the base was readily available or the bis salt product was not easily separable from the monoquaternary starting material, an excess of the base was used; otherwise, either equimolar proportions or an excess of the monosalt was employed. As indicated in the tables, yields were generally good—if one excludes those from hindered bases such as 1-methyl- and 3-methylisoquinoline and from weak bases such as the quinolines and benzoquinolines.

Several methods were tried for the preparation of required N-alkyltetrahydroisoquinolines. These included: reduction of isoquinoline with sodium and alcohol followed by methylation *via* the Eschweiler–Clarke process, reduction of the isoquinoline alkiodide with sodium borohydride[5] or with zinc and hydrochloric acid, and hydrogenation of the N-alkylisoquinolinium bromide over Adams catalyst. Of these the catalytic method proved very satisfactory and most generally applicable.

A reaction sequence similar to that employed by Rice, Grogan and Reid[3] for the preparation of their isoindoline derivatives was used for the synthesis of the 2,3-dihydro-1-benz[de]isoquinoline bis salts, XXII–XXV. This involved the reduction of the appropriate N-(dialkylaminoalkyl)-naphthalimide with lithium aluminum hydride followed by quaternization of the ditertiary amine product with methyl or ethyl iodide. Owing principally to the low solubility of these naphthalimides in ether, the reductions were most successfully carried out by adding the imide in tetrahydrofuran solution to an ether slurry of an excess of the hydride. The naphthalimides required for XXII–XXIV were prepared by fusion of a mixture of naphthalic anhydride with the dialkylaminoalkylamine. Alkylation of the potassium salt of naphthalimide with chloropropylpyrrolidine afforded the intermediate for XXV.

Alkylation of an excess of isoquinoline with chloropropyldimethylamine hydrochloride provided the monoquaternary analog X, in poor yield and accompanied by appreciable amounts of salt by-products. XIX was prepared conveniently by catalytic hydrogenation of II.

Biological Properties.—The more significant relationships indicated between chemical structure and biological activity in the preceding paper[2] are confirmed and extended in the present series.[6] The requirement of a short linking chain for hypotensive activity of appreciable duration is more closely pinpointed. Also, it is again evident that the small cationic head in unsymmetric bisquaternaries must be smaller than triethylammonium (VIII) in order for the compound to lower blood pressure. Limitations with respect to size of the large cationic head become apparent upon comparison of I, II and XXIX; negligible activity is found with the simple pyridine derivative I, but duration of hypotensive response is increased with the bicyclic and further enhanced with the tricyclic derivatives. Thus, for high activity, the small cationic head cannot be greater, nor the large cationic head smaller, than certain critical limits.[7]

Ionic requirements for hypotensive potency in this series are clearly evident from the relative activities of pairs II and X, and XVI and XIX. Both terminal nitrogens apparently must be quaternary (or at any rate essentially completely ionized at physiological pH[2]); if either nitrogen is merely tertiary amino, as in X and XIX, activity is weak and fleeting. The increase in activity with increased concentration of charge about the quaternary of the large head is quite evident in that the compounds in Table II are appreciably more active than related analogs in Table I (note smaller doses used with Table II compounds). The poor activity of IX shows that charge distribution about the nitrogen of the small cationic head similarly influences hypotensive potency.

In the preceding paper[2] it was suggested that steric hindrance, particularly in relation to accessibility of the quaternary nitrogen atoms, might influence not only the ease of approach of the compounds to the receptor sites but also the ease of displacement by other ions after adsorption. These factors together with the ionic bonding energies (influenced by steric factors as well as by degree of ionization of and charge distribution about the nitrogen atoms) are of major importance in determining the selectivity of biological properties of these compounds. Of speculative interest is the effect of α-methyl substitution on the isoquinoline nucleus. The order of hypotensive potency, XI (1-methylisoquinoline) > II > XII (3-methyl analog), is difficult to explain but may be related

(4) A. P. Gray, D. C. Schlieper, E. E. Spinner and C. J. Cavallito, THIS JOURNAL, **77**, 3533 (1955).

(5) R. Torossian, *Compt. rend.*, **235**, 1312 (1952).

(6) In Tables I and II, the biological activities are reported only for selected doses. Comparison of dose–response variations for individual compounds are presented elsewhere with the detailed pharmacology (T. B. O'Dell, *et al.*, *J. Pharmacol. Exptl. Therap.*, in press).

(7) In subsequent papers these limits will be further delineated and it will be shown that upper limits in size of the large cationic head also exist.

