2(3H)-one.—To a stirred suspension of 27.4 g. (0.2 mole) of isonicotinic acid hydrazide in 300 ml. of pyridine was added 21.5 g. (0.2 mole) of dimethylcarbamyl chloride, at room temperature. The temperature rose to 35°; after stirring for one-half hour, a clear solution had formed. This mixture was refluxed for 2.5 hours and allowed to cool. The crystalline solid was filtered. The filtrate was concentrated to dryness *in vacuo*, the residue was stirred with water and filtered to give additional material. The combined solids were recrystallized from water to give 17 g. (41% yield) of product, m.p. 273–275° dec.; a mixed m.p. with the product from K was 273–275° dec.

The same product was obtained by the reaction of isonicotinic acid hydrazide and diethylcarbamyl chloride in pyridine as described in method L. The yield was 37%, m.p. 275–276° dec.; a mixed m.p. with the product from K was 274–276° dec.

The Stepwise Formation of 5-(4-Pyridyl)-1,3,4-oxadiazol-2(3H)-one.—To a stirred suspension of 13.7 g. (0.1 mole) of isonicotinic acid hydrazide in 150 ml. of pyridine at room temperature was added dropwise 10.8 g. (0.1 mole) of dimethylcarbamyl chloride. The reaction mixture was stirred for six hours at room temperature and kept overnight. A clear solution formed after 0.5 hour stirring. The pyridine was removed *in vacuo*, keeping the water-bath temperature below 40°. The semisolid residue was washed with acetonitrile, filtered and recrystallized from acetonitrile to give 12.5 g. (60% yield) of product, m.p. 197–198° dec. A mixed m.p. with 4,4-dimethyl-1-isonicotinylsemicarbazide was 197–198° dec.

Five grams (0.024 mole) of the 4,4-dimethyl-1-isonicotinylsemicarbazide obtained above in 100 ml. of pyridine was refluxed while nitrogen, at the rate of about five bubbles per second, was passed through the solution. The exit gases were bubbled through water to absorb the dimethylamine. The formation of dimethylamine occurred as follows: during the first 2.5 hours, 0.009 mole; during the next six hours, 0.009 mole; and during the following seven hours, 0.002 mole; the total was 0.020 mole or 83% of the theoretical. The dimethylamine was characterized subsequently as N,N-dimethyl-*p*-toluenesulfonamide, m.p. 79–80°; a mixed m.p. with an authentic specimen showed no depression.

The pyridine solution remaining after the removal of dimethylamine was concentrated *in vacuo*. The residual solid was triturated with 50 ml. of water and filtered to give 3.8 g. (97% yield) of product, m.p. 271–272° dec. Recrystallization from water raised the melting point to 273–274° dec.; a mixed m.p. with 5-(4-pyridyl)-1,3,4-oxadiazol-2(3H)-one showed no depression.

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Synthetic Hypotensive Agents. I. Some Powerful New Autonomic Ganglionic Blocking Agents Derived from Nicotine

BY ARTHUR P. PHILLIPS

RECEIVED NOVEMBER 23, 1953

While searching for new useful hypotensive drugs among ganglionic blocking agents it was felt that valuable agents might be obtained by modifying the nicotine molecule. Catalytic hydrogenation of nicotine salts, the dihydrochloride and a series of di-quaternary alkiodides, gave a di-secondary amine and a series of di-tertiary amines, respectively. Reaction of one of the di-tertiary amine reduction products with several alkyl halides gave a new series of di-quaternary ammonium salts. All of these compounds are derivatives of 3-(4'-aminobutyl)-piperidine, and all, the di-secondary and the di-tertiary amines as well as the di-quaternary ammonium salts, possess marked hypotensive action. Several members of the various series have powerful and useful activities in this sense.

