TABLE III

INFRARED SPECTRA

Compound	Important maxima, cm.$^{-1}$ (KBr)[a]								
Diaminopyrimidine									
2-Chloro-4,5	3460–3100(m-s)				1669(s)	1640(m)	1585(s)	1555(m)	1505(m)
6-Chloro-4,5	3400–3000(m-s)				1668(s)	1630(m)	1572(s)	1548(s)	1505(m)
2,6-Dichloro-4,5	3440–3100(m-s)				1650(m)	1628(m)	1560(s)	1550(s)	1485(m)
Acetylpurine									
2-Chloro-9(7)	3080(w)	3050(w)	2960(w)	2915(w)	1738(s)	1595(s)	1572(w)[b]	1565(m)	1372(m)
6-Chloro-9(7)	3115(w)		2950(w)	2915(w)	1740(s)	1580(m)	1563(m)	1548(w)[b]	1380(s)
2,6-Dichloro-9(7)	3110(w)		2940(w)	2913(w)	1737(s)	1595(m)	1560(w)[b]	1549(m)	1372(m)
Purine									
2-Chloro	3050(m)	2990(m)	2920(m)	2900–2500(m-w)	1609(m)	1568(m)	1545(w)[b]	1450(m)	
6-Chloro[c]	3100(m)	3050(m)	2920(m)	2900–2400(m-w)	1603(m)	1572(s)	1551(m)[b]	1450(m)	
2,6-Dichloro	3113(m)	3060(m)	2950(m)	2900–2400(m-w)	1606(m)	1564(s)	1549(m)[b]	1445(w)	

[a] The relative intensities of the bands are indicated by w (weak), m (medium), and s (strong). [b] Shoulder. [c] The infrared spectrum of this sample of 6-chloropurine was practically identical with that of an authentic sample.

cream to white in color and after drying was pure N-acetylpurine. The methanol filtrate and washings, which contained a small amount of acetylated purine but mostly unacetylated material, were evaporated to dryness and the residue dissolved in 10% sodium hydroxide along with the acetylpurine already isolated. (In later runs the untreated residue obtained by the removal of the ethyl orthoformate–acetic anhydride was dissolved in 10% sodium hydroxide). The solution was then heated to 30–40° for 10 minutes, treated with Norit, filtered, chilled and acidified (*p*H 4–6). The chloropurine which precipitated was then removed by filtration, washed with water and dried. The mother liquor and washings were combined and extracted with ether in a continuous liquid extractor for 18–24 hours yielding an additional amount of purine. 2-Chloropurine and 6-chloropurine were purified by recrystallization from water, whereas, 2,6-dichloropurine was purified both by sublimation and by recrystallization from methanol. The melting points, analyses and over-all yields are given in Table I.

BIRMINGHAM, ALABAMA

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

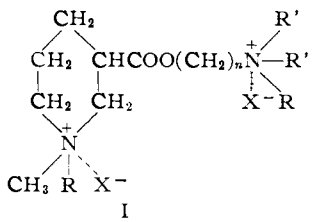
Synthetic Hypotensive Agents. IV. Dialkylaminoalkyl Esters of N-Methylnipecotic and N-Methylisonipecotic Acids and Some Bis-quaternary Ammonium Salts

BY ARTHUR P. PHILLIPS

RECEIVED NOVEMBER 25, 1955

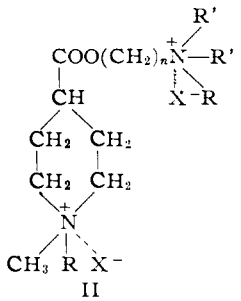
A series of dialkylaminoalkyl esters of N-methylnipecotic and N-methylisonipecotic acids has been made for examination as hypotensive, ganglionic blocking agents. These compounds were modeled after an earlier series of potent ganglionic blocking agents derived from nicotine, 1-methyl-3-(4'-dimethylaminobutyl)-piperidine and its salts, and the nipecotic ester derivatives are exact ester analogs of the latter. Introduction of the carboxylic ester function into the internitrogen chain had as its object the attainment of short-acting ganglionic blocking agents.

A series of dialkylaminoalkyl esters of N-methylnipecotic and N-methylisonipecotic acids and some derived bis-quaternary ammonium salts have been prepared for evaluation as hypotensive, ganglionic blocking agents. These compounds are illustrated by I and II



I

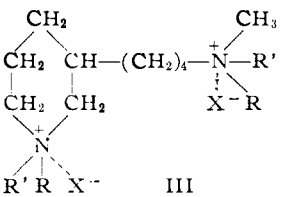
RX = HCl, CH_3I, C_2H_5I, etc.
R' = CH_3, C_2H_5, etc.



