[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES, INDIANAPOLIS 6, IND.]

Exchange Amination. Alkyl and Arylamino-pyrimidines and Purines

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Pyrimidine amine functions were exchanged with primary alkyl, aralkyl and arylamine groups to yield the corresponding N-substituted 4-amino-, 6-amino- and 2-aminopyrimidines. This exchange reaction was particularly useful in the synthesis of 4-substituted amino-2, and 6-hydroxypyrimidines as well as 1,3-dialkyl-6-substituted aminouracils. Adenine was converted to 6-benzylamino-, 6-furfurylamino- and 6-phenylaminopurine by the same reaction.

N-Alkyl and N-arylamino-pyrimidines and purines have been prepared almost exclusively by nucleophilic displacement of chloro, mercapto or alkoxy groups with amines. This procedure is limited by the availability of appropriate chloro, mercapto or alkoxy intermediates. Pyrimidines and purines having primary amino or imino functions on a carbon adjacent to an endocyclic nitrogen are, however, readily available. This paper describes the direct conversion of a number of these aminopyrimidines and 6-aminopurine to their N-alkyl-, N-aralkyl- and N-arylamino-derivatives.

Alkyl and arylamines were allowed to react with 6-amino-2,4-dimethylpyrimidine hydrochloride, at an elevated temperature, to give excellent yields of 6-anilino-, 6-(3′,4′-dimethoxyphenethylamino)-, 6-benzylamino-, 6-*n*-heptylamino-, 6-cyclohexylamino- and 6-*n*-butylamino-2,4-dimethylpyrimidines. The boiling point as well as other physical properties of the cyclohexyl derivative are identical to those previously reported for 6-cyclohexylamino-2,4-dimethylpyrimidine.[1] Methiodides were prepared of the 6-benzylamino- and 6-*n*-heptylamino-2,4-dimethylpyrimidines, resulting in well defined solid derivatives.

The primary and secondary amine groups of 4-amino-6-*n*-octylaminopyrimidine were both replaced when heated with benzylamine hydrochloride. The product, 4,6-bis-benzylaminopyrimidine, was identical to an authentic sample of this prepared[2] from 4,6-dichloropyrimidine and benzylamine.

Very few 4-alkylamino-, or 4-arylamino-, 2- or 6-hydroxypyrimidines have been reported. Those found in the literature were prepared by the hydrolysis of a 2- or 6-alkylmercapto or alkylsulfonyl group.[3-5] The exchange amination reaction reported here is particularly useful in the synthesis of pyrimidines of this type. Cytosine was heated with a mixture of benzylamine hydrochloride and benzylamine to give an 80% yield of 4-benzylamino-2-hydroxypyrimidine. Slightly lower yields of 4-anilino-2-hydroxypyrimidine and 2-hydroxy-4-phenethylaminopyrimidine were obtained when cytosine was treated with aniline hydrochloride and with phenethylamine hydrochloride. In a similar manner 4-amino-6-hydroxypyrimidine[2] gave 4-benzylamino-6-hydroxypyrimidine, 4-anilino-6-hydroxypyrimidine and 6-hydroxy-4-*m*-methylbenzylaminopyrimidine. 4-Amino-6-hydroxy-2-methylpyrimidine underwent exchange amination to yield 4-benzylamino-6-hydroxy-2-methylpyrimidine, 4-hydroxy-2-methyl-6-phenethylaminopyrimidine and 4-anilino-6-hydroxy-2-methylpyrimidine.