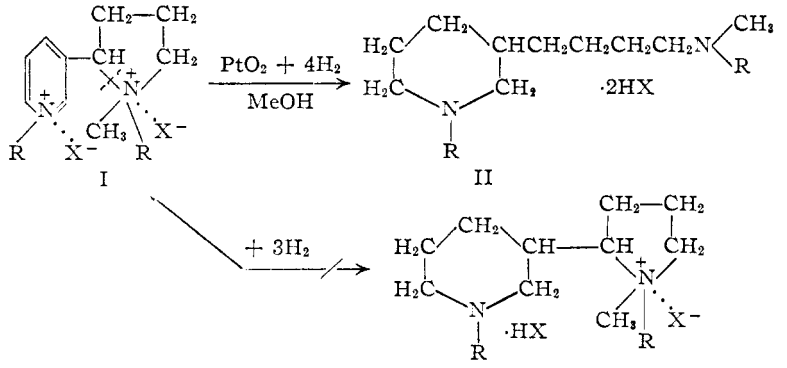
In seeking for useful new hypotensive agents among possible ganglionic blocking agents it was felt that exploitation of the readily available and pharmacologically very active nicotine might furnish valuable compounds. Nicotine was deemed a starting intermediate worthy of chemical modification for several reasons. Firstly, it is itself endowed with strong pharmacological actions, although it is too toxic for any great usefulness as a drug. Secondly, as an undesired by-product of the great tobacco industry it is quite readily available in moderate quantities, and finds its main use only as an insecticide. Thirdly, much of our recent work has centered around salts of di- or polyfunctional organic bases, of which nicotine is a di-basic representative. It was believed that by suitable chemical transformations some derivatives of nicotine might be obtained in which certain of the intense pharmacological effects of nicotine might be retained or enhanced while its toxicity might be considerably diminished. All of these expectations have been realized to a very satisfactory degree.

In the first attempts to modify the chemical structure and pharmacological properties of nicotine, the latter was treated with a series of alkyl halides to give the di-quaternary ammonium salts. Of the series of alkyl halides used for quaternization methyl iodide gave a nearly quantitative yield of the di-methiodide, ethyl iodide gave about a 60% yield of crystalline di-ethiodide, *n*-propyl iodide gave a 10 to 20% recovery of crystalline di-propiodide, while no crystalline solid has so far been isolated from the reaction with *n*-butyl iodide. In each of the cases where the yield of crystalline product was considerably less than 100% the calculated amount of an ether insoluble oil was recovered. Since these non-crystalline fractions are ether insoluble and are salt-like in nature they may represent either mixtures of mono- and di-quaternary salts, or possibly mixtures of stereoisomers which interfere with further crystallization of solid products.

The crystalline di-quaternary salts (I of Chart I) were subjected to catalytic hydrogenation in methanol solution using Adams catalyst at room temperature and three atmospheres overpressure of hydrogen. As platinum is usually an inferior debenzylation catalyst compared with palladized charcoal it was anticipated that only the pyridine ring of the di-salts would be reduced to piperidine, leaving the pyrrolidine ring intact, and giving products of structure III (Chart I). In agreement with this idea the first few hydrogenations showed an absorption of three moles of hydrogen per mole of di-salt. Nevertheless all subsequent reductions showed an uptake of four moles of hydrogen per mole of salt, corresponding presumably to a pre-

liminary debenzylation-type cleavage of the pyrrolidine ring followed by reduction of the pyridine to a piperidine ring, giving rise to the di-tertiary amines of type II (Chart I). Subsequent work indicated that even in the earlier hydrogenations only the type II products had been isolated. Yields in the hydrogenation step were nearly quantitative.

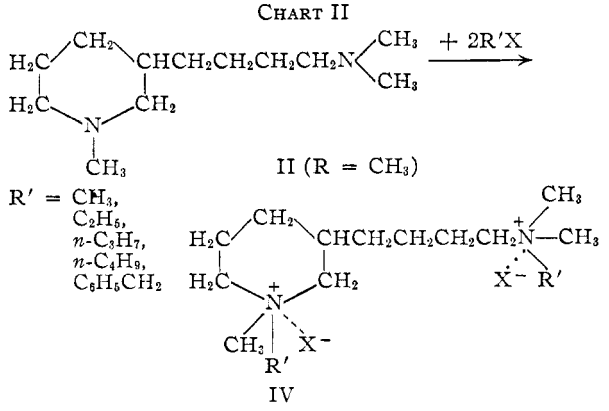
CHART I



R = H, CH_3, C_2H_5, n-C_3H_7, etc.

A number of di-quaternary ammonium salts were prepared by reacting a series of alkyl halides with the di-tertiary amine II (Chart I, R = CH_3) as illustrated in Chart II.

CHART II



The alkyl halides used were the methyl, ethyl, n-propyl and n-butyl iodides and benzyl chloride. The di-quaternary ammonium salts were obtained in nearly quantitative yields in every case.

Pharmacology.—The di-quaternary ammonium salts of nicotine (I, Chart I) have manifested no useful pharmacological actions thus far, although they have low toxicities in contrast with the high toxicity of the parent nicotine.