TABLE I: QUINOLINE AND ISOQUINOLINE SALTS $RN\oplus\ (CH_2)_n—\oplus NR_2'R''2Br\ominus$

	RN	n	NR'₂	R''	Method,[g] yield, %	M.p., °C.[a]	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. Br[b]	Found C	Found H	Found Br[b]	Hypotensive activity % fall/duration hr.[i] 1 (or 2) mg. per kg.	Ganglionic blockade[j]
I	Pyridine	3	$N(CH_3)_2$	CH_3	A, 72	224–226	$C_{11}H_{20}Br_2N_2$	38.84	5.94	46.99	38.88	6.19	46.80	35/0.1	
II	Isoquinoline	3	$N(CH_3)_2$	CH_3	A, 83	218–219	$C_{15}H_{22}Br_2N_2$	46.17	5.69	40.96	46.70	5.67	40.87	40/0.5 (50/2.5)	+
III	Isoquinoline	4	NC_4H_8[d]	CH_3	A, 63	184–192	$C_{18}H_{26}Br_2N_2$	50.24	6.10	37.15	50.69	6.38	36.44	35/0.75 (50/1)	3+
IV	Isoquinoline	5	$N(CH_3)_2$	CH_3	A, 81	222–225	$C_{17}H_{26}Br_2N_2$	48.81	6.28	38.21	48.50	6.47	37.57	15/0.1 (20/0.1)	
V	Isoquinoline	6	$N(CH_3)_2$	CH_3	A, 78	199–201	$C_{18}H_{28}Br_2N_2$	50.01	6.54	36.97	49.96	6.68	37.00	15/0.1 (25/0.1)	
VI	Isoquinoline	3	NC_4H_8[d]	CH_3	A, 83	148–153	$C_{17}H_{24}Br_2N_2$	49.05	5.82	38.40	49.31	6.11	38.07	30/1.5 (40/2.5)	3+
VII	Isoquinoline	3	NC_4H_8O[e]	CH_3	A, 90	196–198	$C_{17}H_{24}Br_2N_2O$	47.23	5.61	36.98	46.64	5.71	36.99	35/2 (50/2)	3+
VIII	Isoquinoline	3	$N(C_2H_5)_2$	C_2H_5	A, 66	203–205	$C_{18}H_{28}Br_2N_2$	50.01	6.54	36.97	49.68	6.64	36.33	0 (0)	
IX	Isoquinoline	3	C_5H_5N[f]		A, 59	202–204	$C_{17}H_{18}Br_2N_2$	49.78	4.42	38.97	49.45	4.59	38.77	25/0.1 (40/0.1)	0
X	Isoquinoline	3	$N(CH_3)_2$	H		214–215	$C_{14}H_{20}Cl_2N_2$	58.53	7.03	24.69[c]	59.13	7.37	24.36[c]	30/0.1	
XI	1-Methyl-	3	$N(CH_3)_2$	CH_3	B, 29	259	$C_{16}H_{24}Br_2N_2$	47.54	5.98	39.54	47.78	5.77	39.10	50/4	3+
XII	3-Methyl-	3	$N(CH_3)_2$	CH_3	B, 33	235–238	$C_{16}H_{24}Br_2N_2$	47.54	5.98	39.54	47.35	5.91	39.33	50/0.1	
XIII	4-Bromo-	3	$N(CH_3)_2$	CH_3	B, 74	237–239	$C_{15}H_{21}Br_3N_2$	38.40	4.51	34.07	38.59	4.75	33.89	40/2	4+
XIV	4-Acetamido-	3	NC_4H_8[d]	CH_3	B, 54	227–229	$C_{19}H_{27}Br_2N_3O$	48.21	5.75	33.77	48.69	5.69	33.57	40/2	
XV	6,7-Dimethoxy-3,4-dihydro-	3	$N(CH_3)_2$	CH_3	F, 49	196[h]	$C_{17}H_{28}Br_2N_2O_2$	45.15	6.24	35.34	45.24	6.75	34.83	15/0.5	
XXVI	7-Quinolinol	3	$N(CH_3)_2$	CH_3	E, 16	234	$C_{15}H_{22}Br_2N_2O$	44.35	5.46		44.65	5.91		25/0.1	
XXVII	8-Quinolinol	3	$N(CH_3)_2$	CH_3	E, 8	201–202[h]	$C_{15}H_{22}Br_2N_2O$	44.35	5.46	39.35	44.15	5.57	38.71	10/0.1	
XXVIII	8-Methoxyquinoline	3	$N(CH_3)_2$	CH_3	F, 26	177	$C_{16}H_{24}Br_2N_2O$	45.73	5.76	38.04	45.39	5.93	37.65	15/0.1	2+
XXIX	Phenanthridine	3	$N(CH_3)_2$	CH_3	B, 28	235	$C_{19}H_{24}Br_2N_2$	51.83	5.49	36.31	52.15	5.61	35.70	50/2.5	
XXX	Phenanthridine	3	NC_4H_8[d]	CH_3	B	239–240	$C_{21}H_{26}Br_2N_2$	54.09	5.62	34.28	54.53	5.60	34.16	50/>2	2+
XXXI	Benzo[f]quinoline	3	NC_4H_8[d]	CH_3	F, 22	221	$C_{21}H_{26}Br_2N_2$	54.09	5.62	34.28	54.24	5.55	33.90	55/>2	2+

