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Structural Study of Nicotine Salts*

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SUMMARY

The structures of three types of nicotine salts have been determined. These salts have acid to base ratios of either 1 : 1, 2 : 1, or 3 : 1. Salt formation between organic acids and nicotine is dependent upon the structure of the acids (aliphatic or aromatic) and their functionality. The 1 : 1 salts of nicotine have amino acids or benzoic-type acids bound to the *N*-methylpyrrolidine nitrogen of nicotine. The 2 : 1 salts are found to bind to one acid group as in the 1 : 1 salts and a second to the nitrogen of the pyridine ring. The 2 : 1 salts of nicotine are formed with formic acid, aliphatic dicarboxylic acids, and/or nitroaromatic acids. Nicotine forms 3 : 1 salts with aliphatic monocarboxylic acids starting with acetic acid. Here one acid is bound as in the 1 : 1 salts while the other two acids dimerize and bind to the nitrogen of the pyridine group.
Infrared (IR), ultraviolet (UV), proton nuclear magnetic resonance (PMR), and carbon nuclear magnetic resonance (CMR) spectroscopy as well as field desorption – mass spectroscopy (FD-MS) were used in this investigation of the structure of nicotine salts.

ZUSAMMENFASSUNG

Die Struktur von drei Nicotinsalztypen mit dem Säure/Base-Verhältnis von 1 : 1, 2 : 1 und 3 : 1 wurde bestimmt. Die Salzbildung zwischen organischen Säuren und Nicotin hängt von der Struktur (aliphatisch oder aromatisch) der Säuren und deren funktionellen Gruppen ab. Bei den 1 : 1-Salztypen sind Aminosäuren oder benzoesäureähnliche Säuren an den *N*-Methylpyrrolidin-Stickstoff des Nicotin gebunden. Bei den 2 : 1-Salztypen ist die eine Säure wie bei den 1 : 1-Salzen und die zweite Säure an den Stickstoff des Pyridinringes gebunden. Die 2 : 1-Nicotinsalze bilden sich mit Ameisensäure, aliphatischen Dicarbonsäuren und/oder nitroaromatischen Säuren. Mit aliphatischen Monocarbonsäuren, beginnend mit Essigsäure, bildet Nicotin Salze, die ein Säure/Base-Verhältnis von 3 : 1 haben. Bei diesen Salzen entspricht die Bindung der ersten Säure der der 1 : 1-Salze, während die anderen beiden Säuren dimersieren und sich an den Stickstoff der Pyridingruppe binden.
Zur Strukturaufklärung wurden folgende Verfahren eingesetzt: Infrarotspektroskopie (IR), Ultraviolettspektroskopie (UV), magnetische Protonenresonanzspektroskopie (PMR), magnetische Kohlenstoffresonanzspektroskopie (CMR) und Desorptionsfeldmassenspektroskopie (FD-MS).

RÉSUMÉ

La structure de trois types de sels de nicotine a été déterminée, ceux-ci présentant un rapport acide/base de respectivement 1 : 1, 2 : 1 et 3 : 1. La constitution de sel entre les acides organiques et la nicotine dépend de la structure des acides (aliphatique ou aromatique) et des groupes fonctionnels de ceux-ci. Les sels 1 : 1 présentent des acides aminés ou des acides de type benzoïque liés à l'azote *N*-méthylpyrrolidine de la nicotine. Pour les sels de rapport 2 : 1, l'un des acides est liés comme dans le cas des sels 1 : 1 et le deuxième acide se combine à l'azote du cycle de pyridine. Les sels de nicotine du rapport 2 : 1 sont constitués d'acide formique, d'acides aliphatiques dicarboxyliques et/ou d'acides nitroaromatiques. La nicotine constitue des sels d'un rapport acide/base de 3 : 1, à partir d'acides monocarboxyliques aliphatiques, à commencer par l'acide acétique. Dans ce cas, la liaison du premier acide correspond à celle des sels du rapport 1 : 1, tandis que les deux autres acides se dimérisent et se combinent à l'azote du groupe pyridine.

Pour l'étude de la structure des sels de nicotine, on a utilisé les procédés suivants: spectroscopie infrarouge (IR), spectroscopie à l'ultraviolet (UV), spectroscopie magnétique à résonance protonique (PMR), spectroscopie magnétique à résonance carbonique (CMR) et spectroscopie de masse du champ de desorption (FD-MS).

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Table 1. Infrared absorption bands (cm^{-1}) of nicotine salts.