All the reactions of primary amines with pyrimidylamines, described above, were carried out in the presence of an acid catalyst, *i.e.*, the amine hydrochloride. Two reactions were performed to determine whether an acid catalyst was actually required. In the absence of an acid *n*-heptylamine and benzylamine each underwent obscure reactions with 4-amino-6-hydroxypyrimidine. A low yield of 1,3-di-*n*-heptylurea was obtained with *n*-heptylamine. Benzylamine yielded a product having an empirical formula $C_{18}H_{17}N_3O$, as determined from its elemental analysis. Its ultraviolet absorption spectrum is pyrimidine-like with two maxima; log a_M at 230 mμ is 4.52, and at 259 mμ is 3.79. The infrared spectrum supports the pyrimidine structure and absorption bands at 2.92, 6.02 and 6.21 μ indicate the presence of NH, amide-like carbonyl and benzyl groupings, respectively. These results suggest the structure 1-benzyl-4-benzylamino-6-keto-1,6-dihydropyrimidine or 3-benzyl-4-benzylamino-6-keto-1,6-dihydropyrimidine. Either of these products obtained from benzylamine or 1,3-di-*n*-heptylurea obtained from *n*-heptylamine must result by complex transpositions involving a ring cleavage. The mechanism of this ring cleavage could be similar to that proposed by Taylor[6] for the reactions of alkylamines with aminopteridines. Since the reactions of 4-amino-6-hydroxypyrimidine with benzylamine and with *n*-heptylamine in the absence of an acid catalyst did not give consistent results, the presence of an acid catalyst is considered essential in effecting a definable exchange amination resulting in the formation of the 4-substituted amino-6-hydroxypyrimidines. A catalyst was therefore used in all the exchange reactions. When 2-amino-4-hydroxypyrimidine (isocytosine) was treated with an alkyl or arylamine hydrochloride, under the same conditions used for the 4- and 6-aminopyrimidines, there was no observable reaction and unchanged isocytosine was recovered. The reaction between 2-amino-4,6-dimethylpyrimidine and benzylamine hydrochloride gave a low yield of 2-benzylamino-4,6-dimethylpyrimidine. Contributions of the two adjacent endocyclic nitrogens would appear to retard an exchange of the 2-amine function, but further examination of

(1) R. Hull, B. J. Lovell, H. T. Openshaw, L. C. Payman and A. R. Todd, *J. Chem. Soc.*, 357 (1946).

(2) C. W. Whitehead and J. J. Traverso, THIS JOURNAL, **80**, 2185 (1958).

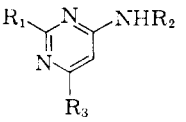
(3) J. M. Sprague and T. B. Johnson, *ibid.*, **57**, 2252 (1935).

(4) F. H. S. Curd, M. I. Davis, E. C. Owen, F. L. Rose and G. A. P. Tuey, *J. Chem. Soc.*, 370 (1946).

(5) H. L. Wheeler and T. B. Johnson, *Am. Chem. J.*, **31**, 596 (1904).

(6) E. C. Taylor, THIS JOURNAL, **74**, 1651 (1952).

TABLE I



R_1	R_2	R_3	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3	n-C_7H_9	CH_3	108[a]	91	$C_{10}H_{17}N_3$	66.99	66.86	9.57	9.75	23.44	23.45
CH_3	C_6H_5	CH_3	102[b]	53	$C_{12}H_{13}N_3$					21.09	21.27
CH_3	C_6H_{11}	CH_3	135[c]	75	$C_{12}H_{19}N_3$					20.47	20.43
CH_3	$C_6H_5CH_2$	CH_3	78–81[d]	71	$C_{13}H_{15}N_3$					19.70	19.46
CH_3	n-C_7H_{15}	CH_3	165[e]	70	$C_{13}H_{23}N_3$					18.99	18.45
CH_3	$C_{10}H_{13}O_2$[f]	CH_3	200[g]	69	$C_{16}H_{21}N_3O_2$					14.62	14.69
OH	C_6H_5	H	266	64	$C_{10}H_9N_3O$	64.16	64.06	4.85	4.94	22.45	22.64
OH	$C_6H_5CH_2$	H	217–218	79	$C_{11}H_{11}N_2O$	65.67	65.54	5.51	5.66	20.88	20.90
OH	$C_6H_5(CH_2)_2$	H	182–185	63	$C_{12}H_{13}N_3O$	66.95	67.21	6.09	5.59	19.52	19.43
H	C_6H_5	OH	248–250	13	$C_{10}H_9N_3O$	64.16	64.16	4.85	5.10	22.45	22.10
H	$C_6H_5CH_2$	OH	230–234	37	$C_{11}H_{11}N_3O$	65.67	65.83	5.51	5.83	20.88	20.87
H	C_8H_9[h]	OH	210–220	39	$C_{12}H_{13}N_3O$	66.95	67.04	6.09	6.49	19.52	19.86
CH_3	C_6H_5	OH	270	57	$C_{11}H_{11}N_3O$					20.88	20.78
CH_3	$C_6H_5CH_2$	OH	225–227	60	$C_{12}H_{13}N_3O$	66.95	66.94	6.09	6.01	19.52	19.43
CH_3	$C_6H_5(CH_2)_2$	OH	224	65	$C_{13}H_{15}N_3O$					18.33	18.40