[a] Many of the salts melt with decomposition. [b] Ionic halogen determination. [c] Analysis for chloride ion. [d] Pyrrolidino group. [e] Morpholino group. [f] NR'_2R'' = pyridine [g] The letter refers to that quaternization procedure, described in the Experimental, which most closely approximates the one employed. [h] Yellow crystals. [i] In anesthetized dogs; dose 1 (or 2) mg. per kg. intravenously; values are: % maximum fall in blood pressure/duration in hours before return to pre-drug level. [j] Superior cervical ganglion in cat; dose 2 mg. per kg. intravenously, block from 0 (zero) to 4+ (complete) for from 30 to 120 minutes.

TABLE II: TETRAHYDROISOQUINOLINE AND 2,3-DIHYDRO-1-BENZ[DE]ISOQUINOLINE SALTS $R—\overset{\oplus}{N}\ominus—(CH_2)_n—\overset{\oplus}{N}R'_2R''2X\ominus$

	Reduced isoquinoline	R	n	NR'₂	R''	X	Method[e] yield, %	M.p., °C.[a]	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. X	Found C	Found H	Found X[b]	Hypotensive action[f] (0.25 mg. per kg.)	Ganglionic blockade[g] (0.5 mg. per kg.)
XVI	Tetrahydro-	CH_3	3	$N(CH_3)_2$	CH_3	Br	C, 76	239–242	$C_{16}H_{28}Br_2N_2$	47.06	6.93	39.15	46.63	6.80	39.13	45/4	3+
XVII	Tetrahydro-	CH_3	3	NC_4H_8[d]	CH_3	Br	C, 62	210–214	$C_{18}H_{30}Br_2N_2$	49.77	6.98	36.80	49.99	7.26	36.16	40/2	±
XVIII	Tetrahydro-	C_2H_5	3	$N(CH_3)_2$	CH_3	Br	D, 76	247	$C_{17}H_{30}Br_2N_2$	48.35	7.17	37.85	48.55	7.33	37.66	45/>3	±
XIX	Tetrahydro-	H	3	$N(CH_3)_2$	CH_3	Br		198–203	$C_{15}H_{26}Br_2N_2$	45.70	6.65	40.55	45.60	6.62	40.06	25/0.1	
XX	1-Me-1,2,3,4-tetrahydro-	CH_3	3	$N(CH_3)_2$	CH_3	Br	F, 44	228–229.5	$C_{17}H_{30}Br_2N_2$	48.35	7.16	37.85	48.55	7.31	37.48	35/3	2+
XXI	3-Me-1,2,3,4-tetrahydro-	CH_3	3	$N(CH_3)_2$	CH_3	Br	F, 50	173–175	$C_{17}H_{30}Br_2N_2$	48.35	7.16	37.85	48.46	7.10	37.69	10/0.2	
XXII	2,3-Dihydro-1-benz[de]-	CH_3	2	$N(C_2H_5)_2$	CH_3	I		201–204	$C_{20}H_{30}I_2N_2$	43.49	5.47	45.96	43.21	5.43	45.82	10/0.1	2+
XXIII		CH_3	3	$N(CH_3)_2$	CH_3	I		241	$C_{19}H_{28}I_2N_2$	42.39	5.24	47.16	42.34	5.30	46.62	55/>2	±
XXIV	2,3-Dihydro-1-benz[de]-	C_2H_5	3	$N(CH_3)_2$	C_2H_5	I		224	$C_{21}H_{32}I_2N_2$	44.53	5.69	44.82	44.35	5.68	44.08	35/3	+
XXV		CH_3	3	NC_4H_8[d]	CH_3	I		208–209	$C_{21}H_{30}I_2N_2$	44.69	5.36	44.98	44.31	5.55	45.19[c]	25/>1	2+

[a] Most of the salts melted with decomposition. [b] Ionic halogen determinations. [c] Microanalysis for total iodine. [d] Pyrrolidino group. [e] The letter refers to that quaternization procedure, described in the Experimental, which most closely approximates the one employed. [f] In anesthetized dogs; dose 0.25 mg. per kg. intravenously; values are: % maximum fall in blood pressure/duration in hours before return to pre-drug level. [g] Superior cervical ganglion in cat; dose 0.5 mg. per kg. intravenously, block from 0 (zero) to 4+ (complete) for from 30 to 120 minutes.

to steric effects and to the relative concentrations of un-ionized, pseudobase species present at the site of action. The relative activities of the tetrahydro analogs of these (XVI $\geqslant$ XX > XXI) can only be ascribed to steric hindrance about the charged ring-nitrogen.[8] The influence of a structural variation should be viewed not only from the aspect of its individual relationship toward a receptor but also in regard to the influence of the particular variation on the sum total of the properties of the molecule, *e.g.*, the seemingly inconsistent effect on activities in these series of the trimethylammonium as compared with the N-methylpyrrolidinium small cationic head (*cf.* ref. 2).