Acid	H-bonding	−COOH	$-COO^{\ominus}$	$-COO^{\ominus}$	Dimerization, OH-bonding and/or C−O stretching		Others	References
Formic	37-2300	1725	1590 B		1200 B		2120-1970++	3, 4, 21
Acetic	32-2200	1725 B 1715 B	1570 B	1430 B 1360 B	1265 B		1050 1009 2100-1900	3, 4, 21
Propionic	35-2300	1725	1595 1578	1462 1465	1380 B	1275 1212	1071 2100-1850	3, 4, 21
Butyric	32-2400	1727 D* 1717 D	1582	1460 1442	1400	1270 1200	1092 1041 2010-1900	4, 8, 21
2-Methylbutyric	32-2400	1722	1598 D 1569 D	1460 1429	1382	1261 1203	1152 2010-1900	4, 8, 21
3-Methylbutyric	32-2400	1725 D 1717 D	1565 B	1468 1431	1370 1385	1292 1200	1120 1098 2110-1850	4, 8, 21
Valeric	32-2300	1721	1570	1449 1430-1380 B		1190	1101 1090 2100-1850	4, 8, 20, 21
Lauric	32-2200	1717	1575	1457	1403	1260-1180	1110 2120-1820	12, 14
Tartaric	37-2300	1730	1652 B	1565	1265 1211	1130 1108	1075 872 1060	10, 17, 18
Citric	37-2200	1728	1585	1400	1215		810 2060-1880	
Malic	3400 B 31-2200	1702	1605 B 1578 B	1450 B	1300	1233 1170	1098	
Oxalic	37-2200 3350	1715	1604		1200		2090-1980	15, 7
Benzoic	2960 B 2780 B	1710 B	1600 1582	1449	1380	1272	1119 1070	3, 8, 9
Gentisic	32-2400 2700-2250		1575	1482 1430	1340	1275 1235	1192 1022 1121-1011	3, 5, 8, 9
Gallic	34-2200	1693	1540 B	1350 B	1194 B		1035	3, 5, 8, 9
Phenylacetic	31-2200	1720	1580	1495 1455			2100-1850	3, 6, 8, 9
Salicylic		1628	1590		1430	1290	1135	3, 8, 9
Phthalic	2600-1900 B	1692	1550	1450 B	1360	1200 B	1120 1020 1105 1095 1010	3, 8, 9
Picric**			1630 1610	1550 1529	1340 1310	1270 1178	1152 1980 1088 2100	6, 22
Sulfosalicylic	31-2500	1695	1612 1590		1290 1260	1162 1120	1071 1021	9
Tannic	37-2200	1712	1601	1595		1325 B	1200 B 1090 1030	2, 11
Pectic	37-2200 3370	1730	1601		1140	1090		1, 16, 23
Alginic	37-2300	1740	1609 B	1409		1080 1031	1015	13, 16
Hydrochloric**	34-2200	2050 B 2000	1640 1617	1560 B	1470	1335	1265 1000 1210 1015	24
Chloroplatinic**	3540 3480	3200-3160 3110-3080	2720 B	1600 1630	1310 1255	1210 1185	1003 668	19
Silicotungstic**	3530 3370	3070	2720 B	1620 B 1567	1270 1200	1190 1010	912 780 870 675	12
Pyruvic	37-2300 T*	1715 B	1622 B		1430 1350	1160 B		5
Glutamic	32-2200	1670	1642	1610 B+	1452	1315-1258 1235	1128	25
Aspartic	3140 32-2200 B	1690	1620	1560 B+	1500	1350-1213 1310-1140	1119 1900 1072 2070	25

* D = doublet, B = broad, T = triplet. ** Frequencies do not conform to headings. + Indicative of zwitterion formation.
++ Frequencies in the range of 2100-1820 are those indicative of ammonium and imminium salts.

INTRODUCTION

The molecular composition and structure of nicotine salts have been topics of investigation and discussion for many years. Controversy over the composition of nicotine salts arises from the fact that these salts exist with varying ratios of acid to base. While this is not unusual in itself, the presence of two basic sites in the nicotine molecule and the existence of 1:1, 2:1, and 3:1 salts makes it somewhat difficult to state *a priori* what the structure of a particular salt is.

Infrared (IR) and ultraviolet (UV) spectroscopic studies have been made of the aromatic acid and dicarboxylic acid salts of nicotine in an attempt to elucidate their structure (3, 5). The data support the structures assigned by *Dezelic* et al. (4, 7) for the 1:1 and 2:1 salts of nicotine and aromatic acids. The conclusions reached by *Dezelic* et al. on the structure of the 2:1 salts of nicotine and dicarboxylic acids were confusing, and additional structural analyses were needed (3). Because of this ambiguity, a structural study of several classes of 1:1, 2:1, and 3:1 nicotine salts was undertaken.

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MATERIALS AND METHODS

Chemicals

Nicotine (Eastman) was purified by treatment with solid sodium hydroxide, filtration, and distillation under vacuum. The nicotine obtained was a colorless liquid (boiling-point: 246–7 °C). All acids used in this report were commercially available and were reagent grade or better. Further purification was not needed.

Preparation of Salts

The preparations for all nicotine, pyridine, and pyrrolidine salts can be found in the literature. Appropriate references are noted as each compound is discussed (Table 1).

Instrumentation

Infrared spectra were obtained with a Perkin-Elmer 283 infrared spectrophotometer. Samples were prepared as Nujol* mulls on AgCl plates. A large variety of nicotine salts were analyzed to establish a data base (Tables 1 and 2). Proton nuclear magnetic resonance spectra (PMR) were produced with a Varian EM 390 (^{1}H) spectrometer. All spectra were run in either $CDCl_3$ or D_2O at 25 °C (Table 6). Carbon nuclear magnetic resonance spectra (CMR) were produced with a Varian CFT-20 (^{13}C) spectrometer. Spectra were run in either $CDCl_3$ or D_2O as shown in Table 3. The temperature for all spectra was maintained at 25 °C. Field desorption mass spectra were obtained with the Varian CH-5 double-focusing FD-MS system.

RESULTS AND DISCUSSION

1:1 Acid-Base Ratio – Nicotine Salts

Aromatic Acid Salts: Nearly all benzoic-type acids form 1:1 nicotine salts. Nicotine gentisate (gentisic acid = 2,5-dihydroxybenzoic acid) is a colorless crystalline solid, melting at 148–9 °C (4). Not all aromatic nicotine salts are solids; but, because it can be obtained in a pure state, nicotine gentisate is chosen for illustration.

* Nujol is a trade name for a commercially available heavy hydrocarbon oil used commonly in the preparation of mulls. Solid nicotine salts were finely ground (< 2 μ particles) and suspended in Nujol (a suitable infrared-transparent medium) to form a two-phase mixture known as a mull.

Table 2. Physical characteristics of nicotine salts.

