[CONTRIBUTION FROM IRWIN, NEISLER AND CO.]

Bis-Ammonium Salts. Unsymmetric Derivatives of Substituted Pyridine Bases that Are Potent and Selective Hypotensive Agents[1]

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

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In continuation of earlier work, a series of unsymmetric bis-quaternary salts has been prepared in which the large head is derived from a substituted pyridine (or piperidine) base. Variations in size and point of attachment of the substituent(s) have been introduced. Among the derivatives have been found compounds that are remarkably potent *and selective* hypotensive agents. Structure–activity relationships as well as certain implications of the biological findings are discussed.

Reports from these laboratories have described several series of unsymmetric bis-quaternary salts in which hypotensive and peripheral autonomic blocking activity could be independently varied.[2] A central component of action was implicated.[2,3] In our earlier reports, requirements for biological activity had been quite sharply delineated with respect to size of the small cationic head, distance between charged nitrogens, charge distribution and degree of ionization. Although the limitations as to size, shape and polarity of the large cationic head had been somewhat less clearly defined, it had been established that pyridine[2] and N-methylpiperidine[4] were too small to provide active derivatives.[5a,b]

In continuing these studies, many facets of the problem of structure–activity relationships have been explored. One approach to a more detailed examination of the structural limits imposed on the large head has been, logically enough, to determine the effects on pharmacological properties of attaching a variety of substituents at different points on a pyridine or piperidine nucleus. This has led not only to further clarification of the question but also to some remarkably potent and pharmacologically selective hypotensive agents. The present paper deals with a selected group of these unsymmetric bis-quaternary salts which are described in Tables I and II.

The route to most of the bis-ammonium salts—*i.e.*, quaternization of the appropriate pyridine (or piperidine) base with bromopropyltrimethylammonium bromide—has become more or less standard in these laboratories[2] and requires no further comment here. The preceding paper[6] describes the preparation of some indolyl- and indenyl-substituted pyridine bases, derivatives of which have been prominent in this study. IV, VII and XIII (Table I) were prepared by the base-catalyzed condensation[7] of benzaldehyde, 1-naphthaldehyde and 3-indolecarboxaldehyde (respectively) with trimethylene-1-(4-picolinium)-3-trimethylammonium dibromide (II).

4-Benzyl-1-methylpiperidine readily was obtained by the catalytic hydrogenation of 4-benzylpyridine methobromide. Hydrogenation of 4-benzylpyridine at room temperature over Adams catalyst proceeded slowly in aqueous acetic acid but provided 4-benzylpiperidine in good yield and without evidence of any concomitant saturation of the benzene ring.[8] XXIV (Table II) was prepared by alkylation of 4-benzylpiperidine with dimethylaminoethyl chloride followed by bis-quaternization of the product with methyl iodide.

Pharmacological Activity.—Of principal interest are the marked hypotensive activity of a number of these compounds and the lack of relationship between hypotensive and ganglionic blocking action. The present series confirms and extends more dramatically previously discussed hypotheses.[2] In order to facilitate comparisons, activities are expressed in potencies relative to unity for hexamethonium bromide.[9] The figures attempt to take into consideration the factors of dosage and intensity and duration of action. It is apparent that whereas ganglionic blocking action varies within a rather narrow range, there is a spread of two orders of magnitude in hypotensive activity.[10]

Inasmuch as the effects of variations in chain length and in the small head were established earlier, these factors are here kept essentially constant. In regard to the large head, the present report more clearly defines the requirement of a bulky, lipophilic, cationic moiety. This may be seen by comparing activities in the series of salts derived from: pyridine (I), N-methylpiperidine (XXIII) and picoline (II) (practically inert); 4-benzylpyridine (III) (comparable to hexamethonium); and 4-diphenylmethylpyridine (V) (more active). Although sufficient size is a minimal requirement for an effective large head, there are

(1) Presented in part before the Division of Medicinal Chemistry at the 131st National Meeting of the American Chemical Society, April 7–12, 1957.

(2) A. P. Gray, W. L. Archer, D. C. Schlieper, E. E. Spinner and C. J. Cavallito, THIS JOURNAL, **77**, 3536 (1955), and references cited therein; T. B. O'Dell, C. Luna and M. D. Napoli, *J. Pharmacol. Exptl. Therap.*, **114**, 317 (1955).

