

ALKALOIDS OF TOBACCO

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I. INTRODUCTION

The alkaloid nicotine was named after Jean Nicot, consul from the king of France, who in 1560 sent tobacco seed from Portugal to Paris (266).

Nicotine, observed by Vauquelin (248) in 1809 and isolated twenty years later by Posselt and Reimann (188), was considered for many years the only alkaloid in tobacco. Since then other alkaloids,—e.g., anabasine, anatabine, isonicotine, *l*-*N*-methylanabasine, *l*-*N*-methylanatabine, nicotelline, nicotimine, nicotine, nicotyrine, and nornicotine,—have been discovered and isolated from tobacco and other plants. The proportion of nicotine, nicotimine, and nicotelline in tobacco, as compared with 1000 parts of nicotine, is 20, 5, and 1, respectively (177).

Henry (86) stated that members of this series of alkaloids, with one exception, have been found only in *Nicotiana* species combined with citric, malic, oxalic, and other organic acids, the one exception being the Australian plant *Duboisia hopwoodii*, from which nicotine was isolated by Petit (169) and Rothera (201). However, in 1939 Marion (134) extracted a basic oil (0.001 per cent) from the root of the milkweed, *Asclepias syriaca* L.; the oil, boiling at 85°C. at 1 mm., was characterized as *l*-nicotine by the formation of a dipicrate and a dipicolonate which were identical with the corresponding derivatives of an authentic specimen of nicotine.

II. NICOTINE

A. OCCURRENCE

Nicotine has been isolated from *Nicotiana affinis* (257), *N. americana* (213), *N. augustifolia* (248, 257), *N. attenuata* (46), *N. chinensis* (59, 257), *N. glauca* (99), *N. glutinosa* (114, 188, 257), *N. macrophylla* (59, 114, 188, 257), *N. paniculata* (257), *N. persica* (22), *N. rusbyi* (112), *N. rustica* (22, 59, 99, 114, 140, 155, 189, 236, 237, 238, 257), *N. suaveolens* (170), *N. sylvestris* (112), and *N. tabacum* (22, 35, 59, 114, 140, 149, 155, 177, 188, 200, 236, 237, 257, 264).

Bernardini (13) and Chaze (35, 38) were unable to detect nicotine in the seed of the tobacco plant, and Anderson (3) concluded that, at most, the mature seed contained only traces of the alkaloid. Nicotine was found in the sprouts and cotyledons of tobacco seed after only 9 to 11 days of germination (3, 250). Rosenthaler (200), in a diurnal study of the influence of light and aging on the nicotine content of the middle fresh leaves of *N. tabacum*, immediately after picking, found that an increase of nicotine took place from morning to night, while a decrease took place from night to morning. The increase is apparently greater than the decrease, since an accumulation of nicotine finally obtains over an extended period. Il'in (95) observed that, in the germination of tobacco seed during 15 days, both in the light and in the dark, nicotine was absent at first, but that after 5 days it was present in considerable and increasing quantities. Chaze (35, 38) showed the presence of nicotine in the interior of the vacuoles of plants only 1 mm. long and observed that, in the course of the development of the plant, the alkaloid appears throughout the aerial portion. It was found in the interior of the vacuoles which arise from the hydration of the aleurone granules when these often still contained crystalloid protein.

Nicotine is distributed throughout the tobacco plant, the amounts being greatest in the lower leaves and gradually growing less with the age of the leaves; the top leaves contain the least alkaloid (144). Cicerone and Marocchi (42) determined the percentage of nicotine to be greatest in the medium zone of the long axis of the leaf; the marginal zone is richer than the central zone, and in the rib the nicotine content decreases from the apex to the base. Kissling (107) and Il'in (97) found that the nicotine content of the tobacco plant increased with the age of the plant; at the time the young plants were bedded out the nicotine content was 0.15 per cent; after the leaves were formed, 0.20 per cent; before full growth, 0.36 per cent; just after full growth, 0.45 per cent; after gathering, 0.54 per cent; after fermentation, 0.60 per cent. Nishiyama (148) found that the nicotine content increases from the lower to the higher leaves. Koeing (110) found that the nicotine content is highest in the higher leaves, shortly before ripening, and lower in greenhouse, close-planted, and irrigated plants than in normal, open-air plants. Vladescu (251) found that nicotine reaches a maximum at the time of flowering (about 45 days), then decreases about 20 per cent, and finally, at the time of the appearance of the lateral buds, rises again to a higher maximum than before and again decreases. The second maximum is also shown to a lesser extent in plants whose buds are removed from time to time.

Pannain (165), using *Xanthi yoka* grown in Abruzzi, found that before flowering the aerial leaves contained less nicotine than the lower leaves. The leaves of the first and second pickings contained double the quantity

of nicotine present in the leaves of the third and fourth pickings. The leaf blades were always richer in nicotine than the ribs. The stems and roots contained less nicotine than other parts of the plant, but the roots contained more than the stems.

In plants sown very early the nicotine content of the leaves increases from below upward; in late plants the opposite condition prevails; in plants of normal cultivation there is an increase of nicotine in the lower leaves toward the middle leaves, and a decrease in the new leaves toward the plant top (4). Topping causes nicotine to migrate into the rest of the plant (39). The amount of nicotine in the stems can be increased 77 per cent by topping and removing the buds and leaves, then fertilizing with sodium nitrate, and gathering and immediately extracting the stems after the first frost (40).

Chaze (37) concluded that nicotine was a waste product of cellular metabolism and, through morphological and microchemical studies of cells, confirmed the idea that alkaloids are waste products (36), whereas Rosenthaler (200) concluded that tobacco alkaloids cannot, in the strict sense of the word, be regarded as excretion products. Theron and Cutler (238) thought nicotine to be present in the plant as a storage product and not as a protective agent. Il'in (96) considered nicotine as a reserve form of nitrogen participating in the general cycle of biological processes of the organism, its physiological function being analogous to that of asparagine.

B. EXTRACTION

Nicotine is isolated from tobacco commercially by treating the tobacco with an aqueous solution of an alkali and steam distilling. Numerous patents have been issued in this and other countries to individuals and corporations for this purpose, the one obtained by Hyatt (94) on May 17, 1938, for the commercial extraction of nicotine from tobacco, being very satisfactory. Tobacco material (such as stocks, stems, and low-grade leaves) is mixed with an alkali, and the saturated mixture is heated at atmospheric pressure to cause the collapse of the nicotine cells and the vaporization of the liquid present. The pressure on the heated mixture is reduced to effect the expansion and rupture of the collapsed cells. The vapors are condensed under the reduced pressure, and the pressure on the residue is alternately restored and reduced, the vapors being condensed from the residue after each reduction in pressure. (Each restoration of pressure is effected by breaking the vacuum with steam as suddenly as possible to cause the collapse of unexploded cells in the residue, and each reduction in pressure serves to expand and explode the cells so collapsed.)

C. BURNING

In the burning of tobacco, there is formed at the zone of glowing a mixture of gases and vapors consisting mainly of nitrogen, carbon dioxide,

carbon monoxide, and unused oxygen. The vapors are chiefly of substances already present in the tobacco which have been vaporized at the zone of glowing, such as resins, resin acids, higher hydrocarbons, and nicotine. On cooling, these vapors condense and, as a consequence of the high concentration, form a disperse phase in the form of a mist or fog. As a disperse system, tobacco smoke is capable of existence only up to temperatures of about 300°C. Above this temperature the disperse phase goes over to the vapor phase (262). The amount of nicotine passing unchanged into smoke varies with the rate of smoking. When a cigaret was burned in a closed vessel and the smoke was passed through a series of wash bottles containing dilute sulfuric acid, the whole of the smoke was recovered. On glowing without suction, 45 per cent of the total nicotine was recovered from the smoke; with intermittent glowing and suction (normal smoking), 25 per cent was in the main smoke stream and 14 per cent in the secondary stream from the glowing portion. However, with rapid continuous suction the corresponding figures were 80 and 3 per cent, respectively. The stump underwent no enrichment in nicotine; hence with normal smoking more than 50 per cent of the nicotine is decomposed (260). Justin-Mueller (100), on the other hand, found that, during smoking, nicotine passed through the combustion zone and was completely burned up.

D. PREPARATION

Auerbach and Wolffenstein (6) obtained nicotine by the reduction of nicotine-*N*-oxide with sulfurous or nitrous acids, while Pinner (183) and Pinner and Wolffenstein (186) obtained it by treating oxynicotine with barium hydroxide for 8 to 10 hr. at 140°C. Auzies (9) made nicotine by passing a mixture of pyrrole, ammonia, and butadiene over a mixture of aluminum and thorium oxides and iron, nickel, and cobalt at 350°C. Upon distilling the double chloride of zinc and nicotine with soda lime, Laiblin (116) found the liquid distillate to consist principally of nicotine. Pinner (179) obtained nicotine by reduction of the perbromide of dibromonicotine with zinc dust and hydrochloric acid. Weidel (258) suggested that nicotine may be formed by the action of ammonia on the aldehyde of pyrotartaric acid. Laiblin (117) obtained nicotine when he treated bromonicotine, $C_{10}H_{12}Br_2N_2 + HBr$, with potash. Chattaway and Parkes (33) found that, when nicotine tetrachloroiodide is treated with an aqueous solution of sodium hydroxide or sodium sulfite, it decomposes, forming nicotine. Parenty and Grasset (166) obtained nicotine by heating nicotine tetraoxalate to 250°C. If the additive compound of benzoyl chloride and nicotine is heated with strong hydrochloric acid at 100°C., nicotine is formed (182). Späth and Zajic (233) obtained nicotine by treating *l*-nornicotine with formic acid and formaldehyde.

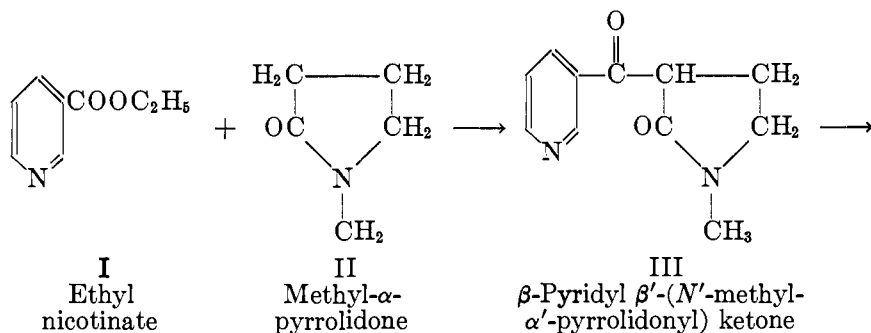
Yamafuji (272) found that the glucoside *tabacilin* is hydrolyzed to glucose, nicotine, and other substances. Barbieri (10) obtained nicotine by treating the tobacco glucoside *tabacin* with strong alkalies; hot concentrated potassium hydroxide converts *tabacol* into nicotine with the liberation of ammonia.

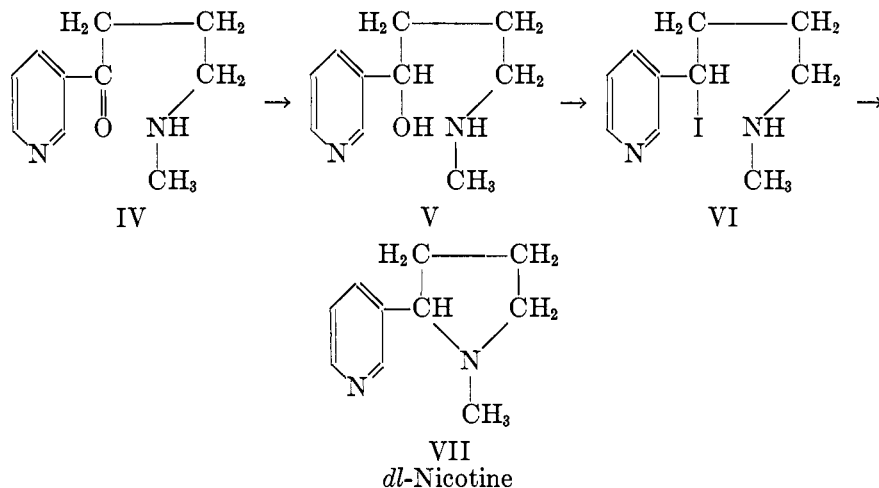
Nicotine may be obtained by steam distilling tobacco in a basic medium, dissolving in a slight excess of hydrochloric acid, recrystallizing several times, and treating with sodium nitrite at a low temperature, the alkaloid being subsequently liberated by alkali, dehydrated, and distilled under reduced pressure (2).

E. SYNTHESIS

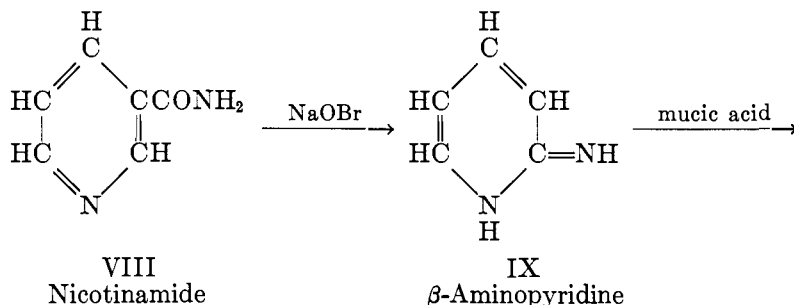
Auzies (8) obtained French patent 425,370 (January 3, 1911) for a synthesis of nicotine, which was effected in four steps: (i) ammonia was conducted over butadiene in the presence of thorium, nickel, aluminum, or copper oxides, with the production of pyrrole; (ii) the pyrrole, after methylating, was hydrogenated in the presence of finely divided nickel; (iii) a mixture of pyrrole and chloroform was heated to 450°C. in the presence of thorium, aluminum, etc., to obtain β -chloropyridine; (iv) nicotine was obtained by heating a mixture of β -chloropyridine and methyl-*l*-pyrrolidine to 425–450°C. in the presence of thorium, aluminum, etc.

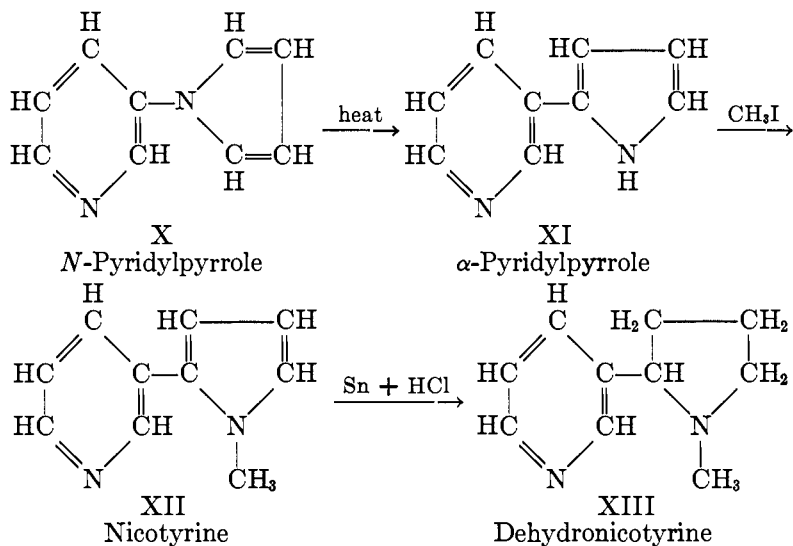
Späth and Bretschneider (223) synthesized nicotine by treating the ethyl ester of nicotinic acid (I) and methyl- α -pyrrolidone (II) with alcohol-free sodium ethylate (giving 70 per cent of β -pyridyl β' -(*N'*-methyl- α' -pyrrolidonyl) ketone (III)). When this ketone was heated for 7 hr. with fuming hydriodic acid at 130°C., the pyrrolidine ring was opened, carbon dioxide was split off, and there was obtained the ketone IV, which was reduced to the alcohol (V) by means of zinc dust in boiling alcoholic alkali. The alcohol, treated with fuming hydriodic acid at 100°C., yielded the iodide VI. The solution of the iodide was made alkaline, was allowed to stand, and was then distilled with steam. The yield of nicotine (VII), identical with racemized nicotine, was 33.4 per cent.