Acid	Appearance and stability	Odor	Molar ratio* of acid : nicotine	Melting point (a) or begin to decompose (b)	Solubility**		
					H_2O	alcohol	others
Formic	yellow oil, decomposes on standing	very slight acid odor	2 : 1	—	soluble	soluble	—
Acetic	yellow oil, decomposes on standing to brown oil	very slight acid odor	3 : 1	—	soluble	soluble	—
Propionic	yellow oil, decomposes on standing to brown oil	very slight acid odor	3 : 1	—	soluble	soluble	—
Butyric	yellow oil, decomposes on standing to brown oil	green apples	3 : 1	—	soluble	soluble	—
2-Methylbutyric	yellow oil, decomposes on standing to brown oil	none	3 : 1	—	soluble	soluble	—
3-Methylbutyric	yellow oil, decomposes on standing to brown oil	none	3 : 1	—	soluble	soluble	—
Valeric	yellow oil, decomposes on standing to brown oil	none	3 : 1	—	soluble	soluble	—
Lauric	yellow oil	soapy	3 : 1	—	insoluble	soluble	—
Palmitic	yellow oil	none	3 : 1+	—	insoluble	soluble	—
Tartaric	colorless crystals	none	2 : 1	88–89 °C	very soluble	soluble	ether
Citric	yellow oil, viscous, stable	none	2 : 1	—	soluble	soluble	—
Malic	colorless crystals, stable	none	2 : 1	102–103 °C	soluble	soluble	—
Oxalic	colorless crystals, stable	none	2 : 1	110 °C	soluble	soluble	—
Benzoic	orange oil, stable	none	1 : 1	—	soluble	soluble	—
Gentisic	colorless crystals, stable	none	1 : 1	147 °C	soluble	soluble	insoluble: $CHCl_3$, ethyl acetate
Gallic	colorless crystals, hygroscopic, decomposes	none	1 : 1	162–163 °C 113–114 °C++	soluble	soluble	insoluble: $CHCl_3$
Phenylacetic	orange oil, decomposes on standing	none	3 : 1	—	soluble	soluble	—
Salicylic	colorless crystals, stable	none	1 : 1	116–117 °C	soluble	soluble	soluble: ether
Phthalic	colorless crystals, stable	none	1 : 1	126–127 °C	soluble	soluble	insoluble: ether
Picric	yellow crystals, stable, solid	none	2 : 1	228–229 °C	insoluble	insoluble	insoluble: ether
Sulfosalicylic	light tan, solid	none	1 : 1	211 °C	soluble	soluble	insoluble: ether
Tannic	tan, amorphous, solid	none	1 : 5	(b) > 190 °C (evolution of gas)	insoluble	insoluble	insoluble: ether
Pectic	solid, amorphous powder, golden	none	1 : 3	(b) 200 °C (char at 240 °C)	soluble	insoluble	insoluble: ether
Alginic	solid, amorphous, stable	none	1 : 2+++	(b) > 160 °C	very soluble	insoluble	insoluble: ether
Hydrochloric	tan, solid, deliquescent		2 : 1	154–55 °C	soluble	soluble	—
Chloroplatinic ($C_{10}H_{14}N_2 \cdot PtCl \cdot 2\ HCl$)	orange, solid	none	1 : 1	(b) > 250 °C	insoluble	insoluble	insoluble: ether
Silicotungstic	colorless crystals, solid	none	1 : 1	stable > 300 °C	insoluble	insoluble	insoluble: ether
Pyruvic	yellow oil, stable	none	2 : 1	—	soluble	soluble	—
Glutamic	white, amorphous, solid	none	1 : 1	199–200 °C	very soluble	soluble	insoluble: $CHCl_3$, ether
Aspartic	white, amorphous	none	1 : 1	(a) > 300 °C	very soluble	insoluble	insoluble: ether

* molar ratio used in reaction

** observed solubilities in approximately 200 mg/ml of solvent

\+ analyzed by CMR

\++ hydrated nicotine gallate: tan powder (melting point: 113–114 °C)

\+++ w/w ratio

Figure 1. Nicotine gentisate.

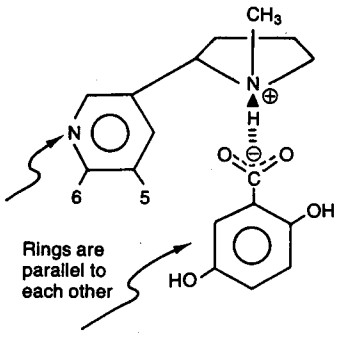
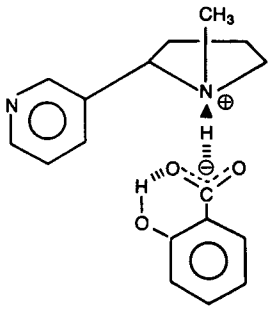


Figure 3. Nicotine salicylate (buttressing effect of the *ortho*-hydroxyl group of salicylic acid).



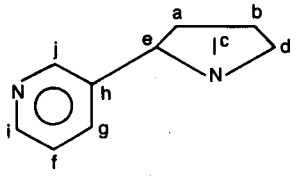
Nicotine gentisate exhibits a major IR band at 1575 cm^{-1} which is indicative of protonation at the nitrogen atom of the *N*-methylpyrrolidine ring (Table 1). The absence of a band at 1530 cm^{-1} leads to the conclusion that the pyridine nitrogen is unprotonated. The stronger basic site in nicotine is the *N*-methylpyrrolidine nitrogen as shown by its dissociation constants: nicotine, $K_1 = 7 \times 10^{-7}$, $K_2 = 1.4 \times 10^{-11}$; pyridine, $K = 2.4 \times 10^{-9}$; *N*-methylpyrrolidine, $K = 1.5 \times 10^{-4}$ (3). The preferred site of bonding would be expected to be the *N*-methylpyrrolidine fragment of nicotine. The formation of an ammonium-type salt is also indicated by the broad absorptions between 2700 cm^{-1} and 2250 cm^{-1}.