[a] B.p. at 0.75 mm. [b] B.p. 165° at 1 mm. [c] B.p. at 0.5 mm. [d] B.p. 155° at 0.4 mm. [e] B.p. at 1 mm. [f] 3,4-Dimethyl phenethyl. [g] B.p. at 1 mm. [h] 4-Methylbenzyl.

the reaction conditions is necessary before this may be considered a fact.

It was particularly interesting to find the exchange amination reaction could occur when both ring nitrogens of the pyrimidine were substituted with alkyl groups or when amino–imino tautomerism does not exist between the extranuclear and endonuclear nitrogens. When 1,3-dimethyl-6-aminouracil was treated separately with the hydrochlorides of furfurylamine, benzylamine and n-heptylamine, the products were 1,3-dimethyl-6-furfurylaminouracil, 6-benzylamino-1,3-dimethyluracil and 1,3-dimethyl-6-n-heptylaminouracil. These 1,3-dialkyl-6-substituted aminouracils are believed to be the first representatives of their type. Previously reported methods of pyrimidine synthesis cannot be applied in their preparation.

Adenine reacted with benzylamine hydrochloride to yield 6-benzylaminopurine and with furfurylamine hydrochloride to yield 6-furfurylaminopurine (kinetin). Aniline hydrochloride and adenine gave 6-anilinopurine which required a number of recrystallizations before it was free of color. Guanine did not appear to react with the amine hydrochlorides and adenosine was degraded to adenine.

Ultraviolet absorption of the parent primary pyrimidylamines and their products, the alkylamino- and arylaminopyrimidines, were determined in neutral, acid and basic alcohol solutions (Table I). Similarity in the absorption characteristics of each parent compound and its derivative supports the structure of the latter. Most of the pyrimidines were titrated and the $pK_{a'}$ values determined in 66% N,N-dimethylformamide are of the order of those expected (Table I).

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Experimental

2,4-Dimethyl-6-substituted Aminopyrimidines (Table I).—A mixture of 15 g. (0.1 mole) of 6-amino-2,4-dimethylpyrimidine hydrochloride and a 10% molar excess of the appropriate amine was sealed in a glass tube. This was heated at 170° in a furnace for 20 hours. The cooled content of the tube was poured into dilute NH_4OH. The product was extracted with ether, dried over $MgSO_4$ and distilled under reduced pressure. In some cases the products crystallized and were recrystallized from a mixture of ethyl acetate and petroleum ether.

6-Benzylamino-2,4-dimethylpyrimidine Methiodide.—Three grams of 6-benzylamino-2,4-dimethylpyrimidine and 2.5 g. of methyl iodide in 50 ml. of ethyl acetate were boiled under reflux for 16 hr. The separated solid was recrystallized from ethanol; yield 4.5 g. (82%), m.p. 190–192°.