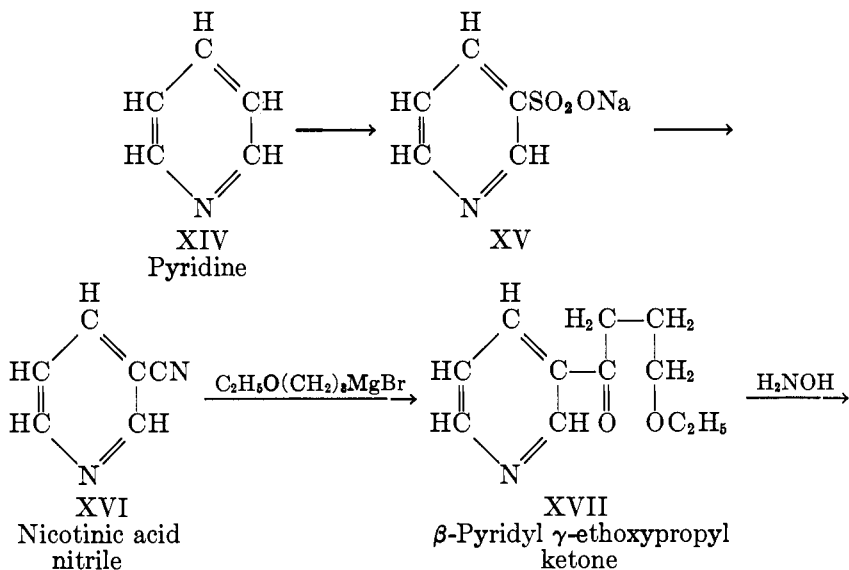


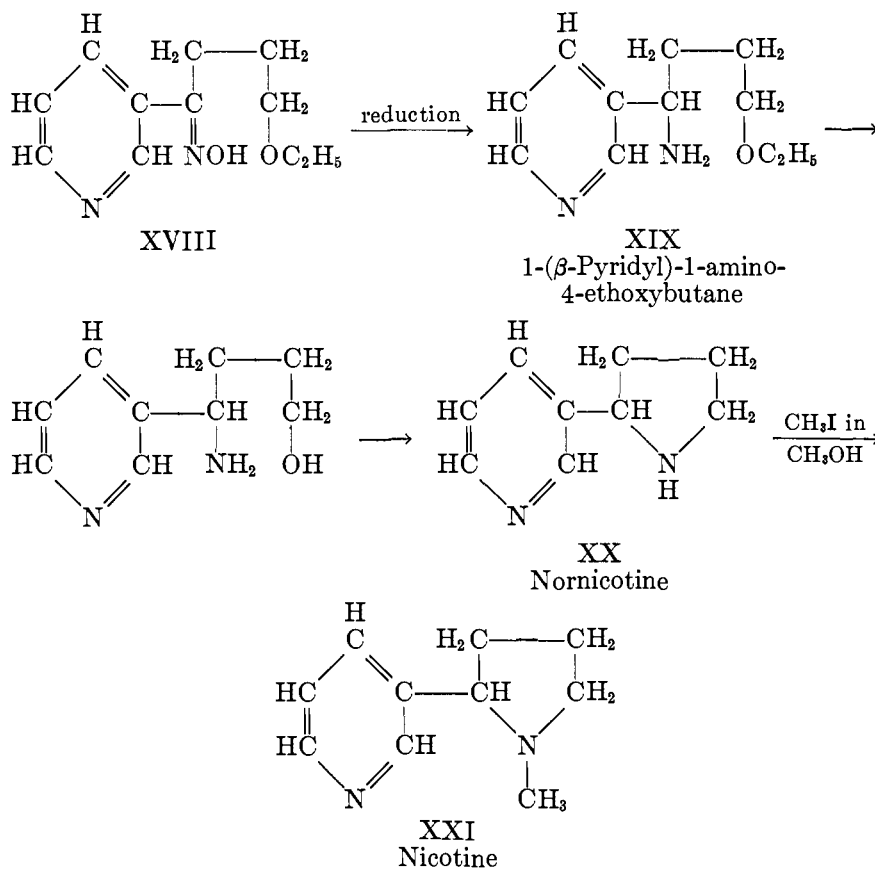
Pictet and Rotschy (178), starting from nicotinic acid, effected the synthesis of nicotine as follows: the amide of nicotinic acid (VIII) was converted, upon treatment with sodium hypobromite, into β -aminopyridine (IX), which, when subjected to dry distillation with mucic acid, formed a pyrrole ring with loss of carbon dioxide and water, giving *N*-pyridylpyrrole (X). When the vapor of this compound was passed through a gently heated ignition tube, molecular rearrangement took place with the formation of the isomeric α -pyridylpyrrole (XI); this substance forms salt-like compounds with alkali metals. Methyl iodide, acting upon the potassium salt, formed nicotyrine (XII). For the purpose of rendering the pyrrole ring of nicotyrine more easily reducible for conversion into nicotine, nicotyrine was converted into a monosubstitution product by means of iodine in alkaline solution. This compound was then reduced to dehydronicotyrine (XIII) by tin and hydrochloric acid. The dibromo addition product of this compound upon reduction with tin and hydrochloric acid gave tetrahydronicotyrine, or inactive nicotine; this racemic compound was converted into its salt with dextrotartaric acid and was thus resolved into *l*-nicotine.





Craig (47) sulfonated pyridine (XIV) with sulfuric acid and then converted the sodium salt (XV) of the product into nicotinic acid nitrile (XVI). The nitrile, when treated with the appropriate Grignard reagent, was converted into β -pyridyl γ -ethoxypropyl ketone (XVII). The ketone formed an oily oxime (XVIII), which upon reduction yielded 1-(β -pyridyl)-1-amino-4-ethoxybutane (XIX). This substance, when deethylated and treated with hydrobromic acid, gave nornicotine (XX) which, upon treatment with methyl iodide in methyl alcohol, formed nicotine (XXI).





F. PHYSICAL PROPERTIES

1. General characteristics

Nicotine is a water-white liquid of sharp burning taste and almost without odor in the cold (131). It is heavier than water and basic in reaction. Its vapor burns in air. It is miscible with water, alcohol, and ether (188). When kept in bottles filled to the stopper and away from light, nicotine remains colorless, only the slightest yellow tint being noticed after 6 months and no change in rotatory power (131). It evaporates appreciably when exposed to air at room temperatures; most of it volatilizes, but part of it turns into a dark resin. Nicotine is volatile in the vapors of ether, light petroleum, or 95 per cent alcohol (145).

2. Boiling point

The following values have been given for the boiling point of nicotine: 109°C. at 20 mm. (131); 115–117°C. at 12 mm. (212, 273); 120°C. at 14

mm. (109); 124–125°C. at 18 mm. (25); 125–140°C. at 16 mm. (265); 240–242°C. (116); 242°C. (175); 243°C. (234); 244°C. (25, 60); 245°C. (123); 246°C. (47, 81, 90, 188, 194, 198); 246.0–246.5°C. at 734.5 mm. (178); 246.1–246.2°C. at 730.5 mm. (171); 246.2°C. at 719.8 mm. (197); 246.6–246.8°C. at 745 mm. (118); 246.7°C. at 745 mm. (2, 26, 62); 247°C. (276); 248°C. (208); 249–250°C. (33); approximately 250°C. (12); 253°C. (183); 266–267°C. (uncorrected) (176).

3. Freezing point

Posselt and Reimann (188) found nicotine to be liquid at -6°C ., and Barral (12) found it to be liquid at -10°C .. Kruyt (113) was unsuccessful in an attempt to crystallize nicotine at -50°C .. Busbey and McIndoo (26) were likewise unable to solidify it at the same temperature, while Pictet and Rotschy (176) were unsuccessful in solidifying nicotine at -79°C .. Tsakalotos (242), attempting to crystallize nicotine by freezing, obtained only an amorphous glass, and the freezing-point curve, which would throw light on the existence of the hydrate, could not be realized experimentally.

4. Density

The following values have been reported for the density of nicotine at the temperatures specified: -80°C ., 1.095; -60°C ., 1.0775 (142); -49.31°C ., 1.0627 (212); -40°C ., 1.06 (142); -39.55°C ., 1.0546; -28.95°C ., 1.0465 (212); -20°C ., 1.043 (142); -19.09°C ., 1.0392; -9.19°C ., 1.0305 (212); 0°C ., 1.027 (142); 1.0258 (19); 0.75°C ., 1.023 (212); 10°C ., 1.0175 (19); 11.41°C ., 1.0147 (212); 15.6°C ., 1.012 (89); 20°C ., 1.0107 (142); 1.01022, 1.0101 (129); 1.0096 (19); 1.00925 (98); 20.55°C ., 1.0072 (212); 30°C ., 1.0014 (19); 1.00124 (203); 30.19°C ., 1.0000; 39.83°C ., 0.9915 (212); 40°C ., 0.99383 (203); 0.9935 (19); 50°C ., 0.9863 (203); 51.01°C ., 0.9837 (212); 60°C ., 0.9789 (203); 60.66°C ., 0.976; 70.86°C ., 0.9665; 79.06°C ., 0.9607; 89.07°C ., 0.9527; 93.45°C ., 0.949 (212).

5. Specific gravity

Values found in the literature for the specific gravity of nicotine are given below: d_4^0 , 1.0212 (168); d_4^4 , 1.033 (12, 215); d_4^{10} , 1.0177 (178); $d_4^{10.2^{\circ}}$, 1.01837 (118); $d_4^{12.5^{\circ}}$, 1.0778 (176); $d_4^{14.2^{\circ}}$, 1.0108 (168); $d_4^{14.8^{\circ}}$, 1.0124 (168); d_4^{15} , 1.027 (12), 1.013 (123), 1.0111 (215); $d_4^{17.1^{\circ}}$, 1.0119 (268); $d_4^{18.8^{\circ}}$, 1.0117 (25); $d_4^{19.27^{\circ}}$, 1.0081 (212); $d_4^{19.4^{\circ}}$, 1.0095 (175); d_4^{20} , 1.0145 (25), 1.01122 (129), 1.01101 (118), 1.011 (211), 1.01071 (69), 1.01049 (85), 1.01002 (129), 1.01 (168), 1.00995 (268), 1.00984 (129), 1.0098 (15), 1.0097 (178), 1.0096 (235), 1.0095 (168, 194), 1.00947 (197), 1.00931 (131), 1.0093 (26), 1.00925 and 1.00924 (197), 1.0092 (98, 178, 197), 1.0091 (242, 243), 1.009

(171); $d_4^{21.1^\circ}$, 1.00865 (98); $d_4^{22.4^\circ}$, 1.027 (142), 1.0212 (168), 1.0121 (25), 1.008 (53); $d_4^{26.1^\circ}$, 1.0064 (87); $d_4^{29.5^\circ}$, 1.0017 (98); $d_4^{30^\circ}$, 1.018 (12), 1.00373 (118), 0.99567 (203); $d_4^{30.18^\circ}$, 1.0001 (212); $d_4^{39^\circ}$, 0.9925 (168); $d_4^{40^\circ}$, 0.99424 (98), 0.99225 (203); $d_4^{41^\circ}$, 0.99037 (168); $d_4^{41.6^\circ}$, 0.9924 (98); $d_4^{41.6^\circ}$, 0.99334; $d_4^{42.7^\circ}$, 0.9926 (268); $d_4^{49.49^\circ}$, 0.985 (212); $d_4^{50^\circ}$, 1.0006 (12), 0.98807 (203); $d_4^{52^\circ}$, 0.984 (98); $d_4^{59.98^\circ}$, 0.9765 (212); $d_4^{60^\circ}$, 0.98324 (203), 0.97799 (98); $d_4^{61.6^\circ}$, 0.9777 (268); $d_4^{62^\circ}$, 0.976 (98); $d_4^{63.7^\circ}$, 0.9755 (268); $d_4^{69.6^\circ}$, 0.9699 (98); $d_4^{70^\circ}$, 0.9688; $d_4^{71.5^\circ}$, 0.9673 (168); $d_4^{73.3^\circ}$, 0.9685 (87); $d_4^{74^\circ}$, 0.96797 (87); $d_4^{76.98^\circ}$, 0.9631 (212); $d_4^{80^\circ}$, 0.96184 (98); $d_4^{82^\circ}$, 0.96081 (268); $d_4^{82.1^\circ}$, 0.9607 (268); $d_4^{86.4^\circ}$, 0.9567 (98); $d_4^{89.4^\circ}$, 0.9552 (87); $d_4^{92^\circ}$, 0.9521 (98); $d_4^{97.64^\circ}$, 0.9465 (212); $d_4^{97.7^\circ}$, 0.94534 (98); $d_4^{99^\circ}$, 0.947 (268), 0.9453; $d_4^{99.2^\circ}$, 0.9449 (168); $d_4^{99.5^\circ}$, 0.94622 (268); $d_4^{101.5^\circ}$, 0.9424 (12); $d_4^{118.22^\circ}$, 0.9297 (212); $d_4^{121^\circ}$, 0.92794; $d_4^{121.8^\circ}$, 0.9277 (268); $d_4^{138.91^\circ}$, 0.9131; $d_4^{163.92^\circ}$, 0.8923; $d_4^{183.16^\circ}$, 0.8763; $d_4^{208.28^\circ}$, 0.8495 (212).

6. Miscibility with solvents

(a) *With water.* Hudson (93) observed that nicotine and water are miscible in all proportions at temperatures below 60°C. and above 210°C. At temperatures between 60°C. and 210°C. the miscibility is limited, except when one of the components is present in very large excess. Above 90°C., a saturated solution of water in nicotine is lighter than a saturated solution of nicotine in water; below 90°C., the reverse is the case. When nicotine is mixed with water, much heat is developed, probably owing to the formation of a hydrate (192). The marked variation of the specific rotation and of the refractive index with the concentration points to the same interpretation. To the presence of such a hydrate the miscibility of the two otherwise immiscible liquids, nicotine and water, may be attributed.

The data of table 1 are graphically presented in figure 1.

Jephcott (98) found that, owing to the so-called closed curve of the solubility of nicotine in water, it is not possible to observe the rotatory power and density of solutions containing between 7 and 87 per cent of nicotine at all temperatures up to 100°C., since separation occurs at about 60°C. Two solutions were therefore prepared which would fall outside this closed curve and which contained 6.638 per cent and 88.338 per cent of nicotine. From these solutions the data in table 2 were obtained.

The formation of hydrates of nicotine and their decomposition at higher temperatures show the true nature of the closed curve of solubility. Nicotine is only sparingly soluble in water, and water is only sparingly soluble in nicotine, but hydrates of nicotine are miscible with water, a state of balance existing at any given temperature between nicotine, its hydrates, and water.