UV data (5) support bonding as shown in Figure 1 and also indicate that the structure of nicotine gentisate is of equimolar composition, i.e. one molecule of gentisic acid is bound to the nitrogen of the *N*-methylpyrrolidine nucleus. Salts of nicotine, pyridine, and *N*-methylpyridine were studied spectroscopically. Comparison of the observed absorptions for nicotine gentisate to those of the acid and base components showed the molecular ratio to be 1 : 1.

Proton nuclear magnetic resonance (PMR) data (Table 6) supported the structure proposed in Figure 1. The *N*-methylpyrrolidine protons are deshielded, as would be expected in the light of the proposed positioning of the aromatic ring of gentisic acid. The chemical shifts of the gentisic acid moiety were virtually unchanged.

The carbon nuclear magnetic (CMR) spectra of this salt are consistent with the assigned structure and compare favorably with the findings of *Hutchinson* and *Pitner* (9, 13) (Table 3). The *N*-methylpyrrolidine carbons were affected (shielded and deshielded) in the expected manner as were carbons g, h, and f of the pyridine skeleton (Figure 2). The CMR spectra of the carbons of gentisic acid were normal and agreed as one would expect with the proposed structure (Figure 1). The CMR and PMR analyses for nicotine and its salts have been discussed in such detail that further discussion of this subject is not included (see discussion in References 9, 10, 13, 14, and 16).

Figure 2. Carbon nuclear magnetic resonance (CMR) designation for carbons of nicotine.



In summary, spectral data along with the physical-chemical data in the literature (3, 5) show that nicotine gentisate exists as an equimolar combination of nicotine and gentisic acid with structure as in Figure 1. The *trans* configuration of L-nicotine remains intact as determined by PMR (16), but the optical rotation of all the salts mentioned herein is dextrorotary (5). The conformation of the salt appears tunnel-like with the two aromatic rings adjacent and the *N*-methylpyrrolidine in a conformation nearly perpendicular to the pyridine ring. These features can be readily seen through the use of molecular models. The methyl group of the *N*-methylpyrrolidine moiety is *trans* to the pyridine ring (14). Attack of the acid must have been *cis* (bottom side) with respect to the pyridine ring on the basis of retention of conformation. This is consistent with the work of *Seeman* and *Whidby* (15).

Aromatic acids of the salicylate type with at least one hydroxyl group *ortho* to the carboxyl group always form crystalline solids with nicotine (7). Hydrogen bonding may exert a buttressing effect to increase molecular rigidity (Figure 3). The nitro function also exerts a buttressing effect. For example, 2,4- and 3,5-dinitrobenzoic acids form beautiful yellow crystalline solids (7). These salts are 2 : 1 complexes.

Amino Acid Salts: Several attempts have been made to prepare amino acid (1 : 1) nicotine salts. Preparations of the glutamic and aspartic acid salts have been reported in the literature (21). Both are white crystalline solids. These salts were prepared and examined since the salts are so similar in structure. α-Amino-dicarboxylic acids form zwitterions and as such have only one free carboxylic acid group for salt formation (20). The nicotine salts formed at the *N*-methylpyrrolidine site of nicotine are believed to be as depicted in Figure 4.

The synthesis and physical properties of the amino acid

Table 3. Carbon nuclear magnetic resonance (CMR) shifts of nicotine, pyrrolidine and pyridine salts.

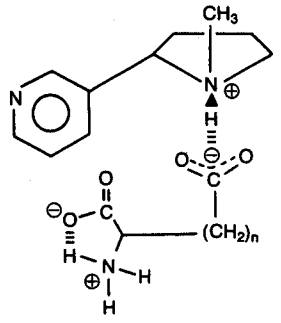
Nicotine salts	Carbon assignments of nicotine *										Carbon assignments of anions								
	C 2 (j)	C 3 (h)	C 4 (g)	C 5 (f)	C 6 (i)	C 2′ (e)	C 3′ (b)	C 4′ (a)	C 5′ (d)	N-CH_3 (c)									
Nicotine in D_2O	149.42	138.91	137.14	125.46	149.05	69.63	35.05	22.93	57.43	40.47									
												C 1	C 2						
Nicotine tartrate	145.64	133.09	146.19	128.60	145.21	70.00	31.52	22.76	57.68	39.85	Tartrate	177.35	73.96						
												C 1							
Nicotine oxalate	144.21	134.13	148.21	129.50	143.28	69.74	31.66	22.81	57.89	40.09	Oxalate	165.64							
												C 1	C 2	C 3	C 4	C 5	C 6	C 7	
Nicotine gentisate	151.37	129.71	138.06	125.92	149.90	70.80	31.06	22.54	57.12	39.23	Gentisate	175.75	154.42	148.80	122.38	118.94	118.16	116.9	
Nicotine in $CDCl_3$	149.55	138.91	134.63	123.38	148.56	68.77	35.44	22.68	56.89	40.27									
												C 1							
Nicotine formate	150.09	130.87	136.78	124.32	149.73	69.21	31.78	21.60	55.62	38.16	Formate	166.25							
												C 1	C 2						
Nicotine acetate	149.22	132.34	137.43	124.67	149.22	69.25	32.13	21.15	55.87	38.66	Acetate	175.41	21.15						
												C 1	C 2	C 3	C 4	C 13	C 14	C 15	C 16
Nicotine palmitate	148.76	134.97	137.03	124.46	148.33	69.10	33.23	22.09	56.14	39.26	Palmitate	179.14	34.61	32.06	30.89	25.09	22.78	22.09	14.11

Pyrrolidine salts	Carbon assignments of pyrrolidine *		Carbon assignments of anions		
	C 1 (b)	C 2 (a)			
Pyrrolidine in $CDCl_3$	47.14	25.70			
				C 1	
Pyrrolidine formate (1 : 1)	44.64	24.57	Formate	167.04	
Pyrrolidine formate (2 : 1)	45.23	24.27			
				C 1	C 2
Pyrrolidine acetate (1 : 1)	44.41	24.66	Acetate	178.10	24.43
				C 1	C 2
Pyrrolidine acetate (2 : 1)	44.86	24.49	Acetate	176.78	176.78