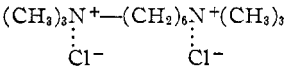
Both the di-tertiary amines of type II (Chart I) and the di-quaternary salts IV (Chart II) were found to be powerful ganglionic blocking agents, and produced strong and prolonged lowering of the blood pressure in anesthetized cats. Although the di-quaternary salts were several times as potent as the di-tertiary amines, the activity–toxicity relationship was more favorable with the latter compounds. In both series the introduction of larger alkyls than methyl on the nitrogens gave less active and more toxic products.

Compound II (Chart I, R = CH_3) appeared to be the most active of the di-tertiary amines. It was at least as active as hexamethonium chloride[1] in its ability to lower blood pressure when administered intravenously and was considerably more effective than hexamethonium when the two were given orally.

The most surprising and interesting result of the current study was the discovery of powerful hypotensive, ganglionic blocking activity in the di-tertiary amines II (Chart I, R = CH_3, C_2H_5, etc.) and even in the di-secondary amine II (Chart I, R = H), for previously it had been believed that mono- or di-quaternary ammonium salt structures were an indispensable requirement for this sort of pharmacological activity. It is hoped that these di-tertiary amines, lacking the di-quaternary salt structure of hexamethonium chloride, may prove to be free of certain side effects of the latter, which may possibly be attributable to its di-quaternary salt groups.

A detailed pharmacological report of the results with these compounds will be made elsewhere by Dr. Stata Norton of these laboratories.

It will be noted that the di-quaternary salts IV, particularly the di-methiodide IV (Chart II, R′ = CH_3), bear a close resemblance in chemical structure to hexamethonium chloride



This correspondence in structure was fortuitous, however, for, as described in the introduction, the prime motivation in the present investigation was the modification of the activity–toxicity relationship in the nicotine molecule by suitable chemical transformations.

Numerous structure–activity relationships, suggested by the findings reported here, are currently being exploited by the examination of many series of structurally similar compounds of quite varied types.

Acknowledgment.—Thanks are due to Mr. S. W. Blackman who performed the microanalyses and to Dr. Stata Norton and Mr. R. V. Fanelli for permission to report a brief summary of the pharmacological results with these compounds.

Experimental

Several illustrative experiments are given below.

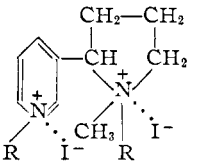
Nicotine Di-methiodide.—A solution of 16 g. (0.1 mole) of pure l-nicotine in 100 cc. of methanol was refluxed on a steam-bath for 20 hours with 20 cc. (0.3 mole) of methyl iodide. On cooling the pale yellow nicotine di-methiodide crystallized; yield 45 g. (100%), m.p. 232–233°. Details for this and the other members of the series are included in Table I

1-Methyl-3-(4′-dimethylaminobutyl)-piperidine Dihydroiodide.—Catalytic hydrogenation of 13.5 g. (0.03 mole) of nicotine dimethiodide in 60 cc. of methanol using 0.1 g. of Adams catalyst with shaking under three atmospheres overpressure of hydrogen in a Burgess–Parr type apparatus gave a rapid reduction. A total of 0.12 mole of hydrogen was absorbed in six hours. After removing platinum, the

(1) Supplied as "Hexameton" chloride by Burroughs, Wellcome and Co. (U.S.A.), Inc.

TABLE I

NICOTINE DI-QUATERNARY AMMONIUM SALTS



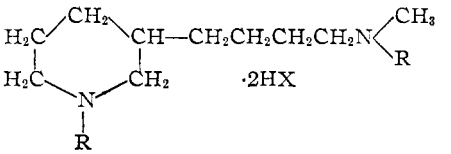
R	Reflux time, hr.	Yield, %[a]	Cryst. solvent	M.p., °C.[b]	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
CH_3	20	100	MeOH	232–233[c]	$C_{12}H_{20}N_2I_2$	32.3	32.5	4.5	4.6
C_2H_5	20	60 (100)	EtOH	220–221[d]	$C_{14}H_{24}N_2I_2$	35.4	35.6	5.1	5.1
n-C_3H_7	20	20 (100)	EtOH	218–219	$C_{16}H_{28}N_2I_2$	38.2	38.5	5.6	5.5
n-C_4H_9	48	(100)	....	.....[e]	$C_{18}H_{32}N_2I_2$				