(3) For more recent support of this thesis, see H. E. Lape, D. J. Fort and J. O. Hoppe, *ibid.*, **116**, 462 (1956).

(4) W. L. Archer, C. J. Cavallito and A. P. Gray, THIS JOURNAL, **78**, 1227 (1956).

(5) (a) Recent publications from other laboratories have described additional groups of unsymmetric bis-quaternary hypotensive agents. It is difficult, however, to glean much information from these pertaining to structure–activity relationships. See L. M. Rice, C. H. Grogan and E. E. Reid, *ibid.*, **77**, 616 (1955); L. M. Rice and C. H. Grogan, Abstracts of Papers, 129th Meeting of the American Chemical Society, Dallas, Texas, April 8–13 (1956), p. 24M; A. J. Plummer, J. H. Trapold, J. A. Schneider, R. A. Maxwell and A. E. Earl, *J. Pharmacol. Exptl. Therap.*, **115**, 172 (1955); D. W. Adamson, J. W. Billinghurst, A. F. Green and S. Locket, *Nature*, **177**, 523 (1956). (b) Just prior to the submission of this manuscript, J. Fakstorp, J. G. A. Pedersen, E. Poulsen and M. Schilling, *Acta Pharmacol. Toxicol.*, **13**, 52 (1957), reported on the ganglionic blocking activity of a series of bis-quaternary salts which can in a way be considered as bridging the gap between symmetric and unsymmetric classes of agents.

(6) A. P. Gray and W. L. Archer, THIS JOURNAL, **79**, 3554 (1957).

(7) See A. P. Phillips, *J. Org. Chem.*, **14**, 302 (1949).

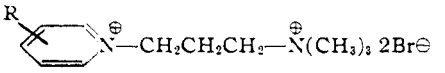
(8) *Cf.* W. L. C. Veer and St. Goldschmidt, *Rec. trav. chim.*, **65**, 793 (1946).

(9) The pharmacology of these compounds will be described in detail by T. B. O'Dell, *et al.*, *J. Pharmacol. Exptl. Therapy*, in press.

(10) Unless otherwise qualified, the term activity in this discussion will refer to hypotensive activity.