TABLE 1
Solutions of nicotine in water

NICOTINE	TEMPERATURE	
	Decomposition	Remixing
<i>per cent</i>	°C.	°C.
6.8	94	95
7.8	89	155
10.0	75	
14.8	65	200
32.2	61	210
49.0	64	205
66.8	72	190
80.2	87	170
82.0	129	130

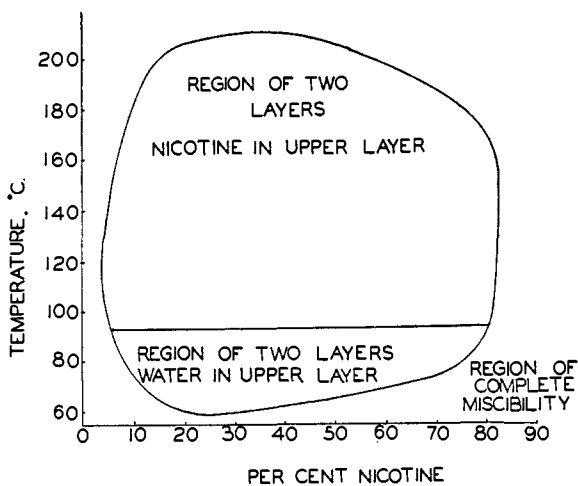


FIG. 1. Miscibility of nicotine and water

TABLE 2
Solutions of nicotine in water

TEMPERATURE	NICOTINE		d_{4}^{t}	$[\alpha]_{D}^{t}$
	<i>per cent by weight</i>	<i>grams in 100 cc. of solution</i>		
°C.				
20	6.638	6.6820	1.00275	-76.82°
85	6.638	6.4188	0.96328	-95.29
20	88.338	90.8200	1.02810	-134.16
90	88.338	86.9360	0.98412	-150.34

As the temperature rises, the hydrate formation reverses, and when the concentration of free nicotine becomes greater than the solubility of nicotine in water at that temperature, separation occurs. By choosing concentrations of nicotine and water such that the limit of solubility of the one in the other is not exceeded, it is possible to note the marked rise in rotatory power as the concentration of free nicotine increases with rise in temperature (242).

Measurements of the viscosity of mixtures of water and nicotine show that there is an exceptionally great increase in viscosity on mixing. The index of refraction for the mixtures shows a straight line. The author considers that the peculiar behavior of this binary system is due to the formation of a hydrate of nicotine.

TABLE 3
Reciprocal solubility of the system nicotine-water

NICOTINE	WATER	TEMPERATURE OF SATURATION	
		Lower	Higher
<i>per cent</i>	<i>per cent</i>	<i>°C.</i>	<i>°C.</i>
5.4	94.6	Homogeneous	
6.5	93.5	92.7	94.5
15.3	84.7	64.3	195.0
33.4	66.6	60.8	208.0
49.6	50.4	62.7	204.0
66.7	33.3	71.8	194.0
71.7	28.3	75.8	185.0
79.2	20.8	86.1	168.0
84.5	15.6	Homogeneous	

According to Seyer and Gallagher (212), nicotine dissolves in its own volume of water to form a sticky, viscous liquid, which, on warming, becomes turbid and separates into two liquid layers, the upper being a saturated solution of nicotine in water, and the lower a saturated solution of water in nicotine. Further warming will again bring about the formation of a single homogeneous phase. Ever since the discovery of the ring-shaped solubility curve of nicotine and water (93), attempts have been made to show the existence of hydrates at the temperatures below the critical (lower) temperature.

Considerable work has been done with the object of establishing the existence of these hydrates. Owing to the viscous nature of the solutions at temperatures below 20°C., it has so far been difficult to obtain reliable freezing-point data and quite impossible to separate any hydrates which might have been formed. While Jephcott (98), upon an examination of

the freezing points of solutions of nicotine, found indications of hydrates, still, most of the evidence supporting the theory of hydrate formation has come from the investigation of other physical properties of nicotine and water solutions. Thus Tsakalotos (244) investigated the viscosity, Skalweit (215) the specific gravity, and Winther (268) the index of refraction and specific rotatory power, all with a view toward offering an explanation of the closed solubility curve.

The system water-nicotine is one of the few known examples of a system in which there are two critical temperatures of solution, i.e., in which the temperature-concentration curve is a closed curve, two strata existing only within a definite interval of temperature above or below which only a single homogeneous phase exists (93). Redetermination of data for the system water-nicotine by Leone (120) confirmed the data of Hudson (93), except for very small variations. Acetone, which is miscible with each component in all proportions, was then introduced as a third component. The data showed that acetone increases the mutual solubility of water and nicotine, reducing the temperature zone of existence of the two phases until, with enough acetone, the two phases disappear. The maximum distance between the two critical points occurs with the mixture containing 31.73 per cent of nicotine, and the maximum concentration of acetone which still allows the existence of a non-miscibility zone is 35.44 per cent, at which concentration this zone is so greatly reduced that it presents only a slight opalescence between 146° and 155°C. With a slightly greater concentration of acetone, two phases are not formed on heating. The molecular variations of the critical temperature calculated by Timmerman (240) are not constant for all proportions of water and nicotine, but tend to increase slightly with increase in the concentration of acetone. In the critical zone between 20 and 40 per cent nicotine, the general relation between the ratios of the molecular variations is constant. The molecular variations of acetone remain within values of 100 to 150 for the lower critical temperatures while, for the higher critical temperatures, they hardly reach 100. For a given sample, the molecular variation in the lower critical temperature is 30-40°C. greater than the corresponding variation in the higher critical temperature. A distinct and constant difference between the values of the molecular increases of the lower critical temperature and the corresponding molecular lowering of the higher critical temperature supports the hypothesis that the two critical points must be interpreted differently.

Nicotine is miscible with most liquids at the ordinary temperature, and the radius of its molecular sphere should approximate that of pyridine (87). The values given in table 4 are calculated for water-nicotine mixtures at 20°C. (193).

It is evident that these results differ materially from any obtained before, inasmuch as the greatest difference between the percentage of nicotine in the initial and the final volumes occurs at a mixture well removed from equimolecular proportions referred to the gaseous state. From the data

TABLE 4
Equimolecular volumes of gaseous nicotine
100C₁₀H₁₄N₂:11.24H₂O

MOLECULAR MIXTURE	CHANGE IN VOLUME*	Δnicotine †
Nicotine-water.....	-1.88	1.545
Nicotine-1.5 water.....	-2.62	1.963
Nicotine-2 water.....	-3.20	2.190
Nicotine-2.5 water.....	-3.70	2.322
Nicotine-3 water.....	-4.17	2.407
Nicotine-3.5 water.....	-4.45	2.368
Nicotine-4 water.....	-4.75	2.338

* Change in volume when the volume of the particular liquid in question is constant at 100 volumes, the signs (+) and (-) referring to expansion and contraction, respectively.

† Differences (Δ) between the proportion by volume of this liquid in the initial and final volumes.

TABLE 5
Equimolecular volumes of gaseous nicotine
100C₁₀H₁₄N₂:25.14CH₂OH

MOLECULAR MIXTURE	CHANGE IN VOLUME*	Δnicotine †
Nicotine-alcohol.....	-1.15	0.742
Nicotine-1.5 alcohol.....	-1.58	0.843
Nicotine-2 alcohol.....	-1.93	0.966
Nicotine-2.5 alcohol.....	-2.20	0.841
Nicotine-3 alcohol.....	-2.45	0.808

* Change in volume when the volume of the particular liquid in question is constant at 100 volumes, the signs (+) and (-) referring to expansion and contraction, respectively.

† Differences (Δ) between the proportion by volume of this liquid in the initial and final volumes.

in table 4 the complexity of nicotine would appear to be one-half that of water, and the equimolecular liquid mixture would be C₁₀H₁₄N₂·2H₂O.

A similar complexity for nicotine is deducible from its mixtures with methyl alcohol at 20°C. (268) (see table 5). Assuming similar complexity, the ratio of the radius of the nicotine molecule to that of water as unity at 20°C. would be

$$\sqrt[3]{\frac{162.132}{1.00995}} \div \sqrt[3]{\frac{18.016}{0.99823}} \text{ or } 2.07$$

A mixture was prepared containing 1 mole of nicotine to 2 moles of water in the liquid state, and the temperature at which partial miscibility commenced was determined. Heated in a sealed tube, the mixture remained homogeneous until a temperature of 75.8°C. was reached, when a cloudiness appeared at the surface; at 76°C. this cloudiness had spread through the mass of the liquid and two layers separated.

The initial volumes of nicotine and water in the mixture at 74°C. are 21.162 cc. and 9.333 cc., respectively, and the final volume is 29.898 cc.; i.e., 100 volumes of nicotine when mixed with 44.10 volumes of water contracted to the extent of 2.82 volumes, so that at this temperature the volume change is still considerable.

The ratio of the radii of the spheres of nicotine and water increases with rise in temperature and at 26.1°, 73.3°, and 89.8°C. is 1.64, 1.65, and 1.66, respectively. These values are so close to that required theoretically for partial miscibility that they may be deemed sufficient confirmation of the complexity found above for nicotine: namely, one-half that of water.

The following table gives the radial ratios of the molecular spheres of the liquids, which, on admixture at the stated critical temperatures of solution, are on the immediate borderline between complete and partial miscibility:

MIXTURE	CRITICAL TEMPERATURE OF SOLUTION OF THE MOLECULAR MIXTURE	RATIO OF MOLECULAR RADI AT THE CRITICAL TEMPERATURE
Nicotine and water	76°C.	1.65

It will be noticed that the ratio, 1.65, is greater than the theoretical value, 1.62. Nicotine and water give the nearest approach to this value, and they also give the greatest contraction in volume on admixture.

(b) *With petroleum.* A sample of American petroleum was purified from unsaturated and aromatic compounds and fractionated repeatedly so as to remove the fractions of lower boiling points. The fraction boiling between 200° and 230°C. was taken for a study of petroleum-nicotine-water mixtures (88).

(1) The initial proportions by volume of the constituents at 15°C. were as follows: petroleum, 33.3; water, 33.3; nicotine, 33.3. After vigorous shaking at 5°C., this mixture of liquids separated into two layers having the relative proportions: petroleum layer, 36; water-nicotine layer, 64. When the mixture was heated to 62°C., the lower aqueous layer became cloudy and separated rapidly into two layers, a lower layer containing

nicotine and an intermediate aqueous layer which increased in volume as the temperature rose until, at 90°C., the relative proportions were as follows: petroleum layer, 41; water layer, 26; nicotine layer, 33. On mixing at the latter temperature, two layers were again formed, owing to the nicotine dissolving in the petroleum. The observed proportions of the layers were now: petroleum-nicotine layer, 67; aqueous layer, 33. Both layers remained clear at temperatures above 63°C. At immediately lower temperatures the nicotine began to separate from the petroleum and fell to the bottom of the tube, leaving at first an intermediate aqueous layer, which, however, on further cooling, mixed with the nicotine, and the liquids resumed their original equilibrium of two layers.

(2) The initial proportions by volume of the constituents at 15°C. were as follows: petroleum, 6.7; water, 33.3; nicotine, 60.0. At 5°C. this mixture of liquids formed two layers in the relative proportions: petroleum layer, 8; nicotine layer, 92. When the temperature was raised to 67°C.,

TABLE 6
Molecular complexity of nicotine

LIQUID	TEMPERATURE	COMPLEXITY IN THE LIQUID STATE WATER = (H ₂ O) ₄	MOLECULAR VOLUMES COMPARED WITH THAT OF WATER AS UNITY AT THE SAME TEMPERATURE		MOLECULAR RADIUS AS COMPARED WITH THAT OF WATER
			Referred to the gaseous state	Referred to the liquid state	
Nicotine.	°C. 20	(C ₁₀ H ₁₄ N ₂) ₂	8.92	4.46	1.65

a cloudiness appeared in the aqueous layer, and three layers were formed which at 90°C. had the following relative proportions: petroleum layer, 8; aqueous layer, 9; nicotine layer, 83. At 100°C., the lower nicotine layer rose to the middle portion and dissolved in the petroleum, so that, on mixing at this temperature, two layers were again formed in the proportions: petroleum-nicotine layer, 75; aqueous layer, 25. On cooling, the nicotine began to separate from the petroleum and fell to the bottom of the tube at 68°C.; its general behavior at lower temperatures was similar to that in the preceding mixture. Very gradual cooling of this mixture resulted in the formation of four layers at some temperatures. These consisted of a small petroleum layer, then a large layer of petroleum and nicotine, and below these an aqueous layer, and then at the bottom a concentrated nicotine layer. These layers, however, were clearly metastable, and on mixing gave two stable layers only.

(3) The initial proportions by volume of the constituents at 15°C. were as follows: petroleum, 60.0; water, 33.3; nicotine, 6.7. At 5°C. the

proportions of the two layers formed were as follows: petroleum layer, 60; water-nicotine layer, 40. The lower aqueous layer became cloudy at 76°C., and then results similar to those obtained with the preceding mixtures were observed.

It will be noticed that at some concentrations the foregoing mixtures of liquids form two layers only, which, within a limited range of temperature, yields three-layer systems, proving how close is the relationship of the molal volumes of the several liquids to the ratio required by theory for partial miscibility.

(c) *With aqueous solutions.* Dubrisay (56) determined the miscibility of nicotine with water and with solutions of sodium hydroxide, hydrochloric acid, and sodium sulfate (see table 7).

TABLE 7
Miscibility of nicotine with water and with solutions of hydrochloric acid, sodium sulfate, and sodium hydroxide

WATER-NICOTINE		N/10 HCl-NICOTINE		N/10 Na ₂ SO ₄ -NICOTINE		N/10 NaOH-NICOTINE	
Concentration	Temperature	Concentration	Temperature	Concentration	Temperature	Concentration	Temperature
<i>per cent</i>	°C.	<i>per cent</i>	°C.	<i>per cent</i>	°C.	<i>per cent</i>	°C.
66.60	70.8	66.6	71.1	40.0	40.5	50.0	51.1
63.33	68.0	50.0	70.2	33.3	47.0	33.3	55.2
55.55	66.8	40.0	70.2	25.0	49.1	25.0	56.0
50.00	63.1	33.3	73.2	20.0	51.9	20.0	57.8
40.00	62.3						
33.33	62.0						
25.00	62.3						
20.00	62.3						

7. Adsorption

The amounts of nicotine adsorbed from 25 cc. of 0.01 *M* solution by 0.5 g. of various adsorbents are as follows: silica, 87.3 per cent; alumina, 1.5 per cent; iron oxide, 2.2 per cent; fuller's earth, 43.7 per cent. The adsorption by hydrous iron oxide was irregular, being 0.2 and 2.7 per cent, respectively, for oxide samples prepared by precipitation from ferric chloride by means of ammonia solution and by the oxidation of electrolytic iron with ozone in the presence of water and platinum foil (77).

8. Volatility

The concentration of nicotine in the vapor phase was determined by Harlan and Hixon (80) at 25°, 30°, 35°, and 40°C. by the "air-bubbling method." These data are reported in table 8.

TABLE 8
Vapor concentrations of nicotine

TEMPERATURE	AIR PASSED OVER NICOTINE	NICOTINE OBTAINED	CONCENTRATION OF NICOTINE	
			<i>mg. per 10 liters of air</i>	<i>p.p.m.</i>
°C.	<i>liters</i>	<i>grams</i>		
25	60	0.01106	1.84	28.5
25	60	0.01056	1.76	27.3
30	60	0.01635	2.73	43.0
30	60	0.01596	2.66	41.9
35	30	0.01250	4.17	66.8
35	30	0.01232	4.11	65.9
40	30	0.01723	5.74	94.3
40	30	0.01812	6.04	99.2

TABLE 9
Viscosity of the system nicotine-water at 20°C. (242, 243)

NICOTINE	DURATION OF FLOW
<i>per cent</i>	<i>seconds</i>
33.4	249.2
49.6	583.0
66.7	1355.0
71.7	1727.5
73.9	1821.0
79.2	1866.0
86.1	1511.0
100.0	247.2

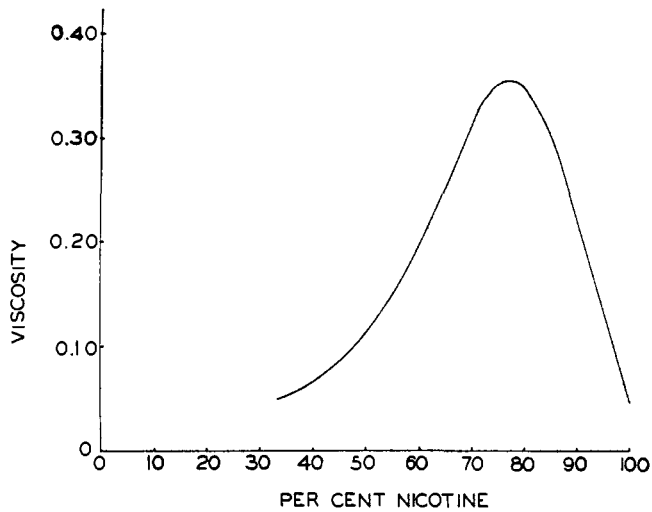


FIG. 2. Viscosity of the system nicotine-water at 20°C.