II

n = 2,3

These aminoalkyl esters of piperidine carboxylic acids were modeled after the series of compounds derived from nicotine,[1] whose structure is shown in III



III

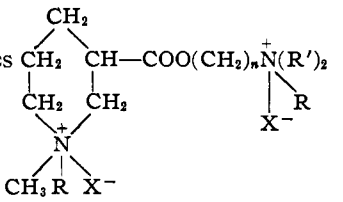
R' and RX have the same meaning as in I and II

The substances derived from nicotine, particularly III (R' = CH_3 and RX = HCl or CH_3I), were potent hypotensive, ganglionic blocking agents in cats. By replacing two of the side-chain methylenes of III with the carboxylic ester function, as in I and II, it was planned that this should offer a point of vulnerability to rupture by physiological agents within the body. In this way it was hoped that a series of short-acting ganglionic blocking agents might be attained, just as earlier a series of potent, short-acting neuromuscular blocking agents, best

(1) A. P. Phillips, THIS JOURNAL, **76**, 2211 (1954).

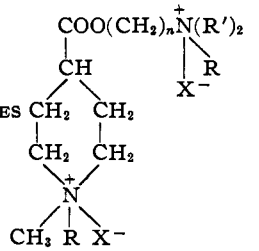
TABLE I

A. NIPECOTIC AMINOALKYL ESTER DERIVATIVES



R	RX	n	Yield, %	B.p. or m.p.[a] °C.	Mm.	Crystn.[b] solvent	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3	...	2	50[c]	153–155	28	....	$C_{11}H_{22}N_2O_2$				
CH_3	HCl	2	100	201–203		A-E	$C_{11}H_{24}N_2O_2Cl_2$	46.0	45.9	8.4	8.5
CH_3	CH_3I	2	100	215–216		M	$C_{13}H_{28}N_2O_2I_2$	31.3	31.5	5.7	5.8
CH_3	C_2H_5I	2	90	162–163		A-AE	$C_{15}H_{32}N_2O_2I_2$	34.3	34.4	6.1	6.4
C_2H_5	...	2	50[c]	162–163	17–18	....	$C_{13}H_{26}N_2O_2$				
C_2H_5	HCl	2	100	150–151		A-E	$C_{13}H_{28}N_2O_2Cl_2\cdot H_2O$	46.9	47.0	9.1	8.9
						Hygros.					
C_2H_5	CH_3I	2	85	236–237		A(M)	$C_{15}H_{32}N_2O_2I_2$	34.2	34.2	6.1	6.1
C_2H_5	C_2H_5I	2	90	217–218		A-AE	$C_{17}H_{36}N_2O_2I_2$	36.8	37.0	6.6	6.6
CH_3	...	3	60[c]	158–160	22	....	$C_{12}H_{24}N_2O_2$				
CH_3	HCl	3	100	192–193		A-E	$C_{12}H_{26}N_2O_2Cl_2$	47.8	47.7	8.7	8.8
CH_3	CH_3I	3	100	211–212		M-AE	$C_{14}H_{30}N_2O_2I_2$	32.8	32.7	5.9	6.0
CH_3	C_2H_5I	3	100	Hygroscopic glass		A-E	$C_{16}H_{34}N_2O_2I_2$	35.5	35.2	6.4	6.5