Perhaps the most significant observation from both a theoretical and practical aspect is the marked variation in the ratios of hypotensive activity to sympathetic ganglionic blockade found among these compounds. From data obtained at several dose levels[6] it was observed that the C_3-compound VI had a greater duration of hypotensive action than the C_4-analog III, but sympathetic ganglionic blockade was more prolonged with III. Especially intriguing is the difference in biological properties of XVI and XVIII. Changing the large cationic head from N-methyl- to N-ethyltetrahydrosioquinoline should have negligible effects on charge distribution but would significantly influence the ease of approach of the compound to a receptor and its displacement therefrom. In a discussion of the pharmacodynamics of unsymmetric carboline derivatives[9] it was shown that minor structural variations in the small cationic head markedly affected the relative centrally-induced hypotensive activity and peripheral ganglionic blockade. This was explained on the basis of slightly greater permeability of the "blood-brain" barrier than of the sympathetic ganglion sheath to these compounds. XVIII shows this effect even more dramatically. Although nearly as potent as XVI as a centrally active hypotensive agent, XVIII is essentially devoid of blocking activity at sympathetic ganglia except at much higher doses. Evidence is therefore at hand that steric factors about *both* cationic groups of the unsymmetric bis-quaternaries not only influence total hypotensive activity but also the relative contribution of the central *vs.* the sympathetic ganglion sites to this activity. Molecular structural requirements for blockade of acetylcholine neurohumoral transmission may be similar, if not identical, for central as for sympathetic ganglion receptor sites but differences in permeability of protective barriers to these sites may modify the relative intensity of blockade.

(8) No attempt was made to separate stereoisomers of the 1- and 3-methyltetrahydroisoquinoline derivatives. The relative activities of these would certainly help in clarifying some of the steric effects. It would seem most probable, however, that the bromopropyltrimethylammonium bromide would approach the tetrahydroisoquinoline N from the side opposite to the 1- (or 3-) methyl group. The predominant isomer in each of the salt products should then be the one in which the side chain was equatorial and the 1- (or 3-) methyl was likewise equatorial and *cis* to the axial N-methyl group (*cf.* D. H. R. Barton, *Experientia*, **6**, 316 (1950)).

(9) C. J. Cavallito, A. P. Gray and T. B. O'Dell, *Arch. intern. pharmacodynamie*, **101**, 38 (1955).

Experimental[10]

Preparation of Intermediates.—1-Methyl-3,4-dihydroisoquinoline, prepared by a modification of the Bischler–Napieralski reaction,[11a] was dehydrogenated by 8 hours reflux over a 30% palladium-on-charcoal catalyst[11b] to yield 70% of 1-methylisoquinoline, b.p. 105–115° (8 mm.), $n^{25}D$ 1.6117; picrate, m.p. 230–231° dec.; methobromide, m.p. 212–213°. Cyclization of N-formylhomoveratrylamine with phosphorus oxychloride in toluene[12] afforded a 61% yield of 6,7-dimethoxy-3,4-dihydroisoquinoline, b.p. 127–133° (0.5 mm.), $n^{25}D$ 1.5932; picrate, m.p. 206–207° dec. (lit.[13] 201–203°).

Tetrahydroisoquinoline, b.p. 101–103° (8 mm.), $n^{25}D$ 1.5618, obtained by reduction of isoquinoline with sodium and alcohol,[14] was methylated with formaldehyde and formic acid[15] to yield 83% N-methyltetrahydroisoquinoline, b.p. 53–54° (0.5 mm.), $n^{26}D$ 1.5374. N-Ethyltetrahydroisoquinoline, b.p. 109° (25 mm.), $n^{25}D$ 1.5350, was prepared by reduction of isoquinoline ethiodide with sodium borohydride[5,16]; reduction of the corresponding butiodide with zinc dust and hydrochloric acid[17] yielded 57% of N-butyltetrahydroisoquinoline, b.p. 79–81° (0.4 mm.), $n^{26}D$ 1.5231.