Pyridine salts	Carbon assignments of pyridine *			Carbon assignments of anions		
	C 1 (c)	C 2 (b)	C 3 (a)			
Pyridine in $CDCl_3$	149.92	135.79	123.71			
					C 1	
Pyridine formate (1 : 1)	147.19	139.08	125.06	Formate	165.00	
					C 1	C 2
Pyridine acetate (1 : 1)	148.38	137.57	124.45	Acetate	174.37	21.14
					C 1	C 2
Pyridine acetate (2 : 1)	147.64	138.72	124.93	Acetate	175.45	21.08

* Sadtler Research Laboratory, Inc.: Carbon-13 NMR nomenclature spectra No. 1207c.

Figure 4. Amino acid salts of nicotine.



n = 1: aspartate n = 2: glutamate

salts have been discussed elsewhere (21). The IR spectra of these salts show zwitterion formation, strong carboxylate bands, and bands indicative of ammonium ion formation as would be expected (Table 1). Ultraviolet spectra of the salts indicate the presence of nicotine (Table 4), although several attempts to obtain PMR and CMR spectra failed to show the presence of nicotine. This is thought to be due to the fact that during analyses both salts precipitated out of all deuterated solvents tried.

Ultraviolet spectra show an equimolar ratio of nicotine and the amino acids. The characteristic solid nature of these salts is most likely due to the fact that they are doubly ionized and somewhat structurally rigid. A high degree of hydrogen bonding is present in these salts. The structure of these salts is believed to be the same tunnel-like form as in the 1:1 aromatic acid salts.

2:1 Acid-Base Ratio – Nicotine Salts

Aliphatic Monocarboxylic Salts: Only three monocarboxylic acids are known to form 2:1 (acid:base ratio) salts with nicotine (2, 6):

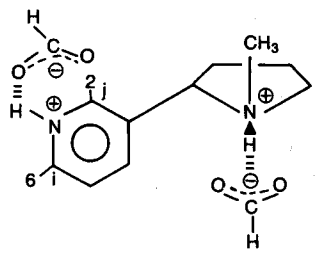
Nicotine formate = $C_{10}H_{14}N_2 \cdot 2\ CH_2O_2$,
Nicotine monochloracetate = $C_{10}H_{14}N_2 \cdot 2\ C_2H_3O_2Cl$,
Nicotine dichloracetate = $C_{10}H_{14}N_2 \cdot 2\ C_2H_2O_2Cl_2$.

Spectral investigations were performed on nicotine formate. Nicotine, pyridine and pyrrolidine were used to prepare salts of varying ratios. Stoichiometric amounts of acids were treated with stoichiometric amounts of bases to prepare:

Pyrrolidine formate = $C_4H_9N \cdot CH_2O_2$,
Pyrrolidine diformate = $C_4H_9N \cdot 2\ CH_2O_2$,
Pyridine formate = $C_5H_5N \cdot CH_2O_2$,
Nicotine formate = $C_{10}H_{14}N_2 \cdot 2\ CH_2O_2$.

The reactions in each case were quantitative. Pyridine formate was a slightly viscous, colorless oil. The pyrrolidine formates as well as nicotine formate were light yellow oils. Comparison of the infrared spectra leads

Figure 5. Nicotine formate.



to the conclusion that nicotine formate has the structure illustrated in Figure 5.

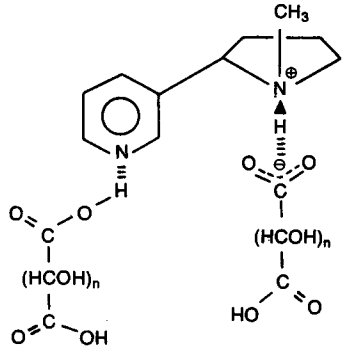
The bands for the ammonium and imminium ions are present in the IR spectrum of the nicotine formate (Table 1). These indicate salt formation at both base locations. Carboxylate bands are present as well as bands at 1725 cm^{-1} and 1200 cm^{-1} due to the pyridine carboxylate hydrogen bonding (1, 3, 8, 17, 18, 19) (Figure 5). PMR data as well as CMR data were used to elucidate the structure of Figure 5 (Tables 3 and 6). PMR and CMR data were straightforward concerning the *N*-methylpyrrolidine ring and were consistent with the findings of *Hutchinson* and *Pitner* (9, 13).

Formic acid forms a 2:1 dextrorotary salt (5) with nicotine in the S(−) configuration as illustrated in Figure 5.*

Aliphatic Dicarboxylic Acid Salts: All aliphatic dicarboxylic acids form 2:1 salts with nicotine. Some of these salts are solids (Table 2). Nicotine quadraoxalate and nicotine bitartrate were chosen for evaluation of their structure because these two salts could be prepared in a pure crystalline state (11, 12). Historic information was also available on nicotine quadraoxalate from the work of *Dezelic* (3).

The information *Dezelic* used to propose the structure of the nicotine salt of oxalic acid (2:1) was based on the formation of pyridine and *N*-methylpyrrolidine salts.

Figure 6. Structure proposed by *Dezelic* for dicarboxylic acid salts of nicotine.



n = 0: oxalic acid n = 2: tartaric acid

* The author has used the S(−) nomenclature for L-nicotine throughout this paper to be consistent with other major works published on nicotine salts (2–7).

Table 4. UV data on nicotine salts.

