Methyl Isobutyl Ketone, a Product of Alkaline Hydrolysis of Junceine.—A solution of 0.20 g. of junceine in 5 ml. of 10% aqueous sodium hydroxide was heated under reflux for one hour. The solvent was boiled off and the distillate collected in four 1.2-ml. fractions. The first three fractions gave a positive sodium nitroprusside test for methyl ketones.[12] They were reunited and dinitrophenylhydrazine reagent[13] was added. After 15-minutes standing at room temperature, the liquid was carefully pipetted off and the residue was crystallized from ethanol; yellow crystals, m.p. 95°. The yield of crude material was 0.085 g. (56%).

Anal. Calcd. for $C_{12}H_{18}N_4O_4$: C, 51.42; H, 5.75. Found: C, 51.34; H, 5.60.

No depression of melting point was observed on admixture with an authentic sample of the 2,4-dinitrophenylhydrazone of methyl isobutyl ketone. The infrared spectra of the two products were also identical.

R_f Value Determinations.—The R_f values of several Senecio alkaloids have been determined before in this Laboratory using butanol–5% acetic acid as the mobile phase.[1,14] However, since the value for retrorsine had not been previously determined, the R_f values of all the alkaloids referred to in this communication were redetermined at the same time. The results are shown in Table II.

TABLE II

Alkaloid	Formula	R_f	ΔR_f
Senecionine	$C_{18}H_{25}NO_5$	0.62	0.18
Retrorsine	$C_{18}H_{25}NO_6$	.44	
Seneciphylline	$C_{18}H_{23}NO_5$	.58	.18
Riddelline	$C_{18}H_{23}NO_6$	.40	
Trichodesmine	$C_{18}H_{27}NO_6$	.54	.16
Junceine	$C_{18}H_{27}NO_7$	.38	

(12) F. Feigl, "Spot Tests"; Elsevier Publishing Co., New York, N. Y., 1954, p. 160.

(13) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 171.

(14) R. Adams and M. Gianturco, THIS JOURNAL, **78**, 398 (1956).

URBANA, ILLINOIS

[CONTRIBUTION FROM THE KETTERING–MEYER LABORATORY, SOUTHERN RESEARCH INSTITUTE, AFFILIATED WITH SLOAN–KETTERING INSTITUTE]

Synthesis of Potential Anticancer Agents. I. Chloropurines[1]

BY JOHN A. MONTGOMERY

RECEIVED NOVEMBER 11, 1955

2-Chloro-4,5-diaminopyrimidine, 6-chloro-4,5-diaminopyrimidine and 2,6-dichloro-4,5-diaminopyrimidine each react readily with ethyl orthoformate–acetic anhydride to give a mixture of the corresponding chloropurine and the N-acetylchloropurine. Since the N-acetylchloropurines are readily hydrolyzed by base to the chloropurines, this unique procedure has preparative value. The infrared spectra of these compounds are discussed.

All the chloropurines which appear in the literature have been prepared by chlorination of purinones with phosphorus oxychloride with or without using a tertiary amine, such as dimethylaniline.[2] Not only do the procedures used and the yields obtained vary widely, but the desired chloropurines are not always obtained.[3]

Attempts to convert chloro-4,5-diaminopyrimidines to the corresponding chloropurines using conventional reagents and procedures, *i.e.*, anhydrous formic acid, formamide, etc., have all failed,[2d,4] due to the hydrolysis of the chlorine atoms to hydroxyl groups. Robins found that in the case of the monochloro-4,5-diaminopyrimidines and formic acid, this hydrolysis takes place during formylation of the amino group and in the case of the 2,6-dichloro-4,5-diaminopyrimidine during the cyclization step.[4b] In either case the other product of the over-all reaction, water, must be formed and, therefore, the hydrolysis cannot be prevented.

A new approach to the synthesis of chloropurines involves the use of ethyl orthoformate, a reagent which has found application in the formation of other heterocyclic systems.[5] Since this work was begun, Richter and Taylor[6] have synthesized hypoxanthine by treating aminomalonamamidine dihydrochloride with ethyl orthoformate–acetic anhydride, closing both the pyrimidine and imidazole ring in one step. Albert, Brown and Cheeseman[7] found ethyl orthoformate very effective when coupled with acetic anhydride, in the preparation of 4-hydroxypteridine.

It has now been found that although a chloro-4,5-diaminopyrimidine reacts very slowly with ethyl orthoformate alone, it reacts readily with ethyl orthoformate–acetic anhydride to form a mixture of the chloropurine and N-acetylchloropurine.