B. ISONIPECOTIC AMINOALKYL ESTER DERIVATIVES



CH_3	...	2	65[c]	145	15	....	$C_{11}H_{22}N_2O_2$				
CH_3	HCl	2	100	219–220		A-Ac	$C_{11}H_{24}N_2O_2Cl_2$	46.0	46.1	8.4	8.4
CH_3	CH_3I	2	100	272–273		M-E	$C_{13}H_{28}N_2O_2I_2$	31.3	31.1	5.7	5.7
CH_3	C_2H_5I	2	95	248–249		M-E	$C_{15}H_{32}N_2O_2I_2$	34.3 I, 48.3	34.8 I, 48.2	6.1	5.9
C_2H_5	...	2	80[c]	154–155	12	....	$C_{13}H_{26}N_2O_2$				
C_2H_5	HCl	2	100	195–196		A-E	$C_{13}H_{28}N_2O_2Cl_2$	49.5	49.4	9.0	9.0
C_2H_5	CH_3I	2	100	262–263		M-AE	$C_{15}H_{32}N_2O_2I_2$	34.2	34.3	6.1	6.3
C_2H_5	C_2H_5I	2	95	240–241		A-AE	$C_{17}H_{36}N_2O_2I_2$	36.8	36.9	6.6	6.9
$(C_2H_4)_2O$[d]	...	2	60[c]	197–200	19	...	$C_{13}H_{24}N_2O_3$				
$(C_2H_4)_2O$[d]	HCl	2	100	168–169		A-Ac-E	$C_{13}H_{26}N_2O_3Cl_2$	47.4	47.1	8.0	8.2
$(C_2H_4)_2O$[d]	CH_3I	2	95	241–242		M	$C_{15}H_{30}N_2O_3I_2$	33.3	33.3	5.6	5.5
CH_3	...	3	90[c]	163–164	21	....	$C_{12}H_{24}N_2O_2$				
CH_3	HCl	3	100	161–162		A-E	$C_{12}H_{26}N_2O_2Cl_2$	47.8	47.5	8.7	8.9
CH_3	CH_3I	3	100	211–212		M-E	$C_{14}H_{30}N_2O_2I_2$	32.8	32.8	5.9	5.9
CH_3	C_2H_5I	3	90	Hygroscopic glass		A-E	$C_{16}H_{34}N_2O_2I_2$	35.5	35.4	6.4	6.4

[a] All melting points and boiling points are uncorrected. [b] A = absolute ethanol, Ac = acetone, AE = ethyl acetate, E = ethyl ether; M = methanol. [c] Made by the ester exchange process. [d] This grouping and the N to which it is attached form the morpholino group.

exemplified by succinylcholine, was attained[2] by an analogous structural modification of the longer-lasting decamethonium. It will be noted that I (R′ = CH_3, RX = HCl or CH_3I, n = 2) is an exact ester analog of the more potent derivatives of the nicotine series (III, R′ = CH_3, RX = HCl or CH_3I).

The series of aminoalkyl esters was prepared by base-catalyzed ester exchange between the methyl (or ethyl) ester of N-methylnipecotic (or isonipecotic) acid and the appropriate dialkylaminoalkanol. Optimum conditions for the ester exchange reaction have *not* been the subject of a thorough investigation here. Usually the N-methylnipecotic (or isonipecotic) methyl (or ethyl) ester mixed with two to five molar equivalents of pure distilled aminoalkanol, containing a trace of dissolved sodium, was refluxed vigorously for a period from 4–24 hours. In some cases methanol (or ethanol) formed in the exchange reaction was allowed to distil off during the heating, in other cases the mixture was simply refluxed. Because of the basic nature not only of the aminoalkanol but of the nipecotic ester, the ester exchange might well proceed satisfactorily without the addition of other basic catalyst. This exchange reaction, even without more careful study, gave yields between 50–90%.

(2) A. P. Phillips, THIS JOURNAL, 71, 3264 (1949).

The di-tertiaryamino ester derivatives were transformed into dihydrochlorides and were quaternized by refluxing with the appropriate alkyl halides in alcohol solution. Isopropyl alcohol was most commonly used as the alkylation solvent to minimize any tendency toward reversal of the preparative ester exchange reaction. The physical properties and analytical data for the two series of aminoalkyl esters are compiled in Table I.

The intermediate methyl esters of N-methylnipecotic and isonipecotic acids were prepared by catalytic hydrogenation in methanol of the methyl chlorides of the methyl esters of nicotinic and isonicotinic acids using Adams catalyst at 25° and 3 atmospheres of hydrogen pressure. This reduction goes moderately rapidly and gives high yields of the reduced esters. The process seems deserving of comment only for reasons of comparison with certain other hydrogenations of pyridine rings performed in this Laboratory. Earlier an extensive series of 2- and 4-stilbazole *methiodides* was found to be reduced rapidly and completely to the stilbazolines[3] under the above stated reduction conditions. The ganglionic blocking agents derived from nicotine[1] were obtained by catalytic hydrogenation, under the same conditions, of nicotine *dialkiodides*. Yet the *methiodides* of methyl nicotinate or methyl isonicotinate were hydrogenated under the same conditions only very sluggishly and incompletely, if at all. In these cases, as in several others which will be reported on later in connection with other series of compounds, the methiodides of simple pyridine derivatives were resistant to reduction under the mild conditions used, and conversion to the methochlorides was necessary to permit a practical hydrogenation rate. It thus appears that iodide may be a weak or partial poison to these reductions with Adams catalyst, but the appearance of the deleterious effects is somewhat controlled by the inherent ease of reduction of the particular system under consideration.