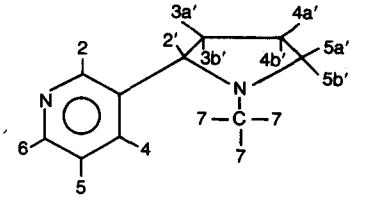
Compound	Absorption maximum (nm)
Nicotine aspartate	256 (M), 265 (S), 255 (S)
Nicotine glutamate	258 (M), 265 (S), 245 (S)

S = shoulder, M = maximum.

Table 5. Field desorption – mass spectroscopy (FD-MS) data.

m/e	Assignment
Nicotine bitartrate	
463	[nicotine bitartrate: M – H^+]$^+$·
313	[nicotine acid tartrate: M – H^+]$^+$·
301	[tartaric acid dimer: M – H^+]$^+$·
233	[*N*-methyl-2-pyrroline monotartrate]$^+$·
163	[nicotine: M – H^+]$^+$·
157	[bipyridyl: M – H^+]$^+$·
151	[tartaric acid: M – H^+]$^+$·
83	[*N*-methyl-1-pyrroline]$^+$·
Tartaric acid	
301	[tartaric acid dimer: M – M – H^+]$^+$·
151	[tartaric acid: M – H^+]$^+$·

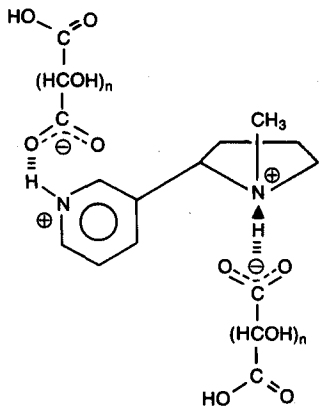
Table 6. Proton nuclear magnetic resonance (PMR) data on chemical shifts of nicotine salts (temperature: 25 °C, solvent: specified).



Nicotine salts	Chemical shifts of protons (ppm)											
	2	4	5	6	7	2′	3a′	3b′	4a′	4b′	5a′	5b′
Nicotine ($CDCl_3$)	8.60	7.68	7.22	8.50	2.04	3.07	1.73	2.21	1.80	1.95	2.31	3.25
Nicotine acetate ($CDCl_3$)	8.80	8.19	7.75	8.68	2.61	4.23	———	2.31*	———		3.15	3.79
Nicotine formate ($CDCl_3$)	8.82	8.70	7.75	8.68	2.71	3.88	———	2.35*	———		3.28	4.37
Nicotine gentisate ($CDCl_3$)	9.00	8.33	7.91	8.92	3.14	4.72	———	2.73*	———		3.72	4.27
Nicotine quadraoxalate ($CDCl_3$)	9.57	9.32	8.72	9.47	3.35	5.25	———	2.97*	———		3.95	4.38
Nicotine bitartrate (D_2O)	9.49	9.15	9.38	8.57	3.32	4.55	———	2.89*	———		3.87	4.35

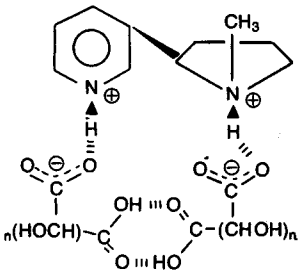
* multiplet 4(H)

Figure 7. Proposed structure for ionically bonded form of nicotine salts of dicarboxylic acids.



n = 0: oxalic acid n = 2: tartaric acid

Figure 8. Proposed structures for nicotine salts of dicarboxylic acids.



n = 0: oxalic acid n = 2: tartaric acid

Both pyridine oxalate and *N*-methylpyrrolidine oxalate form ion pairs. The presence of the pyridinium band at 1530 cm^{-1} and the carboxylate bands at 1625 cm^{-1} and 1404 cm^{-1}, indicative of the formation of the ammonium salt of *N*-methylpyrrolidine, are sufficient evidence for protonation of the nitrogen of each compound.

The structure of nicotine quadraoxalate is in question for two reasons. First, many of the peaks needed for precise IR identification in the range of 1500 cm^{-1} to 1600 cm^{-1} are obscured for most nicotine salts. Second, the pKa values of oxalic acid ($pKa_1 = 1.23$, $pKa_2 = 4.19$) are well within the range of the acids *Barrow* (1) investigated, which raises the possibility that oxalic acid can exist as an ion pair with pyridine and nicotine.

Nicotine quadraoxalate prepared in our laboratory and submitted for IR investigation showed the presence of both ammonium and imminium ion formation, evident from the peaks at 1625, 1404, 1890 and 2090 cm^{-1} (Table 1). Therefore, both oxalic acids are ionically bound to the two nitrogens of nicotine (Figure 7).

The possibility of the dimerization of dicarboxylic acids was considered, and a second possible structure for the 2 : 1 nicotine salt of oxalic acid or tartaric acid was proposed (Figure 8). Molecular models of the two proposed structures (Figures 7 and 8) were constructed, and it became evident that for dimerization to occur the pyridine ring of nicotine would have to rotate approximately 180° for the two oxalic or tartaric acid moieties to dimerize.

IR, PMR and CMR data are consistent for either structure (Figures 7 and 8). Field desorption – mass spectroscopy of nicotine bitartrate (Figure 9) pinpointed the most probable structure for the dicarboxylic acids of nicotine to be as shown in Figure 8. Figure 10 shows the proposed fragmentation pattern for nicotine bitartrate (Table 5). The mass spectrum substantiated the presence of the parent compound, nicotine bitartrate. There were also significant ion currents corresponding to nicotine acid tartrate, tartaric acid dimer, *N*-methyl-2-pyrroline monotartrate, nicotine, bipyridyl, tartaric acid and *N*-methyl-1-pyrroline. The parent decomposes by retro salt formation on the pyridine ring. The nicotine acid tartrate decomposes to nicotine and tartaric acid and also by α-cleavage of the pyridyl moiety to give rise to *N*-methyl-1-pyrroline. Recombination of two pyridyl radicals give rise to the bipyridyl species. The mass spectrum of nicotine quadraoxalate is more complex, but FD-MS does show the presence of the parent compound and decomposition pathways similar to nicotine bitartrate.