9. Viscosity

Values for the viscosity of the system nicotine-water at 20°C. are given in table 9. The curve resulting from a plot of these values (figure 2) shows a maximum at the concentration of 78 per cent nicotine and indicates the formation of a molecular combination between water and nicotine. Measurements of the viscosity of the liquids show that there is an exceptionally great increase in viscosity on mixing. The viscosity of the mixture is eight times greater than that of nicotine and thirty-five times that of water. According to Deželić (53), the viscosity curve with pyrrole shows a definite maximum at a concentration of approximately 60 mole per cent of nicotine (see figure 3).

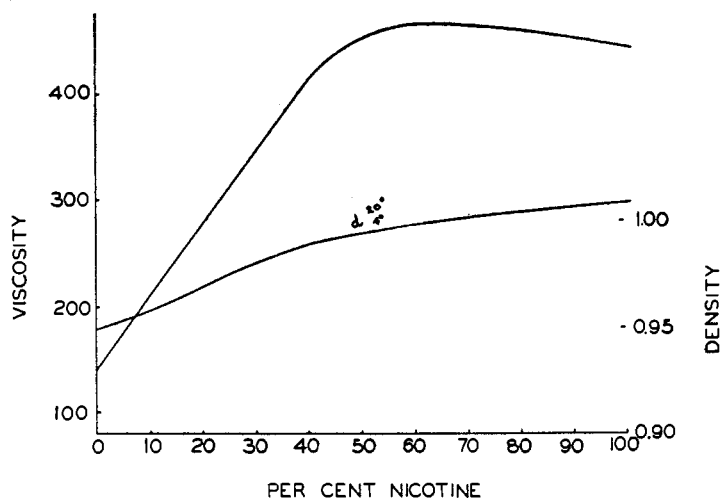


FIG. 3. Viscosity of the system nicotine-pyrrole at 20°C.

The viscosity curve of nicotine and 2,4-dimethylpyrrole possesses a sharply marked maximum which is exactly at 33.3 per cent nicotine (2 moles of 2,4-dimethylpyrrole:1 mole of nicotine); in the system 2,4-dimethyl-3-ethylpyrrole (cryptopyrrole)-nicotine the viscosity curve tapers to a point, a maximum being situated at 32 per cent nicotine (2 moles of cryptopyrrole:1 mole of nicotine) (54) (see figure 4).

10. Vapor pressure

The vapor pressure measurements made by Gorbatshev (75) were carried out by determining the boiling points in a manostat and the saturation pressures within a range of 90–230°C. (see figure 5a). The determination of the vapor pressure by Young and Nelson (273) is by the air saturation

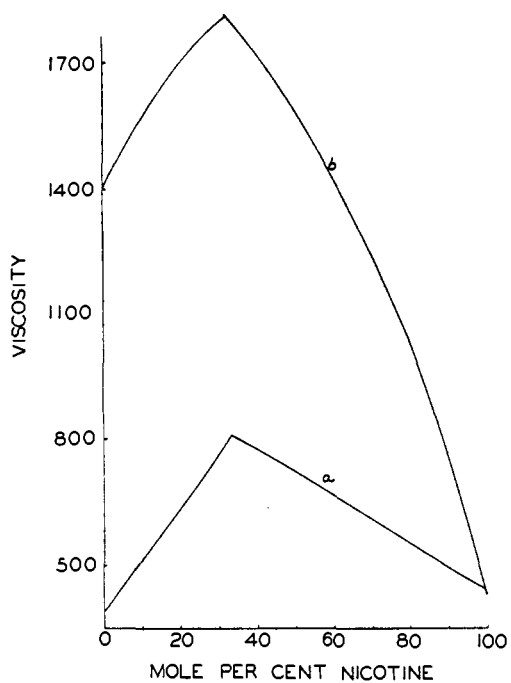


FIG. 4. Viscosity of (a) the system nicotine-2,4-dimethylpyrrole and (b) the system nicotine-2,4-dimethyl-3-ethylpyrrole.

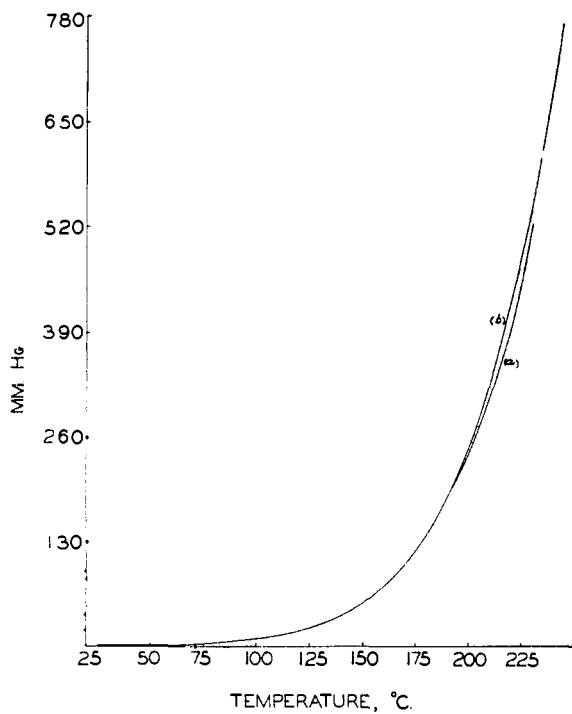


FIG. 5. Vapor pressure of nicotine

method up to 100°C. and by the static method from this point to the boiling point of nicotine (see figure 5b).

Schükarew (208) found the vapor pressure of mixtures of nicotine and water to be constant between 17 and 82 per cent nicotine at the lower critical solution temperature. At the upper critical solution temperature, the vapor pressure of the solution is generally greater than that of the more volatile component.

11. Surface tension

Seyer and Gallagher (212) calculated the surface tension values by means of the formula $\gamma = K Hd$, where γ is the surface tension in dynes, K is a constant for the apparatus employed, H is the corrected difference in height of liquid in the two capillaries, and d is the density of the solutions. The Eötvös constant in the case of nicotine was obtained by plotting the molecular surface energies against temperature on a large scale and then taking the difference in the molecular surface energies from the curves over intervals of about 30°C.

It is futile to draw any conclusions as to the state of nicotine and water in the various solutions from a consideration of the change in molecular surface energy with temperature. Skalweit (215) observed a maximum density at a concentration of 72 per cent nicotine, Tsakalotos (242) a viscosity maximum at 78 per cent, and Jephcott (98) from the specific rotation of nicotine solutions found maxima at concentrations of roughly 40 and 80 per cent nicotine. According to Denison (51), such deviations can scarcely be due to the change in association of either solvent. The most likely explanation of the maxima must be that they represent the points of maximum concentration of nicotine hydrates, which break down as the temperature approaches 60°C.

Semenchenka and Ivanova (209) measured the interfacial surface tension of nicotine by the drop method, using butyric acid, butyraldehyde, butyronitrile, butyramide, propyl alcohol, and propyl chloride at various concentrations and temperatures, as shown in table 11. It was found that all the compounds used had a high surface activity which was directly proportional to the dipole moment for compounds not containing nitrogen and inversely proportional to the dipole moment for compounds containing nitrogen.

12. Density of mixtures of nicotine with other liquids

(a) *Water and nicotine.* Seyer and Gallagher (212) determined the density of six solutions of nicotine and water which contained, per 100 g. of solution, the following quantities of nicotine: (a) 5.35 g.; (b) 10.12 g.; (c) 23.74 g.; (d) 35.15 g.; (e) 54.86 g.; and (f) 72.16 g. From these data the graphs of figure 6 have been drawn. It is noticed that with increasing

TABLE 10
Surface tension and other data of the system nicotine-water

TEMPERATURE	DENSITY	SURFACE TENSION	MOLECULAR SURFACE ENERGY	ΕÖTVÖS CONSTANT K_c
100 per cent nicotine				
°C.		<i>dynes per cm.</i>	<i>ergs per sq. cm.</i>	
-49.31	1.0627	46.58	1331	
-39.55	1.0546	45.39	1307	
-28.95	1.0465	44.12	1277	
-19.09	1.0392	43.16	1244	2.5
-9.19	1.0305	42.22	1227	
0.75	1.0230	41.41	1206	
11.41	1.0147	39.89	1174	2.6
20.55	1.0072	38.61	1141	
30.19	1.0000	37.70	1121	
39.83	0.9915	36.54	1092	2.7
51.01	0.9837	35.37	1063	
60.66	0.9760	34.15	1032	
70.86	0.9665	33.08	1005	2.8
79.06	0.9607	32.17	983	
89.07	0.9527	31.25	959	
93.45	0.9490	30.99	953	2.4
Mixture: 5.35 g. of nicotine per 100 g. of solution				
0.09	1.0029	57.13	404.6	
6.20	1.0025	55.25	391.8	1.6
10.30	1.0021	54.39	385.5	
20.80	1.0003	52.14	370.0	
29.70	0.9978	47.91	340.0	2.2
41.50	0.9940	43.65	326.6	
52.10	0.9893	41.85	299.1	
60.53	0.9845	38.94	279.3	1.1
70.30	0.9793	37.11	267.1	
79.97	0.9740	34.84	252.8	
90.27	0.9685	33.54	243.2	1.3
95.40	0.9685	32.30	234.6	
Mixture: 35.15 g. of nicotine per 100 g. of solution				
0.24	1.0314	51.55	444.5	
7.70	1.0284	50.34	435.5	
19.90	1.0223	47.54	412.7	1.4
24.80	1.0195	46.73	407.4	
30.56	1.0157	45.68	399.3	
35.30	1.0130	44.92	392.1	1.8
46.20	1.0055	42.13	365.5	
55.86	0.9982	40.06	353.4	
Mixture: 72.16 g. of nicotine per 100 g. of solution				
0.42	1.0540	47.37	622.3	
5.50	1.0500	46.75	615.2	
10.20	1.0462	45.88	605.7	1.8
19.85	1.0374	44.29	587.5	
25.02	1.0327	43.30	576.8	
29.17	1.0288	42.65	570.6	1.6
34.97	1.0236	41.77	560.4	
40.30	1.0185	40.90	548.8	
50.45	1.0091	39.67	536.5	
60.00	1.0002	38.49	523.6	1.4
69.85	0.9914	37.10	507.6	
75.05	0.9862	36.58	502.3	

nicotine concentration the temperature-density relationships become almost linear.

Table 12 gives values for the density and specific rotation of mixtures of nicotine and water; these data are represented graphically in figure 7.

TABLE 11
Interfacial surface tension of nicotine

	MOLE PER CENT	TEMPERATURE OF SOLUTION	70°C.	80°C.
Butyric acid.....	0.00	60.2	0.304	0.400
	0.14	64.2	0.075	
	0.26	68.0	0.077	
	0.30	68.8	0.061	
	0.44	72.4	0.065	
Butyramide.....	0.19	61.0	0.210	0.335
	0.24	62.2	0.185	0.286
	0.38	63.7	0.163	0.267
	0.60	65.7	0.152	0.269
Butyronitrile.....	0.16	58.9		0.325
	0.37	57.2	0.105	0.366
	0.57	55.5	0.136	0.463
	0.73	54.3	0.207	0.641
Butyraldehyde.....	0.20	55.9		0.337
	0.35	52.2	0.105	0.470
	0.45	50.2	0.166	0.576
	0.60	47.0	0.265	0.790
Propyl alcohol.....	0.00	60.2	0.304	0.400
	0.21	60.4	0.280	0.370
	0.39	60.5	0.263	0.365
	0.61	60.8	0.270	0.365
	0.80	61.2	0.261	0.360
Propyl chloride....	0.20	53.6		0.381
	0.33	48.4	0.167	0.542
	0.49	43.2	0.290	0.782
	0.68	41.8	0.595	1.123

In table 13 are listed additional values for the density of the system nicotine-water, while the data are represented graphically in figure 8. From the same source were derived the data on the coefficient of contraction of nicotine-water mixtures (see table 14 and figure 9). Table 15 also presents data on the density of the system nicotine-water. The

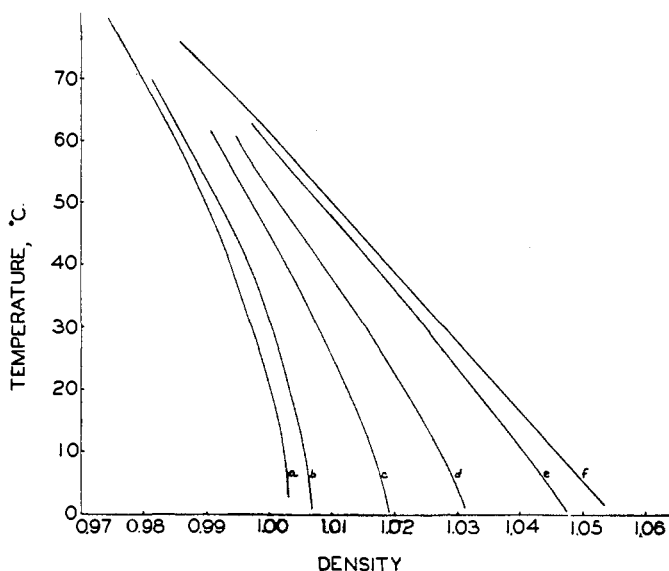


FIG. 6. Density of the system water-nicotine: curve a, 5.35 g. of nicotine per 100 g. of solution; curve b, 10.12 g. of nicotine per 100 g. of solution; curve c, 23.74 g. of nicotine per 100 g. of solution; curve d, 35.15 g. of nicotine per 100 g. of solution; curve e, 54.86 g. of nicotine per 100 g. of solution; curve f, 72.16 g. of nicotine per 100 g. of solution.