Anal. Calcd. for $C_{14}H_{19}IN_3$: N, 11.26. Found: N, 11.49.

2,4-Dimethyl-6-n-heptylaminopyrimidine methiodide: yield 72%, (as described above), m.p. 70–72°. *Anal.* Calcd. for $C_{14}H_{26}IN_3$: N, 11.56. Found: N, 11.31.

4,6-Bis-benzylaminopyrimidine from 4-Amino-6-n-octylaminopyrimidine.—A mixture of 4 g. (0.018 mole) of 4-amino-6-n-octyl-aminopyrimidine,[2] 2.56 g. (0.018 mole) of benzylamine hydrochloride and a few drops of benzylamine was heated at 170° for 2 hr. The cooled residue was washed with ether and then with alcohol to yield 1 g. of insoluble solid. The solid was recrystallized from ethanol; m.p. 236–237°. This was identical to a sample of 4,6-bis-benzylaminopyrimidine.[2]

4-Alkylamino- and 4-Arylamino-2-hydroxypyrimidines.—To 5.5 g. (0.077 mole) of cytosine with an equal molar amount of the appropriate amine hydrochloride was added enough of the free amine to wet the solids. The mixture was heated in an oil-bath at 165° for 6 hr. The solid residue was dissolved in dilute alcohol, clarified with carbon, concentrated and allowed to crystallize.

4-Substituted Amino-6-hydroxypyrimidines (Table I).—To one-tenth mole (11.1 g.) of 4-amino-6-hydroxypyrimidine[2] was added 0.1 mole of the appropriate amine hydrochloride with sufficient free amine to moisten the mass. The mixture was placed in an oil-bath at temperatures of 145–170°. Considerable foaming and bubbling occurred which ceased after 1–4 hr. The residue was triturated with water, the solid product collected and recrystallized from ethanol.

6-Hydroxy-2-methyl-4-substituted Aminopyrimidines (Table I).—To 12.5 g. (0.1 mole) of 4-amino-6-hydroxy-2-methylpyrimidine was added 0.1 mole of the appropriate amine hydrochloride and 10 ml. of the free amine. The

TABLE II

ULTRAVIOLET SPECTRA[a] AND pK'_a VALUES[b]

Pyrimidine	pK_a'	Ultraviolet spectra: Neutral $\lambda_{max.}$ mμ	Neutral log a_M	Acid $\lambda_{max.}$ mμ	Acid log a_M	Alkali $\lambda_{max.}$ mμ	Alkali log a_M
6-NH_2-4-OH	<2.5, 11.3	215	4.49	208	4.32		
		256	3.81	252	3.95	254	3.59
6-NHC_6H_5-4-OH	10.9	248	4.24				
		280	4.24				
6-NHC_6H_7-4-OH[c]	11.7	224	4.49	218	4.34		
6-NH_2-4-OH-2-CH_3		214	4.42				
		258	3.84	253	3.98	253	3.67
6-NHC_7H_7-4-OH-2-CH_3[c]	12.2	223	4.50				
		262	3.99	258	4.20	257	3.94
2-NH_2-4,6-di-CH_3		228	4.09	224	4.09	225	4.10
		290	3.67	298	3.76	290	3.67
2-NHC_7H_7-4,6-di-CH_3[c]	3.9	238	4.29	232	4.27	237	4.32
		298	3.60	310	3.76	297	3.68
6-NH_2-1,3-di-CH_3-2,4-di-O[c]		266	4.31	266	4.31	266	4.31
6-NHC_5H_5O-1,3-di-CH_3-2,4-di-O[c]		267	4.31	267	4.30	269	4.29
6-NHC_7H_7-1,3-di-CH_3-2,4-di-O[c]		268	4.32	268	4.32	268	4.34
4-NH_2-2-OH	4.8, >13	267	3.74	278	3.99	282	3.85
4-NHC_7H_7-2-OH[c]	3.8, 13.5	266	4.00	283	4.15	286	4.03
4-NHC_8H_9-2-OH[c]	4.0, 13.6	268	3.97	283	4.11	285	3.95
4-NHC_6H_5-2-OH	12.9	293	4.26	294	4.17	300	4.26
		232sh		220sh		259	3.94
4-NHC_7H_7-2,6-di-CH_3[c]	6.3	244	4.20	259	4.28	244	4.20
		275sh		263	4.28	275sh	
4-NHC_6H_5-2,6-di-CH_3	5.8	290	4.24				
4-NH-C_6H_{11}-2,6-di-CH_3·CH_3I	>14	260	3.55				
4-NH-*n*-C_7H_{15}-2,6-di-CH_3·CH_3I	>14	264	4.27				
4-NHC_7H_7-2,6-di-CH_3·CH_3I	>14	265	4.40				
2-NH_2-4-OH	3.9; 10.8	220	3.94	255	3.82	274	3.83
		286	3.92				