TABLE I

SUBSTITUTED PYRIDINE SALTS

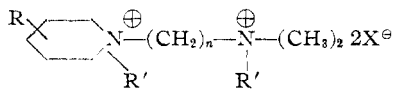


	R	M.p., °C.[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Bromine, %[b] Calcd.	Bromine, %[b] Found	Relative[c,e] hypotensive activity	Relative[d,e] ganglionic blockade
I	Hydrogen	[f]								<0.1	
II	4-Methyl	244–245	$C_{12}H_{22}Br_2N_2$	40.69	41.08	6.27	6.50	45.12	44.63	<0.1	
III	4-Benzyl	172–174	$C_{18}H_{26}Br_2N_2$	50.25	50.32	6.09	6.38	37.15	36.72	1	
IV	4-Phenylethenyl	150	$C_{19}H_{28}Br_2N_2$	51.59	51.94	5.94	6.05	36.14	35.50	0.5	
V	4-Diphenylmethyl	145–150	$C_{24}H_{32}Br_2N_2O$[g]	54.97	54.59	6.16	5.69	30.48	30.74		
					H_2O	3.44	2.12[g]			3	0.5
VI	2-(1-Naphthylethyl)	170–171	$C_{22}H_{30}Br_2N_2$	55.88	56.15	6.12	6.36	32.33	31.58	100	2
VII	4-(1-Naphthylethenyl)	178	$C_{23}H_{28}Br_2N_2$	56.11	55.77	5.73	6.25	32.47	31.90	5	
VIII	2-(3-Indenylethyl)	188–190[h]	$C_{22}H_{30}Br_2N_2$	54.78	54.44	6.27	6.42	33.14	32.68	40	1
IX	4-(3-Indenylethyl)	195–197	$C_{22}H_{30}Br_2N_2$	54.78	54.52	6.27	6.48	33.14	33.05	15	1
X	2-(3-Indolylethyl)	201–203	$C_{21}H_{29}Br_2N_3$	52.18	52.23	6.05	6.17	33.07	32.82	50	3
XI	4-(3-Indolylethyl)	218–219	$C_{21}H_{29}Br_2N_3$	52.18	52.74	6.05	6.25	33.07	33.05	20	3
XII	4-(1-Indolylethyl)	223–225	$C_{21}H_{29}Br_2N_3$	52.18	51.79	6.05	5.87	33.07	32.63	150	2
XIII	4-(3-Indolylethenyl)	275	$C_{21}H_{27}Br_2N_3$	52.40	53.06	5.66	5.32	33.21	33.02	4	1
XIV	2-(1-Methyl-3-indolylethyl)	139–140	$C_{22}H_{31}Br_2N_3$	53.13	53.26	6.28	5.96	32.14	31.83	25	1
XV	4-(1-Methyl-3-indolylethyl)	133	$C_{22}H_{31}Br_2N_3$	53.13	52.83	6.28	6.47	32.14	31.98	80	1
XVa	4-(1-Methyl-3-indolylethyl)[i]	195	$C_{22}H_{31}Cl_2N_3$					17.36[i]	17.30[i]		
XVI	4-(1-Benzyl-3-indolylethyl)	193–194	$C_{28}H_{36}Br_2N_3$	58.64	58.36	6.15	5.95	27.87	27.34	10	
XVII	2-(1-Methyl-3-indolylethyl)-5-ethyl	173–174	$C_{24}H_{36}Br_2N_3$	54.86	54.21	6.72	6.53	30.42	30.28	120	0.5
XVIII	3-(2-Indolyl)	235–237	$C_{19}H_{25}Br_2N_3$	50.12	50.06	5.54	5.49	35.11	34.96	0.5	
XIX	4-(2-Indolyl)	236–238	$C_{19}H_{25}Br_2N_3$	50.12	50.73	5.54	5.30	35.11	34.51	10	
XX	4-(3,3'-Diindolylmethyl)	220	$C_{28}H_{32}Br_2N_4$	57.54	57.43	5.52	5.63	27.35	26.72	5	
XXI	4-(Phthalimidoethyl)	204	$C_{21}H_{27}Br_2N_3O_2$	49.14	49.46	5.30	5.32	31.14	30.89	2	

[a] Most of the salts melt with decomposition. Melting points are corrected for stem exposure. [b] Either volumetric or gravimetric determination of ionic halogen. [c] Intravenously in anesthetized dogs; relative activities are primarily weighted on the basis of duration at about the same per cent. maximum fall. [d] Superior cervical ganglion in the cat; relative activities are primarily weighted on the basis of duration of about the same degree of block. [e] On this scale hexamethonium = 1. The slopes of the dose-response curves for these compounds vary; for purposes of approximation, however, the compounds are compared at doses equivalent (in potency) to 2 mg./kg. of hexamethonium bromide. [f] See Gray, *et al.*, ref. 2. [g] Monohydrate; Karl Fischer titration for water. [h] Sealed tube. [i] Dichloride salt. [j] See ref. 4.

TABLE II

SUBSTITUTED PIPERIDINE SALTS



	R	R'	n	X	M.p., °C.[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Halogen, %[b] Calcd.	Halogen, %[b] Found	Relative hypotensive activity[c,e]	Rel. ganglionic blockade[d,e]
XXII	Hydrogen	CH_3	3	Br	[j]								<0.1	
XXIII	4-Benzyl	CH_3	3	Br	237–238	$C_{19}H_{34}Br_2N_2$	50.67	50.58	7.61	7.73	35.49	35.03	5	
XXIV	4-Benzyl	CH_3	2	I	217–219	$C_{18}H_{32}I_2N_2$	40.77	41.05	6.08	5.96	47.87	47.34	5	0.5
XXV	4-Benzyl	H	2	Cl	>270	$C_{16}H_{28}Cl_2N_2$	60.18	60.50	8.84	8.71	22.21	22.11	<0.1	

[a] See footnotes, Table I.

quite evidently other factors (*e.g.*, shape or configuration and, possibly, flexibility) which determine the influence of this size on activity. Differences in activity between corresponding 2- and 4-substituted pyridine isomers are not consistent, and both types may be very active (X, XI, XIV, XV). However, very marked differences exist among a group of derivatives of approximately the same mass (V–IX). The greater potencies of VI, VIII and IX than of the less flexible and non-planar V should be principally related to the arrangement of bulk-contributing structures (*cf.* also XVIII and XIX). The lower activities of VII and IV, possessing planar heads with completely conjugated systems (compare VI and VII; *cf.* also the indole derivatives, XI and XIII), might be ascribable to more rapid biological destruction as well as to more diffuse distribution of the positive charge. A reasonably good example of the influence of polar structures is provided by a comparison of XI and XXI (although stability also may be a factor). These observations emphasize the difficulties in controlling individual variables in the course of structural modification (note that V and XIII can yield neutralized large heads by the loss of a proton).