TABLE 12
Density and specific rotation of the system nicotine-water (98)

GRAMS OF NICOTINE PER 100 CC. OF SOLUTION	$d_{4}^{20^{\circ}}$	SPECIFIC ROTATION $[\alpha]_{D}^{20^{\circ}}$	GRAMS OF NICOTINE PER 100 CC. OF SOLUTION	$d_{4}^{20^{\circ}}$	SPECIFIC ROTATION $[\alpha]_{D}^{20^{\circ}}$
100.925	1.00925	-168.61°	45.296	1.02936	-86.47°
96.801	1.01823	-153.06	42.882	1.02790	-86.71
93.323	1.02458	-141.65	41.308	1.02661	-85.09
91.781	1.02583	-138.73	39.804	1.02592	-83.79
90.820	1.02810	-134.11	39.025	1.02522	-85.21
86.132	1.03356	-123.21	38.950	1.02538	-84.98
84.632	1.03439	-121.48	35.920	1.02431	-83.52
79.921	1.03784	-111.47	35.696	1.02351	-83.39
78.551	1.03836	-108.39	32.810	1.02107	-81.83
77.764	1.03839	-108.69	31.607	1.02048	-82.48
71.963	1.03990	-100.47	31.253	1.02010	-82.67
70.231	1.03988		30.915	1.02060	-82.60
66.918	1.03890	-97.82	28.664	1.01820	-81.95
66.440	1.03894	-95.63	26.930	1.01725	-81.78
63.110	1.03846	-94.02	25.369	1.01588	-81.67
62.131	1.03728	-93.69	21.235	1.01300	-80.64
61.895	1.03765	-95.12	20.995	1.01299	-80.06
58.250	1.03614	-91.27	15.156	1.00880	-80.99
56.245	1.03603	-89.27	13.027	1.00492	-79.79
54.934	1.03463	-90.12	11.579	1.00611	-79.43
53.750	1.03428	-86.91	10.061	1.00611	-78.66
51.777	1.03278	-89.03	9.971	1.00494	-79.20
50.513	1.03194	-88.19	7.441	1.00317	-79.94
48.062	1.03065	-86.23	6.622	1.00276	-79.25
47.629	1.03131		5.006	1.00153	-80.48
47.412	1.03037	-86.79	2.504	0.99970	-83.15

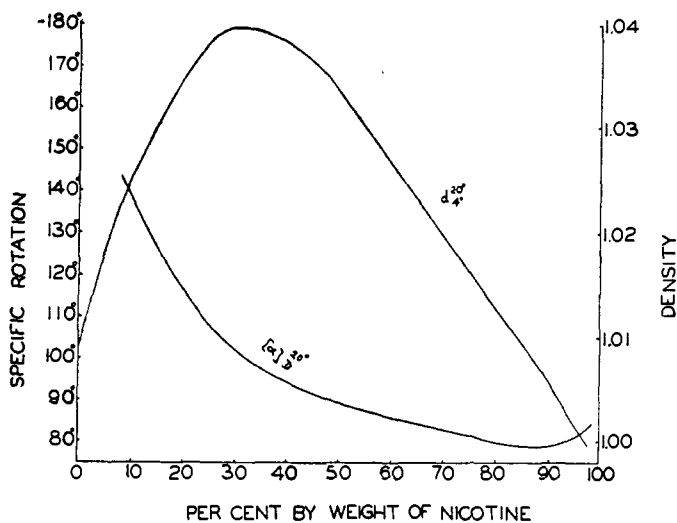


Fig. 7. Density and specific rotation of the system nicotine-water

TABLE 13
Density of the system nicotine-water (19)

PER CENT NICOTINE	DENSITY				
	0°C.	10°C.	20°C.	30°C.	40°C.
100.00	1.0258	1.0175	1.0096	1.0014	0.9936
93.64	1.0390	1.0304	1.0218	1.0133	1.0049
83.66	1.0517	1.0430	1.0340	1.0248	1.0150
69.88	1.0577	1.0496	1.0402	1.0310	1.0217
60.07	1.0588	1.0486	1.0402	1.0316	1.0230
51.60	1.0507	1.0442	1.0367	1.0299	1.0210
35.13	1.0342	1.0296	1.0241	1.0181	1.0118
15.82	1.0148	1.0128	1.0098	1.0058	1.0012

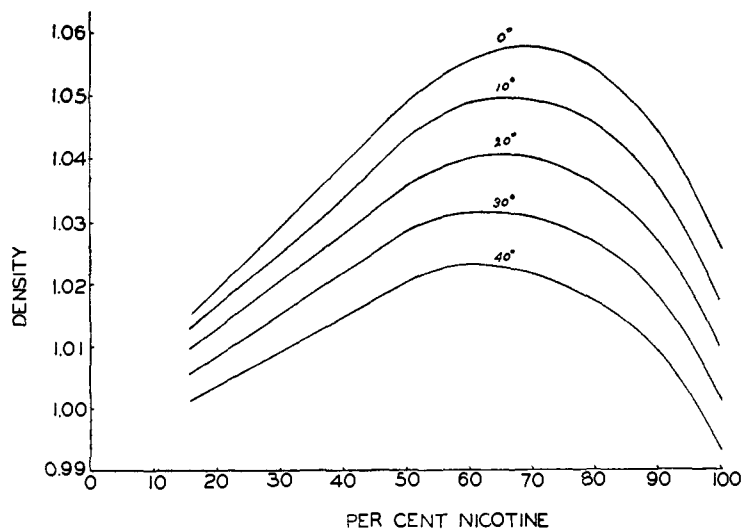


Fig. 8. Density of the system nicotine-water

curves at the lower temperatures (figure 10) show a maximum value which tends to disappear as the lower temperature limit for partial miscibility (about 60°C.) is approached.

Sata (203) determined the densities of the conjugate solutions at various temperatures between 65° and 120°C. At lower temperatures the nicotine phase is the heavier, but reversal occurs at 96°C. and an 8-shaped curve is

TABLE 14
Coefficient of contraction of nicotine-water mixtures (19)

PER CENT NICOTINE	COEFFICIENT OF CONTRACTION				
	0°C.	10°C.	20°C.	30°C.	40°C.
93.63	0.01433	0.01364	0.01266	0.01201	0.01152
83.66	0.02876	0.02730	0.02543	0.02366	0.02225
69.88	0.03770	0.03578	0.03274	0.03032	0.02805
60.07	0.03840	0.03655	0.03382	0.03143	0.02935
51.60	0.03585	0.03394	0.03159	0.02945	0.02736
35.13	0.02458	0.02310	0.02150	0.02001	0.01895
15.82	0.01022	0.01028	0.00972	0.00913	0.00880

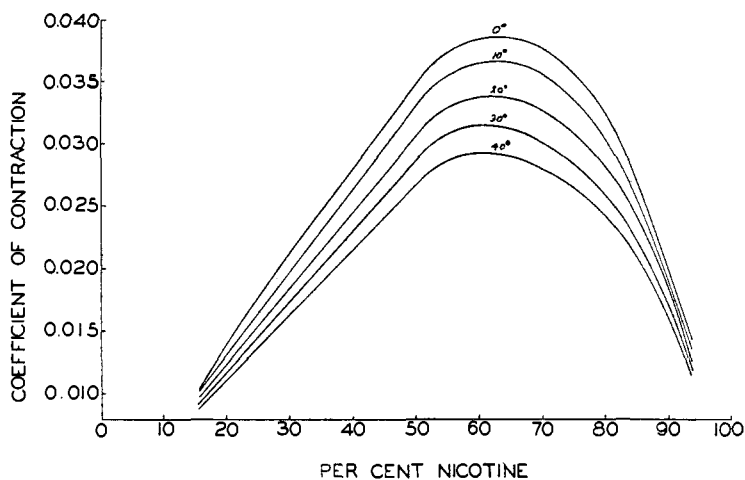


Fig. 9. Coefficient of contraction of the system nicotine-water

obtained on plotting densities of the conjugate against temperature (see table 16 and figure 11).

The curve in figure 12 represents the relation between the percentage composition and the specific rotation of nicotine solutions (see table 17) and may be regarded as built up of three different portions. The points of intersection would lie at about 6 and 69 per cent. The addition of water

TABLE 15
Density of the system nicotine-water (203)

VOLUME PER CENT NICOTINE	DENSITY			
	30°C.	40°C.	50°C.	60°C.
0	0.99567	0.99225	0.98807	0.98324
10	1.00234	0.99856	0.99453	0.98968
20	1.00888	1.00410	0.99886	0.99353
30	1.01513	1.00953	1.00381	0.99755
40	1.02118	1.01449	1.00784	1.00065
50	1.02646	1.01903	1.01033	1.00299
60	1.03023	1.02156	1.01280	1.00407
70	1.03101	1.02228	1.01247	1.00406
80	1.02788	1.01830	1.00875	0.99970
90	1.01773	1.00979	1.00132	0.99280
100	1.00124	0.99383	0.98630	0.97890

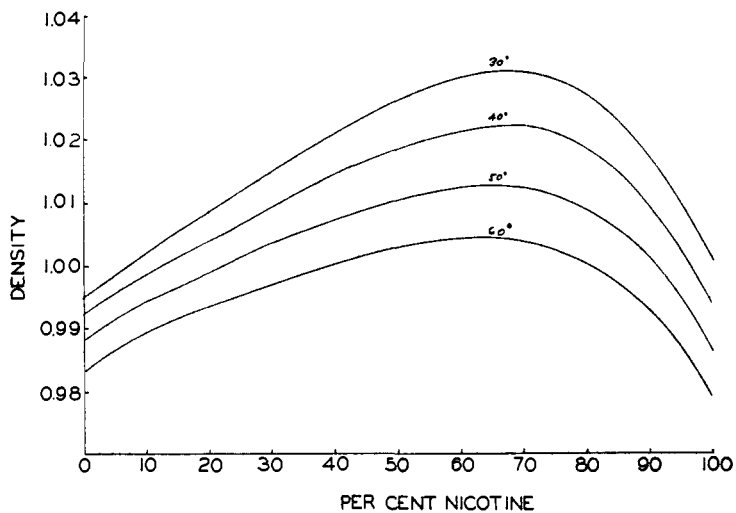


FIG. 10. Density of the system nicotine-water

TABLE 16
Density of the system nicotine-water

TEMPERATURE	UPPER PHASE (WITH NICOTINE- SATURATED WATER LAYER)	LOWER PHASE (WITH WATER- SATURATED NICOTINE LAYER)	TEMPERATURE	LOWER PHASE (WITH NICOTINE- SATURATED WATER LAYER)	UPPER PHASE (WITH WATER- SATURATED NICOTINE LAYER)
°C.			°C.		
65	0.98918	0.99907	95	0.96709	0.96744
70	0.98467	0.99491	100	0.96429	0.96190
75	0.98077	0.98904	105	0.96070	0.95760
80	0.97761	0.98438	110	0.95710	0.95210
85	0.97397	0.97832	115	0.95340	0.94770
90	0.97103	0.97368	120	0.94970	0.94320

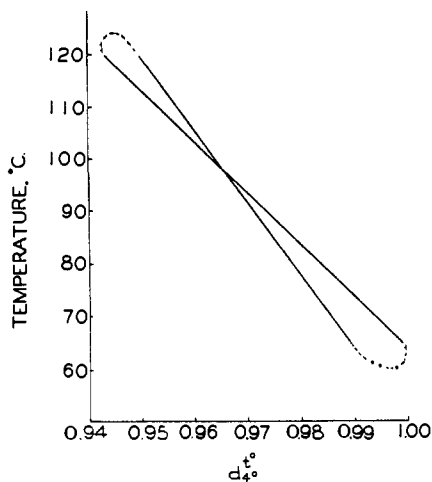


FIG. 11. Density of the system nicotine-water

TABLE 17

Specific gravity and specific rotation of the system nicotine-water (194)

PER CENT NICOTINE	SPECIFIC GRAVITY 20°/4°	$[\alpha]_D^{20^\circ}$	PER CENT NICOTINE	SPECIFIC GRAVITY 20°/4°	$[\alpha]_D^{20^\circ}$
100.000	1.0095	-164.91°	49.301	1.0329	-86.49°
86.889	1.0299	-129.19	35.579	1.0238	-82.17
75.131	1.0394	-103.75	20.746	1.0132	-79.08
72.665	1.0398	-100.27	10.191	1.0054	-77.55
71.315	1.0399	-101.60	9.099	1.0046	-77.56
69.117	1.0402	-99.13	8.167	1.0037	-77.44
67.534	1.0397	-97.79	6.340	1.0026	-77.54
64.921	1.0396	-95.21	4.733	1.0015	-77.34
62.812	1.0391	-93.76	2.545	1.0000	-77.64
59.653	1.0382	-91.64	1.049	0.9990	-78.06
55.401	1.0364	-89.27	0.6175	0.9987	-78.42

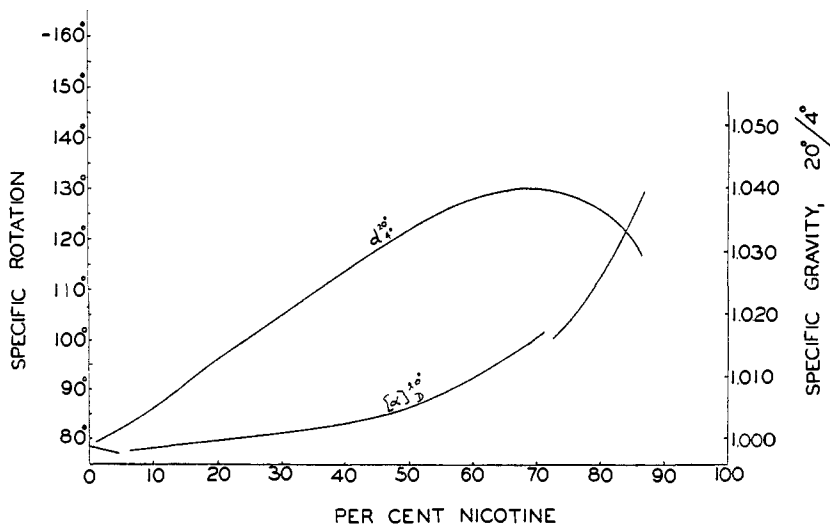


FIG. 12. Specific gravity and specific rotation of the system nicotine-water

to nicotine at first produces a very rapid fall in the rotation, but when the concentration of the nicotine reaches 69 per cent, the fall becomes less rapid, and from 6 per cent onwards there is a rise in the rotation with increasing dilution. The solution containing about 69 per cent of nicotine is the one that possesses the maximum density, and this point also coin-

TABLE 18
Density of the system nicotine-alcohol

PER CENT NICOTINE	d_4^{20} (118)	GRAMS NICOTINE PER 100 G. METHYL ALCOHOL	d_4^{20} (288)
90.09	0.9884	81.233	0.97073
74.93	0.9536	65.111	0.93523
59.93	0.9200	47.611	0.89634
45.08	0.8875	25.213	0.84703
30.03	0.8554	12.066	0.81901
14.96	0.8251	11.920	0.81856
		6.031	0.80639
		3.444	0.80106

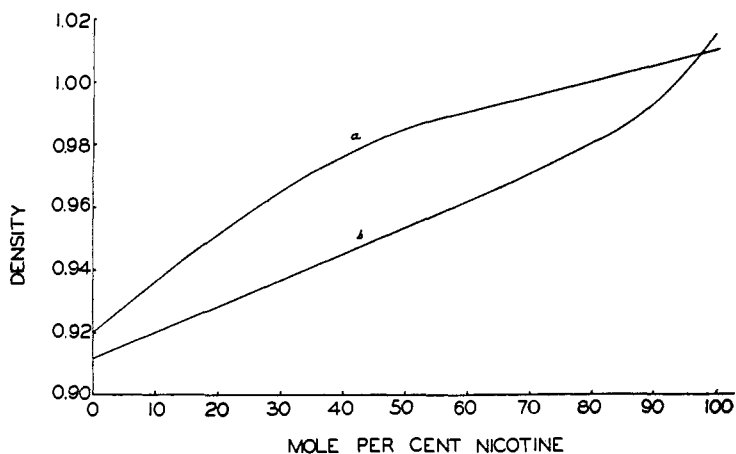


FIG. 13. Density of (a) the system nicotine-2,4-dimethylpyrrole and (b) the system nicotine-2,4-dimethyl-3-ethylpyrrole (cryptopyrrole).

cides with the maximum volume concentration. The solution approximates the composition $C_{10}H_{14}N_2 \cdot 4H_2O$, and Přibram and Glücksmann (194) are inclined to attribute the peculiarities noticed in nicotine solution to the existence of hydrates.

(b) *Alcohol and nicotine.* Values for the density of mixtures of nicotine and ethyl alcohol are given in table 18.