[a] The ultraviolet spectra were determined in 95% ethanol; in 95% ethanol with 50 λ of 2 *N* HCl per 3.3 ml. and in 95% ethanol with 50 λ of 1.7 *N* KOH per 3.3 ml. [b] The pK_a' values were determined in 66% N,N-dimethylformamide. [c] C_7H_7 = benzyl, C_5H_5O = furfuryl, C_8H_9 = phenethyl, O = carbonyl oxygen.

mixture was heated at 145° in the oil-bath. After 0.5–1 hr. the mass melted and then became solid. Water was added, stirred and the solid collected. The solid product was recrystallized from ethanol.

Reaction of *n*-Heptylamine with 4-Amino-6-hydroxypyrimidine in Absence of Acid.—*n*-Heptylamine (20 g.) was heated with 10 g. of 4-amino-6-hydroxypyrimidine at 140° for 4 days. During this time bubbling did not occur as was observed with the amine hydrochlorides and 4-amino-6-hydroxypyrimidine. The cooled mixture was extracted with ethyl acetate. Six grams of starting 4-amino-6-hydroxypyrimidine remained undissolved. The filtrate was diluted with ether to precipitate 3 g. of solid. When recrystallized from ethyl acetate it melted at 88–89° and was identical to an authentic sample of 1,3-di-*n*-heptylurea.

Reaction of Benzylamine with 4-Amino-6-hydroxypyrimidine in Absence of Acid.—Ten grams of 4-amino-6-hydroxypyrimidine was heated with 20 g. of benzylamine at 160–170° for 4 hr. There was a vigorous evolution of vapors that tested basic. After cooling, the mixture partially crystallized and the solid was collected. This was recrystallized from ethyl acetate; yield 0.5–1 g., m.p. 127–130°. The ultraviolet absorption in ethanol showed two maxima at 230 and 260 mμ. There were no titratable groups between *p*H 3.5 and 13. The infrared absorption showed a band at 2.92 μ resulting from an NH group, an intense band at 6.02 μ from an amide-like carbonyl group and a band at 6.21 μ due to the aromatic benzene rings. Characteristics of the product suggest the structure 3-benzyl-4-benzylamino-6-keto-1,6-dihydropyrimidine or 1-benzyl-4-benzylamino-6-keto-1,6-dihydropyrimidine.

Anal. Calcd. for $C_{18}H_{17}N_3O$: C, 74.35; H, 5.89; N, 14.46. Found: C, 73.76; H, 6.23; N, 14.03.

2-Benzylamino-4,6-dimethylpyrimidine.—One-tenth mole (12.3 g.) of 2-amino-4,6-dimethylpyrimidine was mixed with 0.1 mole of benzylamine hydrochloride and heated at 160° for 5 hr. The cooled residue was triturated with water and the solid collected. The product was recrystallized from alcohol; yield 2 g., m.p. 107°.