That there is an upper limit on size of the large head is perhaps best demonstrated by comparison of XV[11] and XVI. Apparently XVI has a larger head than that which appears to be approximately optimum (as exemplified in XV and XII). It is of interest that the indole N-methylated derivatives XIV and XV show reduced ganglionic blocking action in comparison with X and XI, but this effect is unrelated to changes in hypotensive activity. This could be a result of elimination of the bonding capacity of the indole N–H as well as of a reduction in polarity.

Providing that the compounds have minimal

(11) This compound, bearing the laboratory designation IN 391, is the subject of extensive clinical investigations. Intravenously in the anesthetized dog, a dose of 0.025 mg./kg. lowers the blood pressure 50% for more than 4 hr.

structural features, the relative intensities of the measured responses will be influenced by the distribution of the compounds among responsive receptors and the many non-specific adsorption sites throughout the organism.[12] Several of the present compounds have been observed to be more active in barbiturate anesthetized than in unanesthetized dogs. Since these are relatively lipophilic substances, the potentiation by anesthetics could well be the result of competition at sites of loss.[13]

The broad class of short chain, unsymmetric diquaternary salts include compounds of much greater hypotensive activity than the early C_{5-6} symmetric bis-onium types. If we assume that the compounds of both groups act as specific acetylcholine antagonists, hypotheses of spatial relationships of receptor structures formulated on the basis of the earlier blocking agents will require reconsideration. The active C_{5-6} compounds can assume configurations in which the two onium groups are separated by distances equivalent to those in the C_{2-3} unsymmetric analogs. This would make possible bonding at two adjacent anionic sites or, quite possibly, ion pair formation of the bis-onium moiety with a single anionic function in the low dielectric region of the receptor surface.[14] The non-ionic portion of the diquaternary salt would influence the relative distribution of the compound among adsorption sites and also the stability of the cation–receptor complex.

Experimental[15]

Preparation of Intermediates.—Indolyl- and indenyl-substituted pyridine bases are described in an accompanying paper[6]; the method used for the preparation of 3-bromopropyltrimethylammonium bromide has appeared earlier.[16] 2-(1-Naphthylethyl)-pyridine, hydrochloride salt, m.p. 174.5–175.5°, was obtained by the alkylation of α-picoline with 1-chloromethylnaphthalene using sodamide in liquid ammonia.[17] 4-Diphenylmethylpyridine was supplied by the Reilly Tar and Chemical Corp.

4-Phthalimidoethylpyridine.—This compound was prepared in a manner similar to that described for the 2-isomer.[18] A mixture of 14.7 g. (0.1 mole) of phthalimide, 15.9 g. (0.15 mole) of freshly distilled 4-vinylpyridine and 1 ml. of piperidine was refluxed for 5 hr. at an oil-bath temperature of 190–200°. The cooled, solid reaction mixture was dissolved in 10% hydrochloric acid. The acid solution was filtered, made alkaline and the resultant tan precipitate recrystallized from aqueous isopropyl alcohol to yield 16.5 g. of light tan needles, m.p. 157–158°.[19]

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.80; N (basic), 5.55. Found: C, 71.68; H, 4.79; N (basic), 5.71.

The hydrochloride melted at 220° dec. *Anal.* Calcd. for $C_{15}H_{13}ClN_2O_2$: C, 62.39; H, 4.54; Cl, 12.28. Found: C, 62.81; H, 4.70; Cl, 12.27.

The methobromide, prepared in ethanol and recrystallized from ethanol–ether, showed m.p. 204.5–205.5° dec. *Anal.* Calcd. for $C_{16}H_{15}BrN_2O_2$: C, 55.34; H, 4.35. Found: C, 55.38; H, 4.25.