(c) *Mixtures of 2,4-dimethylpyrrole and 2,4-dimethyl-3-ethylpyrrole with nicotine.* The density curve for a mixture of 2,4-dimethylpyrrole with nicotine (2 moles of 2,4-dimethylpyrrole:1 mole of nicotine) shows a clearly convex sag, whereas that for a mixture of 2,4-dimethyl-3-ethyl-

TABLE 19
Density and specific rotation of the system alcohol-water-nicotine (74)

PERCENTAGE		GRAMS OF NICOTINE PER 100 CC. OF SOLUTION AT 20°C.	DENSITY OF THE SOLUTION AT 0°C.	SPECIFIC ROTATION [α]
Alcohol	Water			
99.330	0.670	12.0167	0.83993	-136.44°
88.848	11.152	12.3770	0.86427	-121.91
78.880	21.120	12.1965	0.88755	-113.40
68.855	31.145	12.1300	0.90780	-108.31
59.207	40.793	12.4175	0.92790	-103.99
50.133	49.867	12.1597	0.94418	-99.09
40.273	59.727	12.1342	0.96309	-94.79
21.233	78.767	12.0189	0.98940	-84.08

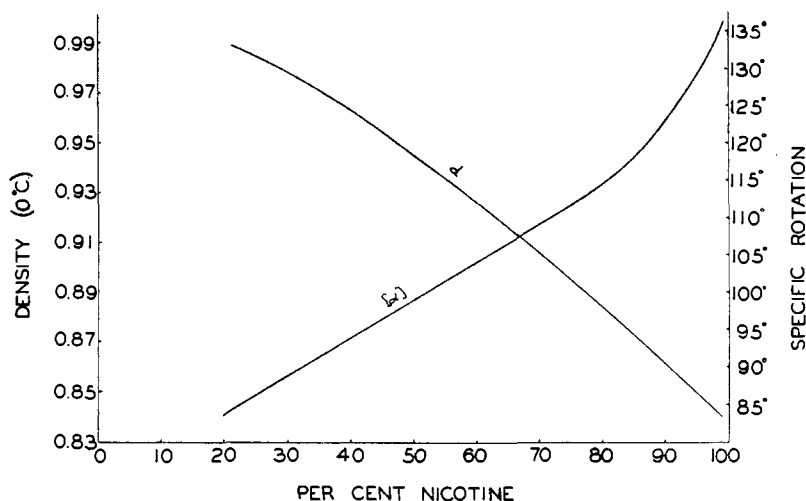


FIG. 14. Density and specific rotation of the system alcohol-water-nicotine

pyrrole (cryptopyrrole) with nicotine (2 moles of cryptopyrrole:1 mole of nicotine) is faintly concave, as shown in figure 13 (54).

(d) *Alcohol, water, and nicotine.* Values for the density and specific rotation of mixtures of ethyl alcohol, water, and pyridine are given in table 19 and represented graphically in figure 14.

13. Thermochemical and dissociation constants

The *heat of combustion* of nicotine at constant volume at 12°C. is 1426.6 Cal.; at constant pressure, 1428.0 Cal. (14, 15); kg.-cal._{15°} (exptl.), 1427.7; kilojoules, 5974.9 (102). Its *heat of formation* from the elements is as follows: (liq) -1.9 Cal.; (dissolved) 5.15 Cal. (14, 15). The *heat of solution* of nicotine is 7.05 Cal. at 11°C. (14, 15) and 6.56 Cal. at 14°C. (44). The *specific heat* of nicotine was found to be 0.420 Cal. (45). Its *molecular heat of solution* is 6.56 Cal. (45); its *heat of dissolution* is 6.6 Cal. at about 15°C. (44). The *heat of neutralization* of nicotine by hydrochloric acid is as follows: first equivalent = 8.05 Cal.; second equivalent = 3.47 Cal. (44). Its *total heat of neutralization* by 4 moles of hydrochloric acid = 12.06 Cal. With sulfuric acid, the first equivalent = 9.54 Cal. and the total heat of neutralization by excess acid = 13.46 Cal. It is evident that the two basic functions have very different energies, a fact which is also shown by color reagents. With litmus as indicator, nicotine has only one basic function, but with dimethyl orange it has two (44). The dissociation constants of nicotine at 15°C. are as follows: $K_1 = 7 \times 10^{-7}$; $K_2 = 1.4 \times 10^{-11}$ (122). Craig and Hixon (48) obtained a value of 9×10^{-7} potentiometrically, and explained the lower value as due to the pyridyl radical being extremely negative. Mendel and Vickery (136) and Vickery and Pucher (249) found that the apparent dissociation constants of nicotine are as follows at 20°C.: $pK_{a1}^1 = 3.22$; $pK_{a2}^1 = 8.11$.

14. Electrometric titration

At a temperature of 26°C., 10 cc. of a 1.333 *N* solution of nicotine was titrated with 1 *N* hydrochloric acid. The neutralization points were at 320 drops, pH = 5.52, and at 640 drops, pH = 1.52 (130). The first section of the potential curve shows the changes produced by the neutralization of the pyrrolidine nitrogen and has the form characteristic of the neutralization of a weak base. The second section shows the neutralization of the pyridyl nitrogen; but this is so weak that the possible formation of a pseudo-base is of no importance, and no drift was observed in the strongly acid solutions in which the dichloride is formed.

The potential curve was plotted with the help of a hydrogen electrode, while drops of 1 *N* hydrochloric acid from a buret were being added to the base in a glass vessel closed with a rubber bung and provided with a glass stirrer. The glass vessel was connected to a beaker of saturated potassium chloride by an agar-agar bridge, also saturated with hydrochloric acid. The cell was completed by a saturated calomel electrode dipping into the beaker containing potassium chloride, and its E.M.F. was determined at room temperature by means of a potentiometer calibrated to read directly in millivolts. The results are shown in figure 15.

The basic dissociation constants of the two nitrogen atoms were then deduced from the values of the pH at half-neutralization as follows: pyridyl nitrogen, 7.94×10^{-12} ; pyrrolidine nitrogen, 4.90×10^{-7} .

Dubrisay (57) determined the exact neutralization of nicotine to occur at a pH of 5.45, suitable indicators being bromocresol purple, sulfoalizarin, *p*-nitrophenol, and methyl red. Nicotine with methyl red gave a pH of 5.26 as the neutralization point in electrometric titration (255). Schick

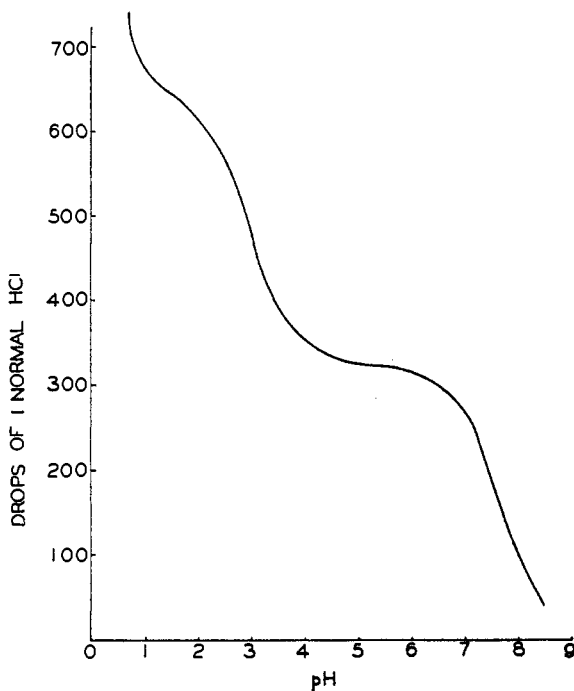


FIG. 15. Electrometric titration of nicotine

and Hatos (204) found that methyl red gave a much sharper and more accurate end point than iodeosin in the titration of nicotine.

15. Specific rotation

The following values have been reported for the specific rotation of nicotine: -160.93° (178); -161.29° (146); -161.50° (276); -161.55° (118, 171, 187, 192, 267); -162.84° (69); -163.0° (52); -163.19° (197); -164.0° (89); -164.18° (85); -164.91° (194); -166.39° (178); -166.77° (197); -167.78° , -168.02° (168); -168.20° (131); -169.40° , -168.52° , -168.61° , -168.66° (98); -168.84° , -169.06° , -169.17° (129); -169.22°

(197); -169.23° , -169.30° , -169.35° (129); -169.40° (235); -169.50° (131); -169.54° (197) (see also table 20).

The data in table 21 (119) show that the specific rotation of nicotine at first suffers a very sharp decrease with increase in the amount of water added, but that the decrease later becomes gradually less. The strongly bowed curve shown in figure 16 is a limb of an hyperbola.

The data of table 22 show that, at temperatures of 5° and 15°C ., a minimum specific rotation (marked *) occurs when the amount of nicotine

TABLE 20
Specific rotation of nicotine (268)

TEMPERATURE	$[\alpha]_D^t$	LIGHT	$[\alpha]^{14.5^\circ}$
$^\circ\text{C}$.			
17.1	-163.71°	Red*	-125.4°
20.0	-163.89	Yellow	-163.4
42.7	-165.25	Green	-204.5
61.6	-166.05	Light blue	-294.7
82.1	-166.52	Dark blue	-336.8
99.0	-166.56		
121.3	-166.61		

* The colors refer to Landolt's ray filter.

TABLE 21
Specific rotation of the system nicotine-water

PER CENT NICOTINE	$[\alpha]_D^{20^\circ}$
89.9155	-133.85°
78.3920	-109.53
65.8872	-94.24
53.4750	-86.58
34.2854	-80.78
17.6793	-76.94
16.3356	-76.88
8.9731	-75.53

is about 10 per cent, and that at a temperature of 20°C . this minimum is found in the solution of about 8 per cent strength. From the molecular weight determination it is seen that nicotine in very dilute solution is present as a normal molecule, while in more concentrated solutions hydrates, and probably molecular aggregations, exist. A much lower rotating power must be ascribed to these than to pure nicotine, but if they are broken up by increasing dilution, as suggested by the decrease in the molecular weight, more and more nicotine appears; thus the decrease in

the specific rotation is gradually arrested and finally an increase in the rotation must follow.

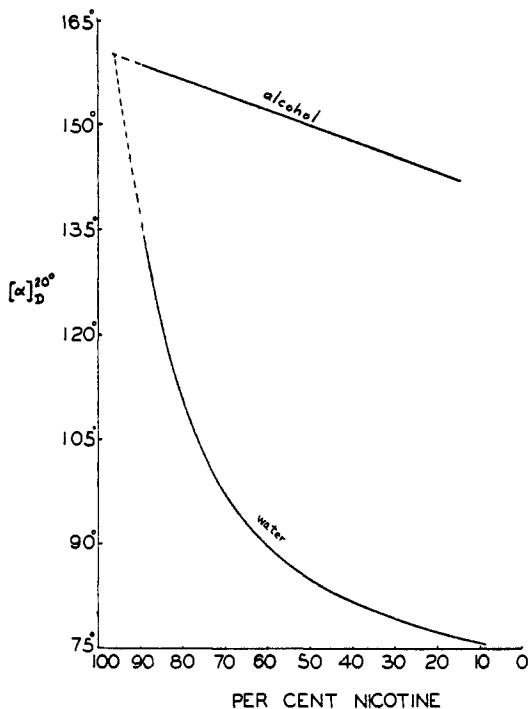


FIG. 16. Specific rotation of nicotine in (a) alcohol and (b) water

TABLE 22
Specific rotation of the system nicotine-water (85)

PER CENT NICOTINE	$[\alpha]_D^{5^\circ}$	$[\alpha]_D^{15^\circ}$	$[\alpha]_D^{20^\circ}$
15.592	-73.39°	-76.18°	-77.59°
11.206	-73.05	-75.96	-77.01
10.258	-72.78 (#)	-75.59 (#)	-76.89
8.307	-73.07	-75.76	-76.84 (#)
5.700	-73.81	-76.00	-76.96
3.016	-74.46	-76.27	-77.25
2.042	-74.74	-76.35	-77.32
1.061	-74.79	-76.83	-77.66

Přibram (192) observed that an aqueous solution containing 20.169 per cent of nicotine and having a density of 1.0149 exhibited, when it was

allowed to remain in the polarization tube, the following increase in rotation:

	$[\alpha]_D^{20}$
Fresh solution	-87.81°
After 12 hr.	-93.13
After 18 hr.	-96.55
After 48 hr.	-96.56

TABLE 23
Specific rotation of nicotine in organic solvents (267)

SOLVENT	PER CENT NICOTINE	$[\alpha]_D$	SOLVENT	PER CENT NICOTINE	$[\alpha]_D$
Acetone.....	93.7	-163.68°	Propyl alcohol	88.55	-160.76°
	56.5	-164.65		60.01	-156.34
	31.6	-163.56		25.37	-149.92
	20.5	-163.46		14.07	-147.35
	14.7	-163.25		9.65	-146.35
	3.1	-162.73		7.46	-145.89
			1.83	-143.67	
Ether.....	82.3	-164.17°	Aniline.....	84.79	-160.78°
	62.9	-163.50		68.42	-157.65
	37.1	-162.78		50.24	-156.86
	18.2	-162.36		27.08	-156.55
	13.3	-162.26		15.97	-156.45
	5.7	-161.72		6.00	-156.41
Benzene.....	84.4	-164.29°	Toluidine....	84.96	-161.40°
	48.0	-164.14		64.17	-158.55
	25.5	-164.10		34.36	-157.65
	19.0	-163.95		19.98	-157.32
	16.4	-163.88		12.34	-156.88
	8.5	-163.67		4.60	-156.55
Ethyl alcohol..	90.09	-158.65°			
	74.93	-154.92			
	59.93	-151.78			
	45.08	-148.81			
	30.03	-145.42			
	14.96	-141.60			

According to Přibram, this phenomenon depends on the formation of a hydrate, since nicotine and water mix with marked evolution of heat. In a freshly prepared 20 per cent solution the conversion does not seem to be

completed at once, but requires a certain time. From the increase in the rotation it must be concluded that the hydrate is more active than the pure base.

TABLE 24
Specific rotation of nicotine

λ	T	OBSERVED ROTATION	$[R]_T^\lambda$
480	22.3°	-197.83°	-251.81°
	-81.5	-191.04	-223.67
508.6	22.4	-169.76	-216.08
	-81.5	-163.38	-191.27
546.1	22.4	-141.96	-180.70
	-72.5	-138.25	-162.85
	-81.5	-136.02	-159.24
	-89.7	-134.69	-156.61
	-45.0	-142.24	-171.54
	-30.0	-142.86	-174.42
	-15.0	-143.15	-176.90
	-5.0	-143.10	-178.20
589.3	5.0	-142.92	-179.40
	22.7	-117.80	-149.97
	-71.5	-114.44	-135.02
	-82.1	-112.57	-131.73
	-89.0	-111.19	-129.40
643.8	22.5	-95.36	-121.38
	-71.2	-92.82	-109.51
	-80.7	-91.34	-106.98
670.8	22.5	-86.76	-110.43
	-72.2	-84.18	-99.23
	-81.6	-82.84	-96.98

As shown in table 23, the specific rotation of nicotine decreases as the dilution with ethyl alcohol increases. The graphic construction in figure 16 leads to a straight line.

Molby (142) measured the specific rotation of nicotine for six different wave lengths and through a low temperature range. In table 24, the column headed $[R]_T^\lambda$ gives the specific rotation for the corresponding temperature as obtained by the equation

$$[R]_T^\lambda = \text{observed rotation}/LD$$

in which L is the length of the liquid column expressed in decimeters and D is the density at the corresponding temperature.

In an equimolecular mixture of nicotine and glacial acetic acid, treated with water, Gennari (69) observed the appearance of anomalous dispersion, but only within very narrow limits of concentration. The specific rotation of nicotine in mixtures of acetic acid and water at 20°C. was found by means of Landolt's ray-filter method (see table 25); for yellow light, however, the sodium flame was used.

Landolt (119) points out that pure nicotine and the mixture of this with one mole of acetic acid possess a normal levorotation, which increases

TABLE 25
Specific rotation of the system nicotine-acetic acid-water at 20°C.