(3) A. P. Phillips, THIS JOURNAL, **72**, 1850 (1950).

The aminoester derivatives I and II have been found, as expected, to be ganglionic blocking agents of short duration. The most potent compound seemed to be the isonipecotic ester II ($R' = CH_3$, $RX = CH_3I$, $n = 2$). This compound upon intravenous injection into anesthetized cats produced ganglionic block and lowering of blood pressure with a potency approximating that of hexamethonium chloride, although of much shorter duration. The hypotensive blood pressure effects lasted between 5–10 minutes.

Acknowledgments.—The author is indebted to Mr. Samuel W. Blackman for the microanalytical results included and to Dr. Kenneth Colville for the results of pharmacological testing.

Experimental

Preparation of N-Methylisonipecotic Acid Diethylaminoethyl Ester.—To a solution of about 0.1 g. of sodium in 25 cc. (theory 6 g.) of freshly distilled diethylaminoethanol (b.p. 162–164°), was added 7.9 g. (0.05 mole) of N-methylisonipecotic acid methyl ester (b.p. 100° at 22 mm.). This mixture was refluxed vigorously in a metal-bath at 170–180° for 20 hr. After removal of excess of diethylaminoethanol the product was distilled *in vacuo*, b.p. 154–155° at 11–12 mm., yield 9.5 g. (80%).

Dihydrochloride.—A sample of the base was treated with excess of ethanolic hydrogen chloride and the hydrochloride was precipitated with ether. After recrystallization from alcohol–ether mixtures the white crystals melted at 195–196°.

Dimethiodide.—A sample, 2.4 g. (0.01 mole), of the above-distilled base was dissolved in 20 cc. of isopropyl alcohol, 5 cc. of methyl iodide was added and the mixture was left for 2 hr. at 40–45°. A heavy white crystalline precipitate formed. After cooling, the product was collected and weighed 5.3 g. (100%). Recrystallization from mixtures of methanol–ethyl acetate gave white crystals, m.p. 262–263°.

See Table I for the details of these and the other compounds.

TUCKAHOE 7, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, HARVARD MEDICAL SCHOOL]

The Preparation of Indanylpiperidinemethanol Derivatives

BY FREDERICK C. UHLE, JAMES E. KRUEGER AND ADRIANNE ELLEFSON ROGERS

RECEIVED OCTOBER 11, 1955

Indanylpiperidinemethanol derivatives formally related in skeletal structure to the alkaloid veratramine have been prepared. Condensation of 5-indanyl methyl ketone with 5-methylpicolinic acid, obtained by carbonation of 5-methyl-2-pyridyllithium, has afforded 1-(5-indanyl)-1-[2-(5-methylpyridyl)]-ethylene (III), reduction of which, with one mole of hydrogen, has given 1-(5-indanyl)-1-[2-(5-methylpyridyl)]-ethane (IV). Addition of 5-methyl-2-pyridyllithium to 5-indanyl methyl ketone has yielded α-(5-indanyl)-α-methyl-(5-methyl-2-pyridine)-methanol (V), catalytic hydrogenation of which has produced α-(5-indanyl)-α-methyl-(5-methyl-2-piperidine)-methanol (VIA). Sodium–alcohol reduction of V has afforded a diastereoisomeric carbinol, VIB. The isomers VIA and VIB have been found to exhibit antiaccelerator cardiac properties of the type characteristic of veratramine in molar quantities of the order of one hundred times those effective in the case of the naturally occurring alkaloid.

Veratramine (I), the pentacyclic, secondary 2-ethyl-5-methylpiperidine derivative native to *Veratrum viride*, has recently been demonstrated to be the prototype of a novel "modified steroid" skeletal arrangement characterized by the five- and six-membered nature of rings C and D, respectively.[1] The alkaloid has, furthermore, been shown to exhibit a marked pharmacodynamic specificity in its capacity to antagonize the consequences of accelerans stimulation as well as to annul the cardioaccelerator effects of epinephrine and related sympathomimetic amines without disturbing their positive inotropic and vasopressor properties.[2]

(1) J. Fried, O. Wintersteiner, M. Moore, B. M. Iselin and A. Klingsberg, THIS JOURNAL, **73**, 2970 (1951); C. Tamm and O. Wintersteiner, *ibid.*, **74**, 3842 (1952); O. Wintersteiner and N. Hosansky, *ibid.*, **74**, 4474 (1952).

(2) O. Krayer, *J. Pharmacol. Expll. Therap.*, **96**, 492 (1949); **97**, 246 (1949).