4-Benzyl-1-methylpiperidine.—4-Benzylpyridine was converted to its methobromide salt, m.p. 84–87°. A solution of 15 g. of the recrystallized salt in 100 ml. of methanol was hydrogenated over 0.5 g. of Adams platinum oxide at 40 p.s.i. and room temperature. The reduction was complete in about 20 minutes. After removal of the solvent *in vacuo*, the residue was distilled to yield 7.2 g. (66%) of 4-benzyl-1-methylpiperidine, b.p. 100–103° (3.5 mm.), $n^{26}D$ 1.5189[20]; picrate, m.p. 185–186°, after recrystallization from ethanol.

Anal. Calcd. for $C_{13}H_{19}N$: N, 7.40. Found: N (basic), 7.34.

4-Benzylpiperidine.—A solution of 51.0 g. (0.3 mole) of 4-benzylpyridine in a mixture of 100 ml. of purified glacial acetic acid and 50 ml. of water was hydrogenated over 1.0 g. of Adams catalyst at room temperature and 50 p.s.i. Hydrogen absorption was complete in 72 hr. The filtered solution was concentrated *in vacuo*, the residue was treated with excess 20% sodium hydroxide and extracted with ether. After washing with water and drying, the organic layer was distilled to yield 44.5 g. (85%) of 4-benzylpiperidine, b.p. 90–92° (0.6 mm.), $n^{25}D$ 1.5357; picrate, m.p. 192–193° dec.[21]

Anal. Calcd. for $C_{12}H_{17}N$: N, 7.99. Found: N (basic), 7.96.

1-Dimethylaminoethyl-4-benzylpiperidine.—A stirred mixture of 28.0 g. (0.16 mole) of 4-benzylpiperidine, 34.6 g. (0.24 mole) of dimethylaminoethyl chloride hydrochloride and 50 g. of anhydrous, powdered sodium carbonate in 200 ml. of 1-butanol was refluxed (oil-bath) for 24 hr. The cooled, filtered solution was concentrated *in vacuo* and the residue was extracted with ether. Drying and removal of the ether and distillation of the residual oil afforded 12.3 g. (31% yield) of the product, b.p. 135–140° (0.5 mm.), $n^{24}D$ 1.5167.

Anal. Calcd. for $C_{16}H_{26}N_2$: N, 11.37. Found: N (basic), 11.22.

The dihydrochloride XXV, recrystallized from wet methanol, melted above 270°.

The dimethiodide XXIV, prepared in ethanol and recrystallized from methanol–ethyl acetate, showed m.p. 225–226° dec.

Preparation of Bis-salts by Quaternization with 3-Halopropyltrimethylammonium Halides. A. Trimethylene-1-(4-picolinium)-3-(trimethylammonium) Dibromide (II).—An ethanol solution of 9.3 g. (0.1 mole) of γ-picoline and 26.1 g. (0.1 mole) of 3-bromopropyltrimethylammonium bromide was refluxed on the steam-bath for 15 hr. The crystalline precipitate that formed upon refrigeration of the solution was recrystallized from ethanol to yield 21.8 g. (62%) of colorless crystals of II, m.p. 244–245° with gas evolution.

B. Trimethylene-1-[2-(3-indolylethyl)-pyridinium]-3-(trimethylammonium) Dibromide (X).—To 130.5 g. (0.5 mole) of 3-bromopropyltrimethylammonium bromide dissolved in 600 ml. of acetonitrile was added 111 g. (0.5 mole) of 2-(3-indolylethyl)-pyridine, and the solution was refluxed for 30 hr. The precipitate was recrystallized from ethanol to yield 120 g. (63%) of pale yellow crystals of X, m.p. 201–203°.

C. Trimethylene-1-[4-(1-methyl-3-indolylethyl)-pyridinium]-3-(trimethylammonium) Dibromide (XV).—A solution of 1420 g. (6 moles) of 4-(1-methyl-3-indolylethyl)-pyridine and 1570 g. (6 moles) of 3-bromopropyltrimethylammonium bromide in 4.5 liters of acetonitrile was refluxed, with stirring, for 18 hr. Recrystallization of the resultant precipitate from isopropyl alcohol afforded a yield of 2390

(12) In a recent review, Veldstra, *Pharmacol. Rev.*, **8**, 339 (1956), refers to these as "sites of loss."

(13) A similar relationship recently has been demonstrated with another type of acetylcholine blocking agent (C. J. Cavallito, J. G. Arrowood and T. B. O'Dell, *Anesthesiology*, **17**, 547 (1956)).