3 : 1 Acid-Base Ratio – Nicotine Salts

Aliphatic Monocarboxylic Acid Salts: In general, nicotine forms 3 : 1 salts with aliphatic monocarboxylic acids starting with acetic acid (2, 6). These salts are yellow oils (Table 2). All compounds investigated in this work had similar IR spectra as well as similar chemical shifts in the proton and carbon magnetic resonance spectra associated with nicotine (Table 3). There are several ways of combining three moles of acid with the ditertiary base nicotine. If we consider that the first acid binds to the *N*-methylpyrrolidine and if the second acid hydrogen binds to the first acid in a structure as proposed in Figure 11, the third acid must bind to the pyridine nitrogen. This acid is ionically bonded as indicated by the imminium bond formation (as illustrated in Figure 12) and apparent in the IR absorptions of such salts between 2100 cm^{-1} and 1900 cm^{-1} (19).

Likewise, a possible structure exists where the first acid binds to the *N*-methylpyrrolidine and the second acid to the pyridine. The third acid would then hydrogen bind to the acid group ionically bound to the pyridine ring (3) (Figure 13).

Spectral information (IR, PMR and CMR) collected for this series of salts indicates a common structure for 3 : 1 nicotine salts (Tables 2, 3 and 6). One acid moiety binds to the *N*-methylpyrrolidine nitrogen, a second binds to the nitrogen of the pyridine ring, and the last acid dimerizes with the acid moiety bonded to the pyridine ring.

Figure 9. Field desorption spectrum of nicotine bitartrate.

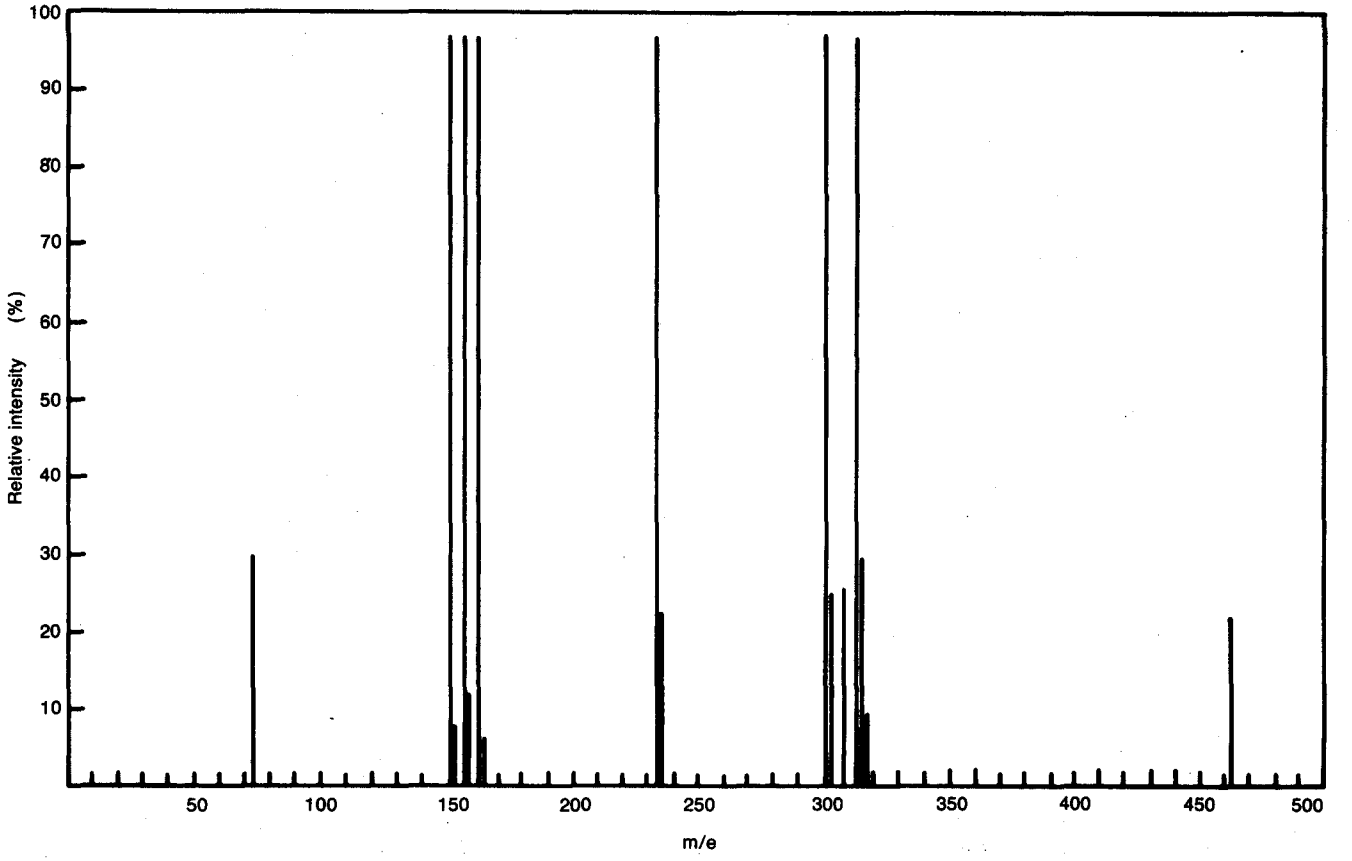
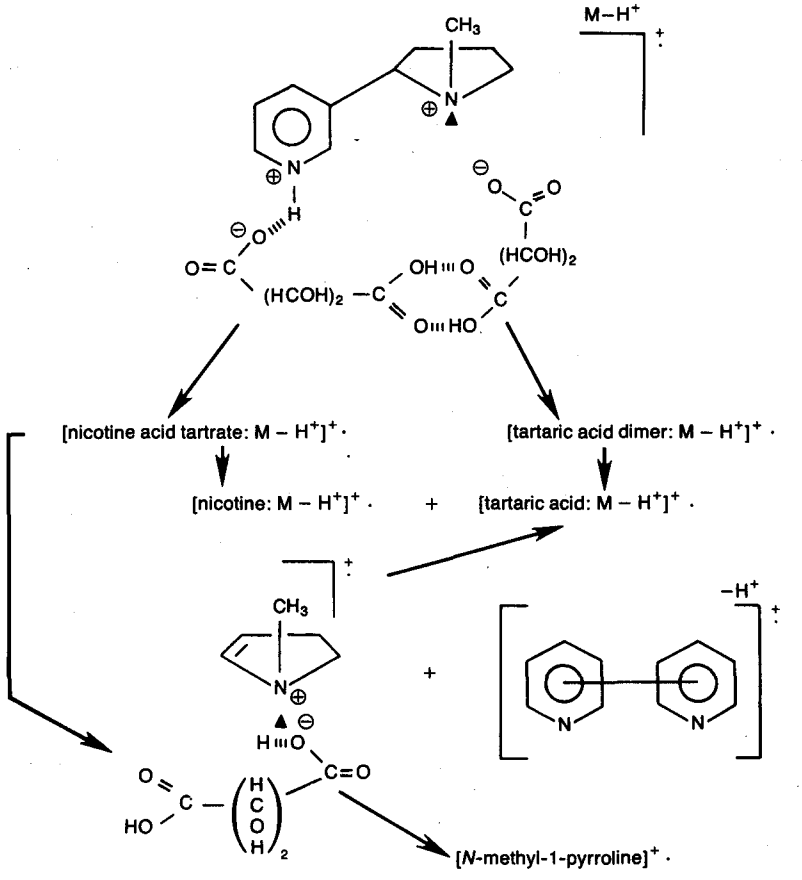