4-Bromoisoquinoline, b.p. 134–140° (13 mm.), m.p. 38–39° after recrystallization from Skellysolve B,[18] and 4-acetamidoisoquinoline, m.p. 165–166°,[19] were prepared according to the published procedures.

Reaction of the sodium salt of 8-hydroxyquinoline with dimethyl sulfate in toluene afforded 8-methoxyquinoline, b.p. 117–121° (2 mm.),[20] low melting solid, negative ferric chloride test. The preparation of the ω-bromoalkyl quaternary ammonium bromides is described in an accompanying paper.[4]

Phenanthridine.—A method for the cyclization of 2-formamidobiphenyl to give phenanthridine in good yield was developed prior to recent publications.[21] The procedure was similar to that described by Taylor and Kalenda except that a mixture of polyphosphoric acid and phosphorus oxychloride was employed.

To the polyphosphoric acid obtained from 100 ml. of 85% phosphoric acid and 180 g. of phosphorus pentoxide was added 50.0 g. (0.25 mole) of 2-formamidobiphenyl. The mixture was stirred, and slowly heated to 100° (oil-bath) as 78 g. (0.5 mole) of phosphorus oxychloride was added dropwise. The use of Dow–Corning Antiform A helped to control the foaming resulting from the evolution of hydrogen chloride. After completion of the addition the reaction mixture was heated with stirring for 4 hours at 150–160°. The crude salts were charcoaled in water and the product precipitated by the addition of 20% sodium hydroxide solution. Recrystallization from Skellysolve B afforded 34.0 g. (75% yield) of phenanthridine, m.p. 105–106°.

1,2-Dimethyl-1,2,3,4-tetrahydroisoquinoline.—A solution of 9.9 g. (0.042 mole) of 1-methylisoquinoline methobromide in 100 ml. of absolute methanol was hydrogenated over 0.5 g. of platinum oxide (Adams catalyst) at room temperature and 40 p.s.i. The hydrogenation was complete in 10 minutes. The filtered solution was concentrated *in vacuo*, the residue was dissolved in water, 20% aqueous sodium hydroxide added, and the precipitated oil was

(10) Microanalyses were performed by the Clark Microanalytical Laboratory, Urbana, Ill. Melting points are corrected for stem exposure.

(11) (a) W. M. Whaley and W. H. Hartung, *J. Org. Chem.*, **14**, 650 (1949); (b) compare E. Späth, F. Berger and W. Kuntara, *Ber.*, **63**, 134 (1930).

(12) *Cf.* J. S. Buck and W. S. Ide, THIS JOURNAL, **60**, 2101 (1938).

(13) E. Späth and N. Polgar, *Monatsh.*, **51**, 190 (1929).

(14) E. Bamberger and W. Dieckmann, *Ber.*, **26**, 1205 (1893). Beilstein gives $n^{23}D$ 1.5798 for tetrahydroisoquinoline; hydrochloride, m. p. 196–197°. The hydrochloride of the tetrahydroisoquinoline prepared by us melted at 200–201°.

(15) L. H. Schwartzman, *J. Org. Chem.*, **15**, 517 (1950).

(16) Later batches of N-ethyltetrahydroisoquinoline were furnished by the Reilly Tar and Chemical Co., Indianapolis, Ind.

(17) E. Wedekind and F. Ney, *Ber.*, **45**, 1298 (1912).

(18) J. J. Padbury and H. G. Lindwall, THIS JOURNAL, **67**, 1268 (1945).

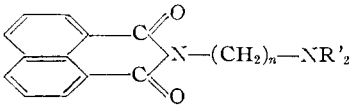
(19) J. J. Craig and W. E. Cass, *ibid.*, **64**, 783 (1942).

(20) *Cf.* A. Kaufmann and E. Rothlin, *Ber.*, **49**, 578 (1916).

(21) D. W. Ockenden and K. Schofield, *J. Chem. Soc.*, 717 (1953); E. C. Taylor and N. W. Kalenda, THIS JOURNAL, **76**, 1699 (1954).

TABLE III

3° AMINOALKYLNAPHTHALIMIDES



					Analyses, %							
					Calcd.				Found			
NR'$_2$	n	Salt	M.p., °C.[a]	Formula	C	H	N[b]	Halogen	C	H	N[b]	Halogen[c]
$N(C_2H_5)_2$	2	...	50–52	$C_{18}H_{20}N_2O_2$			4.73				4.53	
$N(C_2H_5)_2$	2	HCl	257.5–259.5	$C_{18}H_{21}ClN_2O_2$	64.95	6.36		10.66	65.12	6.37		10.54
$N(C_2H_5)_2$	2	CH_3I	246–247	$C_{19}H_{23}IN_2O_2$	52.06	5.28		28.96	52.25	5.33		28.42
$N(CH_3)_2$	3	...	115–117	$C_{17}H_{18}N_2O_2$			4.96				4.85	
$N(CH_3)_2$	3	HCl	295	$C_{17}H_{19}ClN_2O_2$	64.04	6.01		11.12	64.63	6.15		10.96
$N(CH_3)_2$	3	CH_3I	290	$C_{18}H_{21}IN_2O_2$	50.95	4.99		29.91	50.95	4.97		29.74
NC_4H_8[d]	3	...	103–105	$C_{19}H_{20}N_2O_2$			4.40				4.50	