(14) See O. V. Brody and R. M. Fuoss, *J. Phys. Chem.*, **60**, 156 (1956), and earlier papers of Fuoss, *et al.*, for physical chemical evidence of this type of association; S. A. Rice, THIS JOURNAL, **78**, 5247 (1956); *cf.* F. Bergmann and R. Segal, *Biochem. J.*, **58**, 692 (1954).

(15) Microanalyses were performed by the Clark Microanalytical Laboratories, Urbana, Ill.

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

(17) F. W. Bergstrom, T. R. Norton and R. A. Seibert, *J. Org. Chem.*, **10**, 452 (1945).

(18) F. K. Kirchner, J. R. McCormick, C. J. Cavallito and L. C. Miller, *ibid.*, **14**, 388 (1949).

(19) E. Profft, *J. prakt. Chem.*, [4] **4**, 19 (1956), recently reported this compound (impure), m.p. 143–146°.

(20) F. J. Villani, M. S. King and D. Papa, *J. Org. Chem.*, **17**, 249 (1952), report b.p. 129–130° (8 mm.), $n^{26}D$ 1.5295, for this compound prepared by sodium and ethanol reduction of benzylpyridine followed by Eschweiler–Clarke methylation. The high refractive index they report would appear to be a further indication of the difficulty of effecting complete reduction of the pyridine ring with sodium and alcohol.

(21) W. L. C. Veer and St. Goldschmidt[8] report b.p. 150–152° (17 mm.), picrate m.p. 187–188°, for this compound prepared by sodium and ethanol reduction.

g. (79%) of XV as hygroscopic, light tan crystals, m.p. 133° dec.

D. Dichloride Salt of XV (XVa).—A solution of 600 g. of XV in 12 liters of distilled water was passed through a column of Amberlite anion exchange resin, IRA 401 (regenerated with aqueous sodium chloride), and the column was washed with fresh water. The eluate was concentrated *in vacuo* and the residue was crystallized from ethanol–acetone to yield 425 g. (86%) of the dichloride salt, XVa, m.p. 195° dec.

Two alternative routes to XVa have been found quite satisfactory: 1. A solution of 4-(1-methyl-3-indolylethyl)-pyridine and 3-chloropropyltrimethylammonium bromide[22] in dimethylformamide was heated at 120–125° (oil-bath temperature) for 24 hr. and the crude mixed halide product passed through a column of Amberlite IRA 401. 2. A dimethylformamide solution of the pyridine base and 3-chloropropyltrimethylammonium chloride[23] was heated at 120° (oil-bath) for 24 hours, thus directly affording a 55% yield of XVa.

Condensation of II with Aldehydes. A. Benzaldehyde. The Preparation of IV.—To a solution of 6.3 g. (0.018 mole) of II and 3.8 g. (0.036 mole) of freshly distilled benzaldehyde in 50 ml. of methanol was added 1 ml. of piperidine. After 4 hr. reflux on the steam-bath, the deep purple solution was cooled, diluted with ether and the purple precipitate was recrystallized from ethanol to provide 4.3 g. (54% yield) of IV, melting with decomposition and gas evolution at 150°.

B. 1-Naphthaldehyde. The Preparation of VII.—Refluxing a solution of 4.4 g. (0.028 mole) of 1-naphthaldehyde and 10 g. (0.028 mole) of II in 50 ml. of ethanol containing 1 ml. of piperidine for 3 hr., diluting with ether and crystallizing the resultant purple, oily precipitate from ethanol–ether yielded 9.6 g. (69%) of VII, m.p. 178° dec.

C. 3-Indolecarboxaldehyde. The Preparation of XIII.—In similar fashion, 3-indolecarboxaldehyde[24] was condensed with II to yield, after recrystallization from methanol–ethyl acetate, 56% of bright orange crystals of XIII, melting with decomposition and gas evolution at 275°.

Acknowledgments.—The authors wish to thank Mrs. Dorothy Schlieper for assistance with some of the synthetic work and Mr. Dean F. Cortright for the ionic halogen and basic nitrogen determinations.

(22) This salt was prepared from trimethylene chlorobromide and trimethylamine, m.p. 204–206°.

(23) Prepared from 3-chloropropyltrimethylammonium bromide by passage over the anion exchange resin, m.p. 202° dec.