Anal. Calcd. for $C_{13}H_{15}N_3$: C, 73.21; H, 7.09; N, 19.07. Found: C, 72.98; H, 7.06; N, 19.34.

1,3-Dimethyl-6-substituted Aminouracils.—One-tenth mole (15.5 g.) of 1,3-dimethyl-6-aminouracil was mixed with 0.1 mole of the appropriate amine hydrochloride and 15 ml. of the free amine. The mixture was heated at 145° and bubbling continued for 3 hr. Water was added to the cooled mixture and the products crystallized from ethyl acetate.

1,3-Dimethyl-6-furfurylaminouracil: yield 65%, m.p. 190–191°. *Anal.* Calcd. for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 56.35; H, 5.32; N, 17.81.

6-Benzylamino-1,3-dimethyluracil: yield 75%, m.p. 143–144°. *Anal.* Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.58; H, 6.15; N, 16.95.

1,3-Dimethyl-6-*n*-heptylaminouracil: yield 70%, m.p. 85–86°. *Anal.* Calcd. for $C_{13}H_{23}N_3O_2$: C, 61.63; H, 9.15. Found: C, 61.32, H, 9.38.

6-Benzylaminopurine.—A mixture of 2.5 g. of adenine, 2.5 g. of benzylamine hydrochloride and 5 g. of benzylamine was heated at 165–170° for 8 hr. The reaction mixture was extracted with warm ethanol leaving approximately 1 g. of unreacted adenine. The filtrate was clarified with carbon, concentrated and cooled to yield 1.5 g. (54%) of 6-benzylaminopurine, m.p. 225° (reported[7] 229°).

6-Furfurylaminopurine (kinetin) was prepared in the same manner described for the above benzyl derivative; yield 57%, m.p. 266° (reported[8] 266–267°).

(7) C. G. Skinner and W. Shive, THIS JOURNAL, **77**, 6692 (1955).

(8) C. O. Miller, F. Skoog, F. S. Okumura, M. H. Von Saltza and F. M. Strong, *ibid.*, **77**, 2662 (1955).

6-Phenylaminopurine was prepared by the method used for the benzyl derivative. Approximately 2 g. of highly colored product was obtained that melted at about 245°. After several crystallizations from alcohol it melted at 278° (reported[9] 278–281°).

(9) G. H. Hitchings and G. B. Elion, U. S. Patent 2,691,654; Oct. 12, 1954 (*C. A.*, **50**, 1933 (1956)).

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, MEDICAL COLLEGE OF VIRGINIA, RICHMOND, VIRGINIA]

The Isolation and Structure of a Ketoamide Formed in the Metabolism of Nicotine[1]

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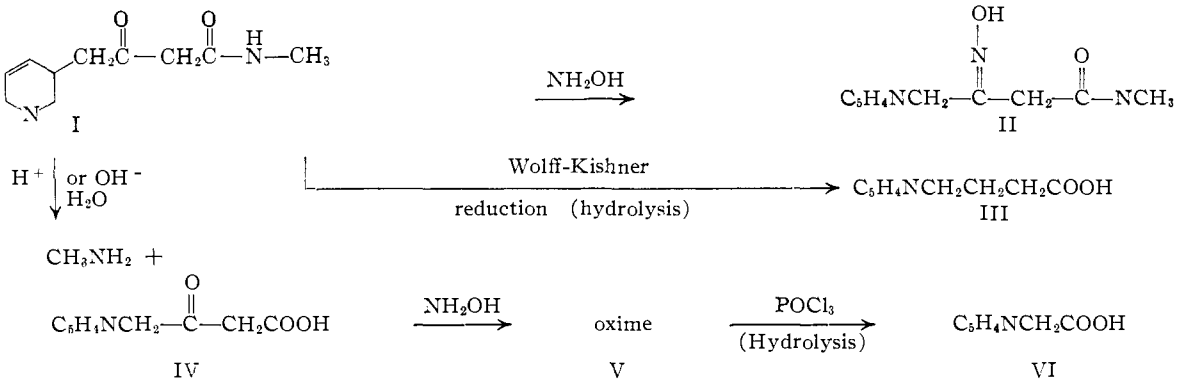
Administration of (−)-nicotine or (−)-cotinine to the dog leads to the excretion of a chloroform soluble amphoteric metabolite which has been separated in crystalline form. Hydrolysis of the metabolite in acidic or basic solution resulted in the formation of methylamine and an oxo acid. The latter yielded γ-(3-pyridyl)-butyric acid upon reduction by the Wolff–Kishner procedure. A Beckmann rearrangement of the oxime from the oxo acid afforded 3-pyridylacetic acid. In consequence the metabolite is assigned the structure γ-(3-pyridyl)-β-oxo-N-methylbutyramide.