Although the N-acetylpurines may be recrystallized unchanged from organic solvents such as ethyl acetate, recrystallization of N-acetyl-2-chloropurine from boiling water resulted in a complex reaction giving approximately equal amounts of 2-chloropurine and another compound, identified tentatively as 2-hydroxy-4-amino-5-formylaminopyrimidine on the basis of its ultraviolet and infrared spectra. The effect of hot water on N-acetyl-2-chloropurine, N-acetyl-6-chloropurine and N-acetyl-2,6-dichloropurine was not investigated further since it was found that if the N-acetylpurines are dissolved in warm 10% sodium hydroxide solu-

(1) This work was supported in part by funds from the C. F. Kettering Foundation.

(2) (a) E. Fisher, *Ber.*, **30**, 549, 2226 (1897); **32**, 435 (1899); (b) R. R. Adams and F. C. Whitmore, THIS JOURNAL, **67**, 1271 (1945); (c) J. Davoll and B. A. Lowy, *ibid.*, **73**, 2936 (1951); (d) A. Bendich, P. J. Russell and J. J. Fox, *ibid.*, **76**, 6073 (1954).

(3) R. K. Robins and B. E. Christensen, *J. Org. Chem.*, **16**, 324 (1951); THIS JOURNAL, **74**, 3624 (1952).

(4) (a) R. K. Robins, K. J. Dille, C. H. Willits and B. E. Christensen, *ibid.*, **75**, 263 (1953); (b) R. K. Robins, K. J. Dille and B. E. Christensen, *J. Org. Chem.*, **19**, 930 (1954).

(5) E. Schipper and A. R. Day, THIS JOURNAL, **73**, 5672 (1951); **74**, 350 (1952).

(6) E. Richter and E. C. Taylor, *Angew. Chem.*, **67**, 303 (1955).

(7) A. Albert, D. J. Brown and G. Cheeseman, *J. Chem. Soc.*, 475 (1951).

TABLE I

Purine	Yield, %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
2-Chloro-9(7)-acetyl		192–195 dec.	42.70	42.59	2.54	2.68	28.50	28.55
2-Chloro	73	231[a]	38.85	38.99	1.96	2.17	36.25	35.45
6-Chloro-9(7)-acetyl		140–142	42.75	42.90	2.54	2.83	28.50	28.50
6-Chloro[b]	86	...[c]	...	...	..	..	...	...
2,6-Dichloro-9(7)-acetyl		154–158	36.39	36.42	1.73	1.78	24.25	24.07
2,6-Dichloro	53	179–181[d]	31.80	31.92	1.06	1.11	29.61	29.57

[a] When heated rapidly from 200° (in an aluminum block). [b] Known compound; see Tables II and III. [c] Decomposes with indefinite melting point. [d] When heated slowly from 170°.

tion, they are readily hydrolyzed in 5–10 minutes to the desired purines in 90–95% yield.[8]

2-Chloropurine, 6-chloropurine[2d] and 2,6-dichloropurine, valuable intermediates in the synthesis of analogs of naturally occurring purines, have been prepared by this procedure. Table I gives the melting points and analyses of the intermediate N-acetylpurines and the two new chloropurines reported here, and the over-all yields of the three purines prepared. Table II shows a comparison of the ultraviolet absorption maxima of the 4,5-diaminopyrimidines, the N-acetylpurines in water appeared to be the same as the unacetylated purines; however, due to the ease of hydrolysis of the N-acetyl group, the spectra obtained may actually be those of the deacetylated purines. Since the N-acetylpurines are isolated by the use of methanol, their spectra were determined in this solvent also, but did not differ appreciably from the spectra obtained in water.

TABLE II

ULTRAVIOLET DATA

Compound	pH	Maxima λ, mμ	Maxima εM × 10⁻³
2-Chloro-4,5-diamino-pyrimidine	1	285	8.45
	7	251.5, 294.5	6.55, 5.87
	13	251.5, 294.5	6.45, 5.84
6-Chloro-4,5-diamino-pyrimidine	1	268, 305	7.38, 10.05
	7	253.5, 289	7.48, 8.92
	13	253.5, 389	6.98, 8.36
2,6-Dichloro-4,5-diamino-pyrimidine	1	259, 296	6.5, 7.1
	7	259, 296	6.7, 7.4
	13	259, 296	6.7, 7.29
2-Chloro-9(7)-acetyl-purine	..[a]	271.5	7.37
6-Chloro-9(7)-acetyl-purine	..[a]	264	9.60
2,6-Dichloro-9(7)-acetyl-purine	..[a]	273	7.62
2-Chloropurine	1	270.5	8.07
	7	272	7.99
	13	278.5	8.15
6-Chloropurine	7	265.5	9.53[b]
	13	274	8.72[b]
2,6-Dichloropurine	1	274	7.99
	7	277	7.86
	13	280	7.70

[a] Run in methanol because of ease of hydrolysis of the N-acetyl group in water. [b] It was necessary to dry the compound *in vacuo* over P_2O_5 at 80° for four hours to obtain these values.