[a] The non-parenthetical figures indicate the yields of purified crystalline material; the figures in parentheses show the yields of salt-like, ether-insoluble product, some of which has been uncrystallizable up to the present. [b] Melting points are uncorrected. [c] Reported by C. Stahlschmidt, *Ann.*, **90**, 218 (1854), who gave satisfactory analytical figures but no melting point. He did not seem to visualize its di-quaternary salt nature as we do today, 100 years later. A. Pictet and P. Genequand, *Ber.*, **30**, 2117 (1897), also reported this compound with analyses and gave its melting point as 216°. [d] A. von Planta and A. Kekulé, *Ann.*, **87**, 1 (1853), treated nicotine with ethyl iodide and obtained a crystalline product with a satisfactory analysis; they gave no melting point. [e] Not obtained crystalline. Stahlschmidt, reference (*c*) above, treated nicotine with amyl iodide but was never able to obtain the salt, or any of its double salts, in the crystalline or solid state.

filtrate was concentrated to 30 cc. and the product was crystallized out by the addition of excess ethyl acetate. The yield after several recrystallizations from the same solvent mixture was 12.5 g. (90–95%); m.p. 189–190°. Details for the compounds of this type are shown in Table II.

TABLE II

CATALYTIC HYDROGENATION PRODUCTS OF NICOTINE SALTS



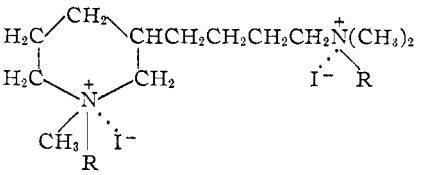
R	X	M.p., °C.[a]	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
H	Cl	201–202[b,c]	$C_{10}H_{24}N_2Cl_2$	49.3	49.3	10.0	9.9
CH_3	I	189–190[d,e]	$C_{12}H_{28}N_2I_2$	31.7	31.9	6.2	6.0
CH_3	Cl	239–240[d]	$C_{12}H_{28}N_2Cl_2$	53.1	53.3	10.4	10.4
C_2H_5	I	160–161[d]	$C_{14}H_{32}N_2I_2$	34.9	35.0	6.7	6.6
n-C_4H_7	I	179–180[d]	$C_{16}H_{36}N_2I_2$	37.6	37.8	7.1	7.2

[a] Melting points are uncorrected. Yields in all the hydrogenations were greater than 90%. [b] Crystallized from ethanol. [c] Reported by F. Blau, *ibid.*, 26, 628 (1893), and by E. Maass and A. Hildebrandt, *Ber.*, 39, 3697 (1906), who gave its melting point as 201–202°. [d] Crystallized from mixtures of methanol and ethyl acetate. [e] O. Hromatka, *Ber.*, 75, 522 (1942), prepared the di-hydrobromide, m. p. 216°, by catalytic hydrogenation of nicotine di-methobromide over a 10% platinized charcoal catalyst. Hromatka studied a number of nicotine derivatives, not similar to those of our current investigation, with the exception of the compound mentioned here. He was motivated, as he states in his paper, by objectives very similar to ours, but did not uncover any useful pharmacological properties in the group of compounds he investigated.

Di-methiodide of the Above.—After liberation of the di-tertiary base from the above dihydroiodide with alkali the base was extracted with ether and dried over anhydrous potassium carbonate. After filtration and evaporation of the ether a solution of 2 g. (0.01 mole) of the base in 25 cc. of methanol was refluxed with 5 cc. of methyl iodide for 20 hours. Addition of excess ethyl acetate gave 4.8 g. (100%) of the dimethiodide melting at 271–272°. Details for this and other members of this type of product are collected in Table III.

TABLE III

DI-QUATERNARY AMMONIUM SALTS FROM 1-METHYL-3-(4′-DIMETHYLAMINOBUTYL)-PIPERIDINE



R	M.p., °C.[a]	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
CH_3	271–272	$C_{14}H_{32}N_2I_2$	34.8	34.9	6.7	6.8
C_2H_5	236–237	$C_{16}H_{36}N_2I_2$	37.7	37.7	7.1	6.9
n-C_3H_7	194–195	$C_{18}H_{40}N_2I_2$	40.1	40.1	7.5	7.7
n-C_4H_9	179–180	$C_{20}H_{44}N_2I_2$	42.4	42.2	7.8	8.0
$C_6H_5CH_2$	222–223[b]	$C_{26}H_{40}N_2Cl_2$	Cl, 15.7	Cl, 15.6		

[a] Melting points are uncorrected. Yields were nearly quantitative in every case. The products were crystallized from mixtures of methanol and ether. [b] This compound repeatedly exploded in the combustion furnace during several attempts to do carbon and hydrogen analyses. It is a dichloride rather than diiodide.

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