The metabolism of (−)-nicotine in the dog leads[3] to the excretion of (−)-cotinine and a variety of Koenig positive components. The rôle of cotinine in the metabolism of nicotine in both the dog and the human is evinced in many ways including metabolism to (−)-desmethylcotinine in the former[4] and hydroxycotinine in both species.[4,5]

During studies on the metabolism of (−)-cotinine and (−)-nicotine it was observed[4] that the urine of dogs following administration of (−)-cotinine contained a chloroform-soluble metabolite which, in contrast to cotinine, hydroxycotinine and desmethylcotinine, was removed from aqueous solution by Dowex 1 (OH^-). Chromatographic evidence has indicated the possible presence of this same substance in the urine of both humans and dogs following administration of (−)-nicotine.

In the current studies (−)-cotinine has been administered to dogs in quantities sufficient to permit isolation of this new metabolite and subsequent structural determination by the reactions



The pooled urine from mongrel dogs following administration of (−)-cotinine was made alkaline with ammonia and then exhaustively extracted with chloroform. An acidic aqueous solution of the residue obtained by evaporation of the chloroform was placed upon a column of Dowex 50 (H^+) which removed all of the Koenig positive components. An ammoniacal eluate of the resin was passed through a column of Dowex 21K (OH^-) or Dowex 1 (OH^-). The effluent contained the Koenig positive compounds cotinine, desmethylcotinine and hydroxycotinine which have been subjected to previous study. By elution with dilute acid or copious quantities of water an additional Koenig positive compound was obtained in crude form. The aqueous solution of this metabolite was concentrated to a yellow oil. A solution of the latter in chloroform was chromatographed on alumina to obtain a crystalline product (I) which melted at 114–116° after recrystallization from benzene. The compound in solution showed no optical rotation. The analyses for C, H and N were in good agreement with the empirical formula $C_{10}H_{12}N_2O_2$.

The analytical data and positive Koenig reaction of the compound immediately suggested a 3-pyridyl compound derived from the metabolic oxidation of cotinine. The metabolite yielded a crystalline oxime (II) and upon reduction under Wolff–Kishner conditions yielded γ-(3-pyridyl)-butyric acid (III). The latter was identified by

(1) For preliminary reports see: E. R. Bowman, L. B. Turnbull and H. McKennis, Jr., *Fed. Proc.*, **18**, 371 (1959); *Bull. Va. Section Am. Chem. Soc.*, **36**, 184 (1959). Aided by grants from the Tobacco Industry Research Committee and the American Tobacco Company.

(2) Public Health Research Fellow of the National Heart Institute.

(3) (a) H. McKennis, Jr., L. B. Turnbull and E. R. Bowman, THIS JOURNAL, **79**, 6342 (1957); (b) *ibid.*, **80**, 6597 (1958).

(4) H. McKennis, Jr., L. B. Turnbull, E. R. Bowman and E. Wada, *ibid.*, **81**, 3951 (1959).

(5) E. R. Bowman, L. B. Turnbull and H. McKennis, Jr., *J. Pharmacol. Exp. Therap.*, **127**, 92 (1959).