The principal bands of the infrared spectra are listed in Table III. The 4,5-diaminopyrimidines show medium to strong maxima at 3450–3000 cm.$^{-1}$ (N–H), strong at 1670–1650 cm.$^{-1}$ (NH of N=C—NH), and three bands medium to strong between 1585–1505 cm.$^{-1}$ (aromatic pyrimidine bands). The N-acetyl purines exhibit weak maxima at 3115–3080 cm.$^{-1}$ (aromatic CH), 2960–2940 cm.$^{-1}$ (–CH_3), 2915–2913 cm.$^{-1}$ (–CH_3), strong at 1740–1737 cm.$^{-1}$ ("active N-acetyl"), three medium to strong bands between 1595–1549 cm.$^{-1}$ (aromatic purine bands), and a medium to strong band at 1380–1372 cm.$^{-1}$ (C–CH_3). They do not show the characteristic purine absorption (due to acidic N–H) between 2900–2400 cm.$^{-1}$. The purines show three medium bands between 3113–2920 cm.$^{-1}$ (aromatic CH), medium to weak absorption between 2900–2400 cm.$^{-1}$ (acidic NH), and three medium to strong bands between 1609–1545 cm.$^{-1}$ (aromatic purine); 2-chloropurine and 6-chloropurine show a medium band at 1450 cm.$^{-1}$ (CH) which is weak and not as well defined in 2,6-dichloropurine.

Acknowledgment.—The author is indebted to Mr. J. P. Holmquist for the microanalytical results reported, to Mr. J. W. Murphy for the ultraviolet and infrared spectral determinations, and to Dr. W. C. Coburn for his aid in the interpretation of the infrared data.

Experimental

The melting points recorded here were determined in an oil-bath and are uncorrected.

Spectral Data.—The ultraviolet spectra were determined with a Beckman Model DK-2 spectrophotometer, whereas the infrared spectra were run in pressed potassium bromide pellets with a Perkin-Elmer Model 21 spectrophotometer.

4,5-Diaminopyrimidines.—The requisite 2-chloro-4,5-diaminopyrimidine,[4b] 6-chloro-4,5-diaminopyrimidine[4a] and 2,6-dichloro-4,5-diaminopyrimidine[10] were all prepared by known procedures. Spectral data for these compounds are shown in Tables II and III.

Reaction of 4,5-Diaminopyrimidine with Ethyl Orthoformate–Acetic Anhydride.—2-Chloro-, 6-chloro- and 2,6-dichloropurine were all prepared by essentially the same procedure. The 4,5-diaminopyrimidine was suspended in ten times its weight of a one-to-one mixture of ethyl orthoformate and acetic anhydride, the mixture heated slowly with stirring to reflux (the initial reaction is exothermic), and refluxed for one hour after all the solid dissolved. The excess ethyl orthoformate–acetic anhydride was then removed *in vacuo* (20 mm.) and, in the initial runs, the chloro-9(7)-acetylpurine isolated in pure form by washing the solid residue with cold methanol. The solid which remained was

(8) The facile cleavage of the N-acetylpurines appears similar to that of a diacylimide,[9] the C=N of the imidazole moiety corresponding to the other acyl group. If such is the case, then one could expect cleavage of these N-acetylpurines to occur on either side of the acetylated nitrogen to give a purine or a 5-formamidopyrimidine. It is not too surprising that mode of cleavage of the N-acetylpurines is dependent on pH.

(9) B. R. Baker, J. P. Joseph and R. E. Schaub, THIS JOURNAL, **77**, 5905 (1955).

(10) P. Bitterli and H. Erlenmeyer, *Helv. Chim. Acta*, **34**, 835 (1951).

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

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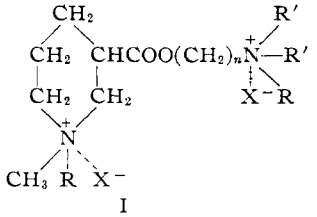
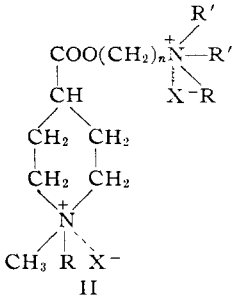
A series of dialkylaminoalkyl esters of N-methylnipecotic and N-methylisonipecotic acids has been made for examination as hypotensive, ganglionic blocking agents. These compounds were modeled after an earlier series of potent ganglionic blocking agents derived from nicotine, 1-methyl-3-(4′-dimethylaminobutyl)-piperidine 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



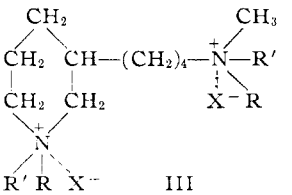
I



II

RX = HCl, CH_3I, C_2H_5I, etc.
R′ = CH_3, C_2H_5, etc. 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).