[a] The salts melt with decomposition. [b] These values are for basic nitrogen. [c] Ionic halogen determinations. [d] Pyrrolidino group.

taken into ether. After drying and removal of the ether, the residual oil was distilled to yield 5.1 g. (76%) of 1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline, b.p. 116–117° (20 mm.), $n^{25}D$ 1.5370.[22]

2,3-Dimethyl-1,2,3,4-tetrahydroisoquinoline.—3-Methylisoquinoline methobromide melted at 247–248° dec.

Anal. Calcd. for $C_{11}H_{12}BrN$: Br, 33.56. Found: Br, (ionic), 33.25.

Hydrogenation of the methobromide over Adams catalyst afforded an 85% yield of 2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline, b.p. 113–115° (20 mm.), $n^{25}D$ 1.5331.

Anal. Calcd. for $C_{11}H_{15}N$: N, 8.69. Found: N (basic), 8.55.

1-(3-Chloropropyl)-pyrrolidine.—This base was prepared by reaction of pyrrolidine with 1-bromo-3-chloropropane in benzene, essentially by the method employed by Marxer[23] for the preparation of analogous tertiary aminopropyl chlorides. Distillation of the crude product afforded a 67% yield of the material, b.p. 99° (50 mm.).

1-(3-Chloropropyl)-pyrrolidine hydrochloride, recrystallized from ethanol and ethyl acetate, melted at 134–136°.

Anal. Calcd. for $C_7H_{15}Cl_2N$: Cl (ionic), 19.26. Found: Cl, 19.22.

N-(Dialkylaminoalkyl)-1,8-naphthalimides. A. N-(Dimethylaminopropyl)-1,8-naphthalimide.—This compound and the diethylaminoethyl analog were prepared in a manner similar to that described by Rice, Grogan and Reid[3] for the related phthalimide derivatives. To 19.8 g. (0.1 mole) of naphthalic anhydride[24] was added with cooling 11.2 g. (0.11 mole) of dimethylaminopropylamine (American Cyanamid Co.). The reactants were intimately mixed and heated for 2.5 hours at 180° (oil-bath). The melt, which solidified on cooling, was dissolved in chloroform, and the chloroform solution, after washing with 10% sodium carbonate solution, and then with water, was extracted with dilute sulfuric acid. The acid extract was made strongly alkaline and the product was dissolved in chloroform. After drying and removal of the solvent the residue was charcoaled and twice recrystallized from ethanol to yield 17.8 g. (63%) of material, m.p. 115–117°.

B. **N-(Pyrrolidinopropyl)-1,8-naphthalimide.**—Naphthalimide[25] was converted in 90% yield to the potassium salt.[25] To a mixture of 17.0 g. (0.072 mole) of the dry potassium salt and 50 ml. of xylene, heated to reflux, was added dropwise with stirring 10.8 g. (0.073 mole) of 1-(3-chloropropyl)-pyrrolidine. After completion of the addition, the reaction mixture was refluxed for 5–6 hours. Insoluble material was filtered off and washed with fresh, hot xylene. The combined filtrates were washed with water and extracted with dilute sulfuric acid. The acid extract was made strongly alkaline and the precipitate dissolved in ether. Evaporation of the dried organic layer and recrystallization from benzene and Skellysolve B afforded 8.5 g. (35% yield) of the product, m.p. 103–105°.

(22) M. Freund and G. Bode, *Ber.*, **42**, 1759 (1909), report b.p. 121–125° (20 mm.).

(23) A. Marxer, *Helv. Chim. Acta*, **24**, 209E (1941).

(24) *Cf.* R. C. Elderfield and S. L. Wythe, *J. Org. Chem.*, **19**, 690 (1954).

(25) G. F. Jaubert, *Ber.*, **28**, 360 (1895).

Analytical data for these naphthalimides and for some of their salts are given in Table III.

2-(3-Dimethylaminopropyl)-2,3-dihydro-1-benz[de]isoquinoline.—Lithium aluminum hydride reduction of the substituted naphthalimides afforded the corresponding 2,3-dihydro-1-benz[de]isoquinoline derivatives in yields of 50–60%. An example will suffice to illustrate the method.