MIXTURES	$[\alpha]_{\text{red}}$	$[\alpha]_{\text{D}}$	$[\alpha]_{\text{green}}$	$[\alpha]_{\text{light blue}}$	$[\alpha]_{\text{dark blue}}$
Equimolecular mixtures of glacial acetic acid and nicotine.....	-55.63°	-74.18°	-95.22°	-120.3°	-143.54°
Mixtures of the same with water:					
original mixture					
per cent					
water					
per cent					
82.806 17.194	-11.79°	-16.00°	-20.27°		
81.259 18.741	-9.20	-12.57	-16.83	-21.99°	-26.68°
78.866 21.134	-4.13	-5.82	-8.20	-10.92	
77.844 22.156	-1.70	-2.72	-4.39	-6.63	-9.93
77.450 22.550	-0.12	-0.54	-1.48	-2.80	-5.00
76.390 23.610	+0.78	+0.52		-0.75	
76.300 23.700	1.36	0.98	+0.74		-1.40
76.230 23.770	5.90	7.44	8.85	+9.87	
76.100 23.900	12.92	16.74	20.72	24.56	+28.00

with the refrangibility of the light. As nicotine acetate rotates to the right, it appears that a part of the nicotine in the mixture exists in the uncombined condition.

The peculiarities in dispersion which appear when water is added to the equimolecular mixture of acetic acid and nicotine can best be seen from the diagram in figure 17. This extends from the red to the light blue, as $[\alpha]$ for dark blue had to be omitted on account of incompleteness in the observations. It will be seen: (1) That in mixtures with 18.74 and 22.55 per cent of water there is normal levorotation for the different colors, and that this decreases (the dispersion also) with increase in the amount of water. (2) That the solutions containing from 23.77 to 23.90 per cent of

water possess dextrorotatory power, which, with the dispersion, is increased in a marked degree by a slight increase in the amount of water. (β) That with an amount of water varying from 23.61 to 23.70 per cent, the rotation and also the dispersion are very small, the first solution showing complete inactivity for green rays and the second for light blue rays. Here then is a case of the appearance of a minimum of rotation with increasing refrangibility of the light.

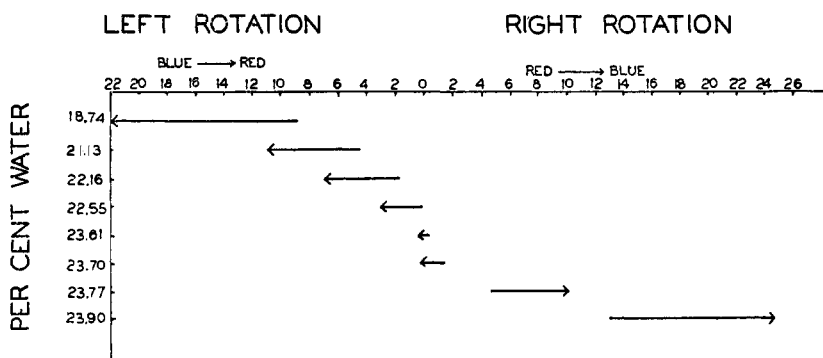


FIG. 17. Dispersion of nicotine-acetic acid (equimolecular solution) in water

A sample of nicotine which possessed the specific rotation $[\alpha]_D^{20} = -164^\circ$ gave, when dissolved in benzene, the following values (85):

PER CENT NICOTINE	$[\alpha]_D^{20}$	PER CENT NICOTINE	$[\alpha]_D^{20}$
84.36	-164.29°	19.00	-163.95°
48.02	-164.14	16.36	-163.88
25.47	-164.10	8.52	-163.67

There is here but a very small change in the specific rotation, amounting to only 0.2 per cent with change in concentration.

In like manner (see table 23) the specific rotation of nicotine remains almost unchanged when it is dissolved in ether or acetone, while with aniline or toluidine as solvent there is a slight decrease, to about $[\alpha]_D^{20} = -156.5^\circ$. The decrease in ethyl alcohol or propyl alcohol is somewhat more, while in water it is very marked. Tables 26, 27, and 28 present data for the rotatory dispersion of nicotine in various solvents. The data of table 28 are shown in graphic form in figure 18.

Milward-Liquier and Descamps (141) conclude that aqueous nicotine solutions to which hydrochloric acid has been added until one of the basic functions has been completely neutralized behave like mixtures of

two optically active constituents, the dispersions of which are different and the proportions of which vary with the pH of the solution. One of the

TABLE 26
Specific rotation of nicotine in various solvents (268)

SOLVENT	PER CENT NICOTINE	$[\alpha]_D^{20}$
Water.....	14.095	-70.0°
Methyl alcohol.....	11.920	-118.0
Ethyl alcohol.....	10.518	-131.0
Isobutyl alcohol.....	10.732	-141.0
Benzene.....	9.647	-160.0
Chloroform.....	7.824	-157.0
Ethylene bromide.....	4.676	-174.0
Aniline.....	7.995	-156.0

TABLE 27
Rotatory dispersion of nicotine at 20°C. (129)
Specific rotation $[\alpha]_{5461} = -204.14^\circ$

VISIBLE SERIES		PHOTOGRAPHIC SERIES	
λ in Å.	α ($l = 6$)	λ in Å.	α ($l = 1$)
Li 6707.8	-756.89°	Fe 4272	-399.5°
Cd 6438.5	-832.25	Fe 4251	-405.8
Zn 6362.3	-855.35	Fe 4202	-419.8
Li 6103.7	-943.75	Fe 4199	-2531.9*
Na 5892.9	-1025.71	Fe 4176	-428.0
Cu 5782.1	-1074.81	Fe 4145	-438.5
Hg 5780.1	-1076.14	Fe 4132	-442.9
Cu 5700.2	-1112.92	Fe 4072	-462.8
Hg 5460.7	-1237.38	Fe 4062	-2804.4*
Cu 5218.2	-1387.58	Fe 4046	-472.7
Ag 5209.0	-1394.17	Fe 4005	-488.7
Cu 5153.3	-1432.91	Fe 3967	-504.0
Cu 5105.5	-1467.84	Fe 3953	-510.5
Cd 5085.8	-1482.41	Fe 3903	-531.3
Zn 4810.5	-1717.49	Fe 3887	-539.4
Cd 4799.9	-1727.78		
Zn 4722.2	-1806.25		
Hg 4358.3	-2266.31		

* $l = 6$.

constituents is the non-electrolytically dissociated molecule and the other is the optically active ion. These conclusions hold both in the visible and in the ultraviolet range.

Tate and Warren (235) find that existing data concerning the optical rotation of nicotine in aqueous solution are conflicting. The earlier work of Popovici (187) and of Pfibram (192) indicates irregularities in the specific rotation at low concentrations. Jephcott (98), in the course of an examination of solutions ranging in concentration from 2.5 to 100 per cent, found a minimum value of $[\alpha]_D^{20} = -78.7^\circ$ at 10 per cent, the value rising

TABLE 28

Rotatory dispersion of nicotine at 20°C. in (a) acetone, (b) water, (c) acetic acid, and (d) butyric acid (129)

(a) 28.7734 G. OF NICOTINE PER 100 G. OF SOLUTION		(b) 25.4983 G. OF NICOTINE PER 100 G. OF SOLUTION		(c) 15.5230 G. OF NICOTINE PER 100 G. OF SOLUTION		(d) 14.0793 G. OF NICOTINE PER 100 G. OF SOLUTION	
λ in Å.	α ($l = 4$)	λ in Å.	α ($l = 6$)	λ in Å.	α ($l = 6$)	λ in Å.	α ($l = 4$)
Li 6708	-126.03°	Li 6708	-91.83°	Li 6708	+28.97°	Li 6708	+16.54°
Zn 6363	141.81	Cd 6438	101.17	Cd 6438	31.76	Zn 6363	18.61
Li 6104	156.81	Zn 6363	104.23	Zn 6363	32.54	Li 6104	20.37
Na 5893	169.81	Li 6104	115.04	Li 6104	35.63	Na 5893	21.90
Cu 5782	177.87	Na 5893	125.37	Na 5893	38.60	Hg 5780	22.83
Hg 5782	178.06	Cu 5782	131.35	Hg 5780	40.31	Cu 5700	23.67
Cu 5700	184.17	Hg 5780	131.53	Cu 5700	41.59	Hg 5461	25.89
Hg 5461	204.48	Cu 5700	136.20	Hg 5461	45.89	Cu 5218	28.64
Cu 5218	228.89	Hg 5461	151.95	Cu 5218	50.90	Cu 5153	29.53
Cu 5153	236.61	Cu 5218	171.03	Cu 5153	52.22	Cu 5105	30.20
Cu 5103	242.28	Cu 5153	176.86	Cu 5105	53.35	Zn 4810	34.61
Zn 4811	283.11	Cu 5106	181.36	Cd 5086	53.78		
Zn 2722	297.16	Cd 5086	183.21	Zn 4811	60.77		
Hg 4358	371.56	Zn 4810	213.65	Zn 4722	63.53	Li 4603	9.44
		Cd 4800	214.83	Zn 4680	64.80	Hg 4358	10.66
		Zn 4722	225.02				
		Hg 4358	285.03				
					α ($l = 1$)		
				Li 4602	11.21		
				Hg 4358	12.79		
				Fe 4281	13.28		
				Fe 4202	13.88		
				Fe 4187	14.00		
				Fe 4144	14.33		
				Fe 4132	14.41		

to $[\alpha]_D^{20} = -83.15^\circ$ at 2.5 per cent, which was the most dilute solution examined. Tingle and Ferguson (241) and Lowry and Lloyd (129) found that the optical rotation was directly proportional to the concentration.

Working with a polarimeter using "j" light, Tingle and Ferguson (241) carried out experiments which showed (*i*) that, for solutions containing between 4 and 0.37 per cent of nicotine, the rotation of aqueous nicotine

solutions is in simple inverse proportion to the concentration; (ii) that the presence of potassium hydroxide and potassium salts has no influence on the rotation of nicotine salts; (iii) that nicotine is not lost by vaporization when an acid solution of nicotine sulfate is evaporated.

In the determination of the rotation values of dilute aqueous nicotine solutions, nicotine which had been freshly distilled in a vacuum was brought to a standard dilution with pure distilled water free from ammonia and carbon dioxide; these solutions were subsequently diluted to lower concentrations. Three such standard solutions were prepared, and

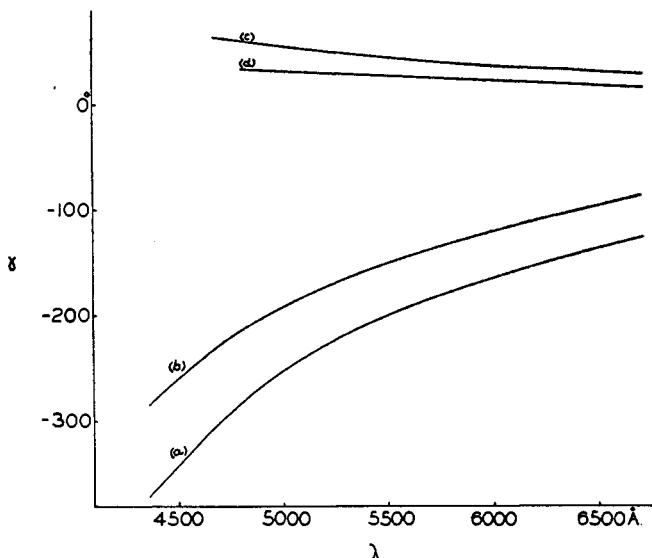


FIG. 18. Rotatory dispersions of nicotine at 20°C. Curve a, 28.7734 g. of nicotine per 100 g. of its solution in acetone; curve b, 25.4983 g. of nicotine per 100 g. of its solution in water; curve c, 15.5230 g. of nicotine per 100 g. of its solution in acetic acid; curve d, 14.0793 g. of nicotine per 100 g. of its solution in butyric acid.

measurements were made with a Hilger polarimeter and a Schmidt and Haensch saccharimeter. The readings were directly proportional to the concentration, thus confirming Tingle and Ferguson's data. The specific rotation was shown to be constant between 0 and 10 per cent, the values determined being $[\alpha]_D^{20} = -79.4^\circ$ and $[\alpha]_{5461}^{20} = -96.1^\circ$.

Figure 19 shows the relation between specific rotation and temperature through the range from -90° to 24°C . with wave length $\lambda = 546.1$. It seems that the specific rotation decreases with decreasing temperature very much more rapidly at the low temperatures than at ordinary temperatures. The liquid was very viscous at -90°C ., this being the lowest tem-

perature at which observations could be made with anything like the length of liquid column used.

A series of observations extending over a period of 2.5 hr. was made with wave length 546.1μ , while the temperature was gradually lowered from 20° to -45.3°C . The results were plotted in the curve as shown in figure

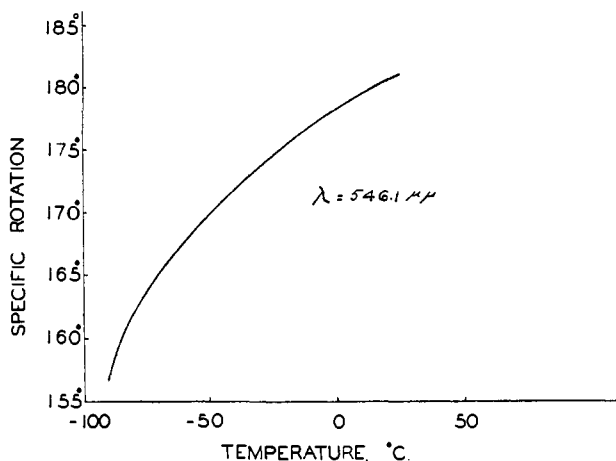


FIG. 19. Relation between specific rotation of nicotine and the temperature

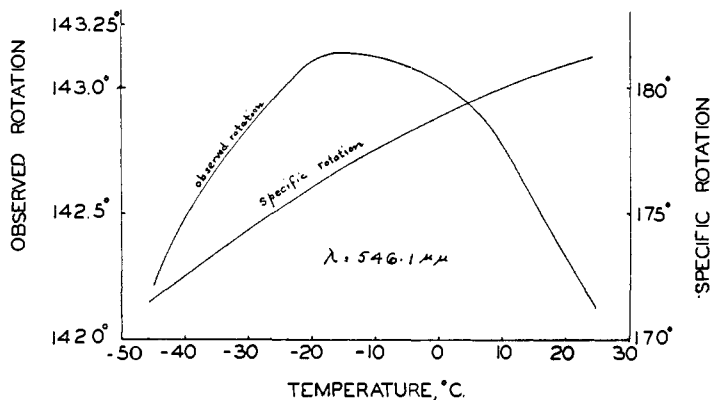


FIG. 20. Observed and specific rotations of nicotine

20 to such a scale as to show the temperature at which an apparent rotation is reached.

Each point plotted is the mean value for five readings of both rotation and thermal E.M.F. The specific rotation at the same temperatures was computed and the curve plotted to show the contrast between observed

rotation and specific rotation. The maximum observed rotation is at a temperature of approximately -15°C .

It is of interest to see graphically a comparison of the relative effects of temperature upon the rotation of different wave lengths. In figure 21 (upper curve) the rotations observed at 22.4°C . are plotted as abscissae and the decrease in the observed rotation at -80°C . as ordinates. In the same figure (lower curve), the specific rotations at room temperature are plotted as abscissae with the decrease in specific rotation, for the corresponding specific rotations at -80°C ., as ordinates. From the measurements with wave lengths at the central part of the spectrum it might therefore appear that the temperature effect is relatively the same for all wave

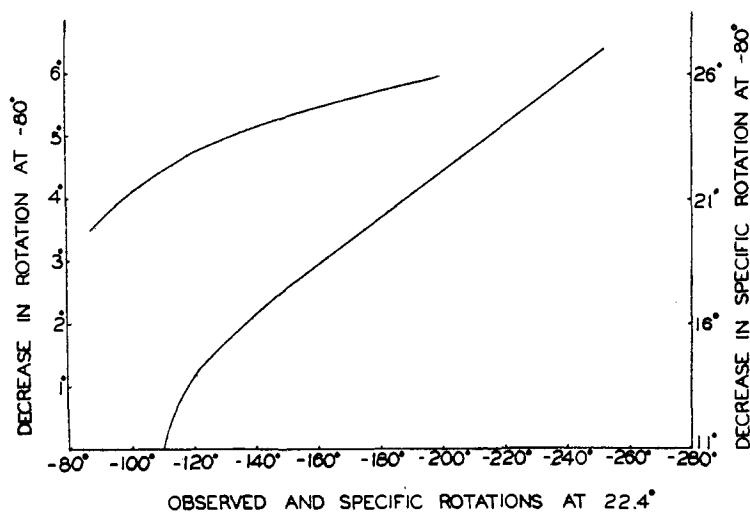


FIG. 21. Observed and specific rotations of nicotine at 22.4°C .

lengths, but the measurements with the longer wave lengths show greater relative decreases (142).