(24) Prepared as described by F. T. Tyson and J. T. Shaw, THIS JOURNAL, **74**, 2273 (1952), from indole and dimethylformamide with phosphorus oxychloride.

DECATUR, ILLINOIS

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Quinone Imides. XLIV. The Orientation of Groups in Addition Reactions to Substituted p-Quinonedibenzimides

BY ROGER ADAMS AND HARRY J. NEUMILLER, JR.[1]

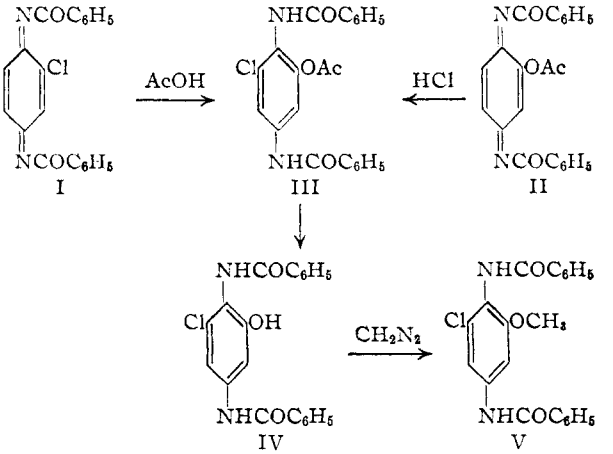
RECEIVED FEBRUARY 1, 1957

The acetoxychloro-*p*-phenylenedibenzamide isomer, which results both from the addition of acetic acid to 2-chloro-*p*-quinonedibenzimide and from the addition of hydrogen chloride to 2-acetoxy-*p*-quinonedibenzimide, has been identified as 2-acetoxy-6-chloro-*p*-phenylenedibenzamide. The oxidation of 2-methoxy-*p*-phenylenedibenzamide with lead tetraacetate affords 2-methoxy-*p*-quinonedibenzimide which adds hydrogen chloride to give a mixture of 2-chloro-5-methoxy- and 2-chloro-6-methoxy-*p*-phenylenedibenzamides, both identified by unequivocal syntheses.

In a recent paper[2] the orientation of groups in the adducts of 2-substituted *p*-quinonedibenzenesulfonimides and 2-substituted *p*-quinonedibenzimides was summarized. 2-Chloro-*p*-quinonedibenzenesulfonimide adds hydrogen chloride to afford a mixture of 2,3- and 2,5-dichloro-*p*-phenylenedibenzenesulfonamides. The addition of hydrogen chloride and a number of other reagents to 2-methoxy-*p*-quinonedibenzenesulfonimide results in substituted *p*-phenylenedibenzenesulfonamides having exclusively the 2,5-orientation.

In contrast to the foregoing, the addition of hydrogen chloride to 2-chloro-*p*-quinonedibenzimide (I) affords 2,6-dichloro-*p*-phenylenedibenzamide; the addition to 2-methyl-*p*-quinonedibenzimide yields exclusively 6-chloro-2-methyl-*p*-phenylenedibenzamide. The 2-phenylmercapto analog gives 3-chloro-2-phenylmercapto-*p*-phenylenedibenzamide and the 2-benzenesulfonyl derivative gives a mixture of 2-benzenesulfonyl-3-chloro- and 2-benzenesulfonyl-6-chloro-*p*-phenylenedibenzamides.

Previous investigators demonstrated that both the addition of acetic acid to 2-chloro-*p*-quinonedibenzimide (I) and the addition of hydrogen chloride to 2-acetoxy-*p*-quinonedibenzimide (II) yielded the same acetoxy-chloro-*p*-phenylenedibenzamide isomer as the sole product of each reaction.[3] The product has now been identified as 2-acetoxy-6-chloro-*p*-phenylenedibenzamide (III).



For the purpose of its identification, III was hydrolyzed with dilute aqueous sodium hydroxide to

(1) An abstract of a thesis submitted by Harry J. Neumiller, Jr., to the Graduate College of the University of Illinois, 1956, in partial fulfillment of the requirements for the Degree of Doctor of Philosophy; Minnesota Mining and Manufacturing Fellow, 1952–1954; University of Illinois Fellow, 1953 and 1954–1955.

(2) R. Adams and M. D. Nair, THIS JOURNAL, **78**, 5927, 5932 (1956).

(3) R. Adams and D. S. Acker, *ibid.*, **74**, 3657 (1952).