Figure 10. Fragmentation pattern for nicotine bitartrate.

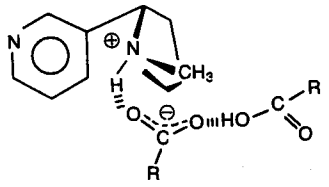


A series of experiments were conducted to confirm the proposed structure of the 3:1 nicotine salts. Compounds (A-E) (Figure 14) were prepared as 1:1 and 2:1 salts of pyrrolidine acetate and pyridine acetate and compared to the 3:1 salt nicotine acetate:

A	pyrrolidine acetate	1:1,
B	pyrrolidine acetate	2:1,
C	pyridine acetate	1:1,
D	pyridine acetate	2:1,
E	nicotine acetate	3:1.

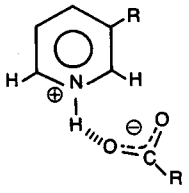
The structures for A-E are shown in Figure 14 as determined by IR, PMR, and CMR.
The chemical shifts of D and A correlate extremely well with those of E. The IR data indicate that E is the correct structure of nicotine acetate and 3:1 nicotine salts in general.

Figure 11. Possible structure of an acid dimer bonded to the *N*-methylpyrrolidine moiety of nicotine.



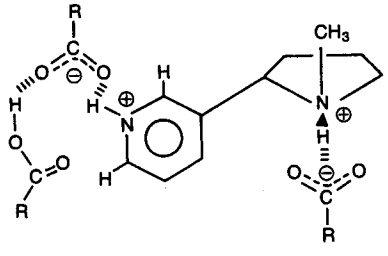
R = alkyl moiety

Figure 12. Possible structure of a 3:1 monocarboxylic acid salt of nicotine.



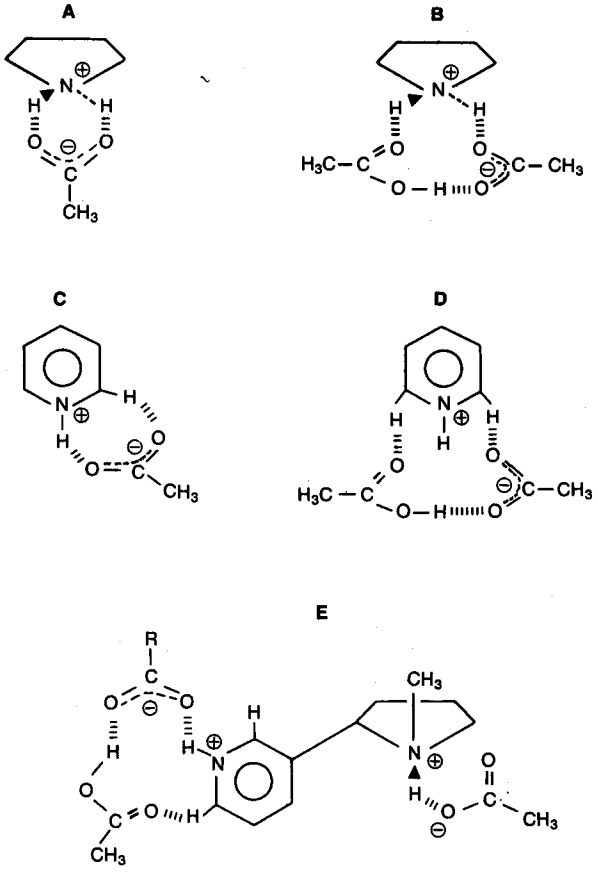
R' = *N*-methylpyrrolidine acid dimer

Figure 13. Proposed structure of the 3:1 monocarboxylic acid salts of nicotine.



R = alkyl moiety

Figure 14. Proposed structures of 1:1 and 2:1 salts of pyrrolidine acetate and pyridine acetate compared to nicotine acetate.



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