To a slurry of 7.6 g. (0.2 mole) of lithium aluminum hydride in one liter of dry ether was added, dropwise, with stirring 18.7 g. (0.066 mole) of N-(dimethylaminopropyl)-1,8-naphthalimide dissolved in 200 ml. of dry, purified tetrahydrofuran. Stirring was continued and the reaction mixture was refluxed for 7 hours. The mixture was cooled and water was added cautiously to decompose excess reagent. The organic layer was washed with water and extracted with dilute sulfuric acid. After the addition of 40 g. of tartaric acid, which helps prevent the precipitation of aluminum hydroxide, the acid solution was made strongly alkaline with 20% sodium hydroxide and extracted with ether. The organic layer was dried over sodium sulfate and distilled to yield 9.7 g. (58%) of the product, b.p. 154–156° (0.5 mm.), $n^{25}D$ 1.5870.

The dihydrochlorides, dimethiodides and the diethiodide (XXIV) of the 2-(*tert.*-aminoalkyl)-2,3-dihydro-1-benz[de]-isoquinolines were prepared in the usual way and recrystallized from methanol or ethanol. Data for the bisquaternaries are given in Table II; for the bases and hydrochlorides, in Table IV.

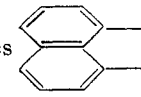
Preparation of Bis Salts by Quaternization with ω-Bromoalkyl Quaternary Bromides.—In general, acetonitrile was found to be a highly satisfactory solvent for quaternization of the unsaturated bases, whereas the tetrahydro analogs afforded better yields in an alcoholic solvent. Proportions of base and ω-bromo alkyl quaternary bromide used depended on ease of isolation of the product as well as on availability of the starting materials. Some representative examples of these quaternizations follow. Data on the bis salt products are given in Tables I and II.

A. **Reaction of Isoquinoline with 3-Bromopropyltrimethylammonium Bromide. Compound II.**—An acetonitrile solution of 80.0 g. (0.3 mole) of 3-bromopropyltrimethylammonium bromide and 60.0 g. (0.46 mole) of isoquinoline (redistilled) was refluxed for 16 hours on the steam-bath. The precipitate was recrystallized twice from *n*-propyl alcohol to yield 97.8 g. (83%) of II, m.p. 218–219°.

B. **Reaction of 3-Methylisoquinoline with 3-Bromopropyltrimethylammonium Bromide. Compound XII.**—A solution of 5.0 g. (0.035 mole) of 3-methylisoquinoline and 13.7 g. (0.053 mole) of 3-bromopropyltrimethylammonium bromide in 50 ml. of acetonitrile was refluxed for 24 hours. The precipitate was recrystallized three times from ethanol–ethyl acetate to yield 4.6 g. (33%) of white crystals, m.p. 235–238° dec.

C. **Reaction of N-Methyltetrahydroisoquinoline with 3-Bromopropyltrimethylammonium Bromide. Compound XVI.**—To an ethanol solution of 12.5 g. (0.048 mole) of the bromide was added 5.9 g. (0.04 mole) of the tetrahydro base. After 10 hours refluxing on a steam-bath, the solution was cooled, diluted with ethyl acetate and the precipitate collected and twice recrystallized from ethanol. A yield of 12.4 g. (76%) of XVI, m.p. 239–242° dec., was obtained.

TABLE IV

2-(TERT-AMINOALKYL)-2,3-DIHYDRO-1-BENZ[DE]ISOQUINOLINES 

NR'$_2$	n	Salt	B.p., °C.	Mm.	$n^{25}D$	Formula	Analyses, % Calcd. C	H	N	Cl	Found C	H	N[b]	Cl
$N(C_2H_5)_2$	2	..	162–165	0.5	1.5791	$C_{18}H_{24}N_2$			10.44				10.04	
$N(CH_3)_2$	3	..	154–156	0.5	1.5870	$C_{17}H_{22}N_2$	80.26	8.72	11.02		79.73	8.59	10.76	
$N(CH_3)_2$	3	HCl	275[a]			$C_{17}H_{24}Cl_2N_2$	62.38	7.39		21.66	62.37	7.21		21.15[c]
NC_4H_8[d]	3	..	175–180	0.3	1.5970	$C_{19}H_{24}N_2$			9.99				9.42	
NC_4H_8[d]	3	HCl	275[a]			$C_{19}H_{26}Cl_2N_2$	64.58	7.42		20.07	64.99	7.56		20.05[e]

[a] Melting point (decomposition), °C. [b] By titration for basic nitrogen. [c] By titration for ionic halogen. [d] Pyrrolidino group. [e] Microanalysis for total halogen.

D. Reaction of N-Ethyltetrahydroisoquinoline with 3-Bromopropyltrimethylammonium Bromide. Compound XVIII.—An isopropyl alcohol solution of 5.2 g. (0.032 mole) of the base and 8.4 g. (0.032 mole) of the bromide was refluxed for 30 hours on the steam-bath. The product, which crystallized out of the cooled solution, was recrystallized from ethanol to yield 10.3 g. (76%) of XVIII, m.p. 240° dec.

E. Reaction of 7-Quinolinol with 3-Bromopropyltrimethylammonium Bromide. Compound XXVI.—An acetonitrile solution of 1.0 g. (0.0069 mole) of 7-quinolinol[26] and 2.7 g. (0.01 mole) of the bromide was refluxed for 16 hours, during which time no precipitate formed. The solution was concentrated to a small volume and the resultant precipitate was recrystallized twice from alcohol–ether to yield 0.45 g. (16%) of green-tinted crystals, m.p. 234° dec.

F. Reaction of 8-Methoxyquinoline with 3-Bromopropyltrimethylammonium Bromide. Compound XXVIII.—A solution of 5.1 g. (0.032 mole) of 8-methoxyquinoline and 8.4 g. (0.032 mole) of the bromide in 25 ml. of acetonitrile was refluxed for 24 hours. The precipitate was recrystallized twice from *n*-propyl alcohol and ether to yield 3.5 g. (26%) of XXVIII, bright yellow crystals, m.p. 177° dec.

(26) C. J. Cavallito and T. H. Haskell, THIS JOURNAL, **66**, 1166 (1944).

Reaction of Isoquinoline with 3-Chloropropyldimethylamine Hydrochloride. Compound X.—A mixture of 20.6 g. (0.13 mole) of 3-chloropropyldimethylamine hydrochloride[2] and 33.6 g. (0.26 mole) of isoquinoline in 500 ml. of isopropyl alcohol was refluxed for 40 hours on the steam-bath. A small amount of insoluble material was removed and the filtrate was concentrated under reduced pressure to a smaller volume, diluted with ethyl acetate and the precipitated solid collected. After four recrystallizations from isopropyl alcohol, a yield of 8.6 g. (23%) of the product, m.p. 214–215° (with preliminary softening), was obtained.

Catalytic Hydrogenation of II. Compound XIX.—A solution of 10.0 g. (0.026 mole) of II in 100 ml. of absolute methanol was hydrogenated over 0.5 g. of platinum oxide at 50 p.s.i. Hydrogen absorption was complete in 15 minutes. The filtered solution was concentrated to about 50 ml. and diluted with ethyl acetate until just cloudy. On cooling there was obtained 7.2 g. (72% yield) of XIX, m.p. 198–203°.

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DECATUR, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA]

Some Spirohydantoins and Ureas Derived from Alkylamino-substituted Alicyclic Ketones

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A number of spirohydantoins and ureas derived from alkylamino-substituted alicyclic ketones have been prepared as potential anticonvulsants. The Bucherer method was used for the preparation of the hydantoins. 2-Benzylaminomethylcyclohexanone gave a 2-benzylhexahydro-7a-hydroxyphthalimidine instead of the expected hydantoin. The cleavage of certain Mannich bases during reductive amination has been demonstrated.

Since the discovery that 5-ethyl-5-phenylhydantoin was active as an anticonvulsant, a large amount of work has been reported on the preparation and testing of 5,5-disubstituted hydantoins. Spirohydantoins derived from alicyclic ketones have been reported also.[1] Recently spirohydantoins prepared from 1-menthone[1a] and carvomenthone[1c] were shown to possess promising anticonvulsant activity when administered to mice. Further testing has shown that these compounds are not useful for controlling convulsions in man. No toxic symptoms, however, were observed in man even when the compounds were administered in very large doses.

(1) (a) A. R. Day and C. F. Kelly, *J. Org. Chem.*, **4**, 101 (1939); (b) R. Tiffeneau and M. Beauvallet, *Presse Med.*, **51**, 417 (1943); (c) E. S. Rothman and A. R. Day, THIS JOURNAL, **76**, 111 (1954).

In view of the low water solubility of the above spirohydantoins and the fact that large amounts must be administered for anticonvulsant activity, the preparation of derivatives which possessed increased solubility in water seemed desirable. To accomplish this purpose basic side chains were introduced into appropriate ketones by means of the Mannich reaction and the resulting amino ketones converted to the corresponding spirohydantoins by the Bucherer method.[2] Closely related to the amino-substituted spirohydantoins are the corresponding amino-substituted ureas. Two examples of this type of compound were prepared also. The amino-substituted ureas were made from the

(2) H. T. Bucherer and V. A. Lieb, *J. prakt. Chem.*, [2] **141**, 5 (1934).