16. Study of anomalous rotatory dispersion (270)

Nicotine is levorotatory and its salts are dextrorotatory. Lowry and Singh (131) have shown that the alkaloid in the homogeneous condition at 20°C . exhibits simple rotatory dispersion in the negative region. Genari (69) observed that an equimolecular mixture of nicotine and glacial acetic acid, within certain limits of dilution with water, exhibits anomaly in the positive region. Nicotine salts are therefore assumed to be of relative configuration *d*.

The rotation of the base is due to the asymmetry of the α -pyrrolidine

carbon atom; in the salts, however, a new center, the asymmetric pyrrolidine nitrogen atom, is involved (125). No decision as to the configuration of the free base is at present possible, for the respective configurations and dominance of the two centers are unknown.

Patterson and Fulton (168) have shown that the rational zero (for nicotine and its sulfate) is 3° , and if this rotation could be realized for the green rays, the rotatory dispersion would be visibly anomalous in the positive region. But a deduction as to the relative configuration of the free base from the data given would require careful consideration of the occurrence and movement of maxima in the negative region in the temperature-rotation curves for the homogeneous base at high temperature, and similarly for the base in inert solvents, and also the construction of separate characteristic diagrams, as well as a composite one.

The fact that nicotine and its sulfate in various solvents fit on the same characteristic diagram suggests that the α -pyrrolidine carbon atom is of relative configuration *d*.

The variation of the diffusion coefficients for the extreme limits of concentration employed at 20°C . for nicotine was 0.456 to 0.273 for 0.1 *N* to 1 *N*. The mean value of the temperature coefficient of diffusion is about 0.016 (153).

17. Magnetic rotatory dispersion (127)

The magnetic rotatory dispersion of nicotine was measured with the same magnet and by the same methods as those of a long series of aliphatic compounds which had been examined by Lowry (124). Readings were made for twelve wave lengths in the visible spectrum.

The results as given in table 29 show: (i) the double deflection observed with a column 1 dm. long, after correction for the effect of the end plates; (ii) the values of Verdet's constant deduced from these readings; and (iii) the ratio of the rotation at any wave length to that at the wave length of the green (Hg) line. The observed ratio $\delta_{4358}/\delta_{6461}$ is 1.664.

18. Refractive dispersion (127)

Measurements of the refractive index of nicotine were made by Gifford and Lowry (72) by the hollow-prism method, but the scope of the work was limited by the strong absorption of light by the thick column of liquid in the prism. The observations were therefore confined to a range of wave lengths in the visible spectrum between 7685 and 4341 Å., although the absorption of the liquid does not become important before 3000 Å. in the ultraviolet. Since the refractive dispersion is most interesting in the immediate neighborhood of the absorption band, it was thought advisable to make a further series of measurements in the ultraviolet, by

the interferometric method which Lowry and Allsopp (126) have developed for measuring the refractive indices of thin films of liquid. Under these more favorable conditions the measurements have been extended to 2864 Å., i.e., within 200 Å. from the head of the absorption band, with a maximum molecular extinction coefficient $\log \epsilon = 3.43$ at 2650 Å. in cyclohexane. Measurements were also made, with an improved Pulfrich refractometer, of the refractive index for twenty-eight wave lengths in

TABLE 29

Magnetic rotatory power of nicotine at 20°C.

Double rotation, 2α , of water at 5461 Å. = 7.10°; Verdet's constant for water at 5461 Å. = 0.01534 min./cm. gauss

λ in Å.	2α (CORR.)	VERDET'S CONSTANT δ	$\frac{\delta}{\delta_{5461}}$	λ IN Å.	2α (CORR.)	VERDET'S CONSTANT δ	$\frac{\delta}{\delta_{5461}}$
		min./cm. gauss				min./cm. gauss	
Li 6707.86	7.60°	0.01643	0.593	Ag 5467.71	12.79°	0.02764	0.998
Cd 6438.47	8.47	0.01831	0.661	Hg 5460.73	12.82	0.02770	1.000
Zn 6326.35	8.85	0.01911	0.690	Ag 5209.04	14.21	0.03072	1.109
Li 6103.60	9.72	0.02100	0.758	Cd 4799.91	17.09	0.03689	1.332
Na 5892.62	10.53	0.02274	0.821	Li 4602.50	18.67	0.04033	1.456
Hg 5780.13	11.00	0.02379	0.859	Hg 4358.34	21.34	0.04609	1.664

TABLE 30

Refractive index of nicotine at 15°C. (72)

$[\alpha]_{5461}^{20} = -205^\circ$ in a 1-dm. tube

WAVE LENGTH	n	WAVE LENGTH	n
A' 7685 K α	1.52061	E 5270 Fe	1.53514
B' 7065 He	1.52294	F 4851 H β	1.54035
6708 Li	1.52452	Φ 4678 Cd	1.54317
C 6563 H α	1.52526	4471 He	1.54699
D 5893 Na	1.52939	4413 Cd	1.54808
A 5608 Pb	1.53177	G 4341 H γ	1.54935
5461 Hg	1.53291		

the visible spectrum. These are less exact than Gifford's measurements, since they are only valid to the fourth decimal place, but they are probably more trustworthy, by reason of a closer control of temperature and more recent purification of the material. These data are plotted in the curve shown in figure 22.

Tate and Warren (235), using the Zeiss immersion refractometer at 15.5°C., obtained the values shown in table 31 for nicotine-water solutions.

19. Absorption spectra (195)

The optical properties of nicotine appear to be controlled by two characteristic frequencies: the first corresponds to the familiar absorption band in the middle ultraviolet, with a maximum $\log \epsilon = 3.43$ at 2640 \AA . in cyclohexane; the second characteristic frequency is in the Schumann

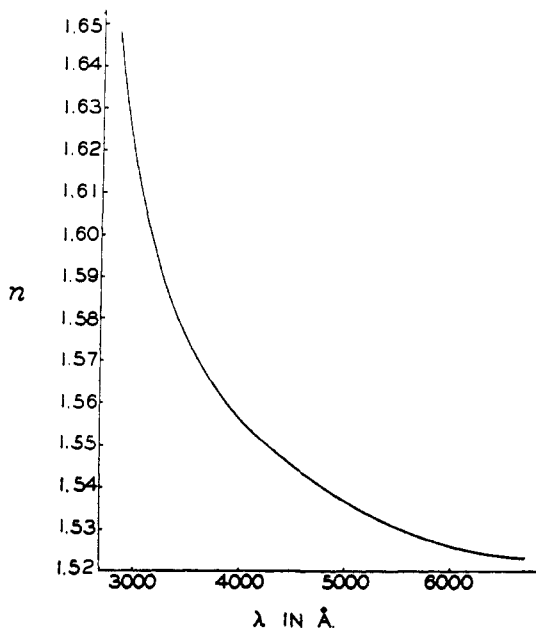


FIG. 22. Refractive indices of nicotine at 20°C.

TABLE 31

Refractive index of the system nicotine-water

CONCENTRATION, GRAMS OF NICOTINE PER 100 ML. OF SOLUTION	n	CONCENTRATION, GRAMS OF NICOTINE PER 100 ML. OF SOLUTION	n
2.652	1.33873	7.293	1.34817
3.646	1.34086	7.707	1.34906
4.580	1.34283	10.028	1.35384
5.574	1.34489	10.160	1.35403

region at 1326 to 1740 \AA . The position and magnitude of this absorption band have not been observed directly, since it lies beyond the limit of transmission of light by air or by quartz, but it appears to be far more intense than the bands which have been recorded in the more accessible part of the ultraviolet. Direct evidence of the existence of a second absorption band is provided by the development of a strong general absorp-

tion in all those derivatives of nicotine in which the pyridyl nitrogen is ionized, although it is not observed either in nicotine itself or in those derivatives in which only the pyrrolidyl nitrogen is ionized. This general absorption may represent the foot of the intense band in the Schumann region, but it might be due to a third absorption band in an intermediate position near the edge of the Schumann region.

The relative influence of these two absorption bands varies greatly in different optical properties and in different derivatives. The most remarkable fact is the dominance by the near ultraviolet band of the optical rotatory power of nicotine, which can be expressed very nearly by a single term of Drude's equation, with $\lambda_0 = 2450 \text{ \AA}$. (129). This predominance persists in chloronicotine and in methylnicotine (128), where both nitrogen atoms are tetravalent and neutral, as well as in nicotine isomethiodide (129) where the pyrrolidine nitrogen remains neutral, although the pyridyl

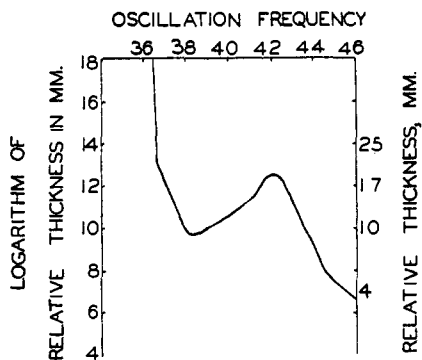


FIG. 23. Absorption of nicotine vapor: $N/1000$ solution of nicotine

nitrogen is ionized by the addition of a methyl radical. When, however, the pyrrolidyl nitrogen, which is attached directly to the asymmetric carbon atom, is ionized, the influence of the ultraviolet absorption band disappears abruptly.

Hartley (82) examined the absorption of a 1-mm. layer of a 10 per cent nicotine-alcohol solution and found that there was general absorption at about $\lambda 2800$; through a thickness of 5 mm. the rays were absorbed at about $\lambda 3132$, but no band was observed. In the author's experiments with $N/10$ solutions through a layer 2 mm. thick, the rays were absorbed at $\lambda 2800$, and through a layer 30 mm. thick at $\lambda 3050$; for $N/100$ solutions, through a 2-mm. layer, the rays were absorbed at $\lambda 2720$ and, through a 30-mm. layer, at $\lambda 2810$, and no band was observed. Upon the examination of $N/1000$ solutions, a band was discovered; its absorption curve has been represented in figure 23. The head of the band of nicotine, expressed in oscillation frequencies, is 3820.

20. *Selective solvent action of nicotine-water solutions on a third substance*

The selective solvent action of the system nicotine-water is shown in table 32.

TABLE 32

Selective solvent action of the system nicotine-water (271)

40 cc. of nicotine in 100 cc. of water; density, 1.007; freezing point of solution, $-2^{\circ}\text{C}.$;
20 cc. of solution used as solvent

THIRD SUBSTANCE USED	w WEIGHT OF THIRD SUBSTANCE USED	e° ELEVATION OF THE FREEZING POINT
	<i>grams</i>	$^{\circ}\text{C}.$
Benzene	0.0770	0.0300
	0.1385	0.0480
	0.2130*	0.0720
	0.2977	0.0810
	0.3185	0.0830
Carbon tetrachloride.	0.0965	0.0100
	0.2020	0.0220
	0.2985*	0.0270
	0.3995	0.0300
	0.5250	0.0310
Chloroform	0.0795	0.0230
	0.1640	0.0360
	0.3020	0.0750
	0.4070*	0.0950
	0.5220	0.1150
	0.6536	0.1260
Methyl salicylate.	0.0655	0.0430
	0.1430	0.0630
	0.2145	0.1080
	0.2995*	0.1250
	0.3920	0.1250
	0.5070	0.1250
Bromonaphthalene.	0.0460	0.0450
	0.0975*	0.0600
	0.1375	0.0680
	0.1780	0.0700
	0.2170	0.0700

* The system separates into two liquid phases.

The depression of the freezing point of a solvent produced by the addition of a solute may be diminished by the subsequent addition of a third substance; the diminution may be due to various causes based on the decrease

in the concentration of the solute molecules or to complexes in the solution. When a solute is added to a binary mixed solvent in only one of whose components it is soluble, the freezing point of the constituent in which it is insoluble is always raised. When the concentration of the semi-solute is plotted against the elevation of the freezing point, a continuous curve results with a break at the point of formation of two liquid phases. It thus seems evident that a semi-solute when dissolved in a mixed solvent forms solvents with the constituent in which it is soluble, and as a result raises the freezing point and the vapor pressure of the other constituent.

21. Inhibition phenomena

Rane and Prasad (196) concluded that the effect of nicotine in inhibiting the evolution of hydrogen by the action of hydrochloric acid (see table 33) is somewhat analogous to the phenomenon of passivity.

TABLE 33

Effect of 0.02 g. of nicotine on the rate of solution of iron in hydrochloric acid (196)

TIME	VOLUME OF HYDROGEN EVOLVED	
	Without the alkaloid	On the addition of nicotine
<i>hours</i>	<i>cc.</i>	<i>cc.</i>
1	91.7	
2	143.6	
3	177.4	91.2
4	224.3	109.8
5	286.7	110.4
6	248.4	133.0

G. CHEMICAL PROPERTIES

That nicotine is a feeble base is shown by the fact that dilute aqueous solutions containing the alkaloid and hydrochloric or acetic acid in molecular proportions exhibit a contraction on mixing instead of the augmentation of volume noticed with strong bases and acids. Even when pure nicotine and pure liquid acetic acid are mixed in molecular proportions, a contraction of about 2.5 per cent in volume occurs (146).

Nicotine is a diacid base, since it forms well-crystallized salts with one and two equivalents of acids. It combines with two molecules of an alkyl halide, for example, with two of methyl iodide, forming a methiodide from which moist silver oxide separates nicotine methyl hydroxide; by this behavior nicotine shows itself to be a ditertiary base (7).

1. Oxidation

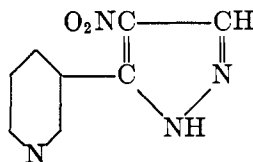
(a) *Autooxidation.* Ciamician and Silber (41) reported the autooxidation of nicotine under the influence of light. Their experiments were carried out as follows: A solution of 12 g. of nicotine in 100 cc. of water was placed in each of three 5-liter flasks with oxygen and left in the light for 6 months. The solutions became a deep yellow in color and faintly acid; the oxygen was almost completely used up. After dilution of the contents of the flasks, an excess of barium carbonate was added and the product was distilled with steam. Both the distillate and the residue were examined. In the distillate were found unchanged nicotine, a small quantity of ammonia, and methylamine. From the residue there was isolated a large quantity of a product having the same composition as the oxynicotine of Auerbach and Wolffenstein (6) and of Pinner and Wolffenstein (183, 185, 186) but having a different melting point for its picrate and nicotinate. Ciamician and Silber concluded that the autooxidation of nicotine under the influence of light furnishes, besides a tar-like mass as the principal product, oxynicotine, which, by further oxidation, yields nicotinic acid and methylamine.

(b) *Oxidation by ultraviolet light.* Custis (50) found, as the result of studying the effect of light on nicotine solutions, that (i) there is a change in nicotine content when solutions of nicotine are exposed to sunlight; (ii) this change is more marked in the presence of air, a fact which indicates an oxidation process; (iii) the power of causing the change is limited to light of short wave lengths; (iv) ultraviolet light produces a change in the nicotine solutions; (v) the alkalinity of nicotine solutions does not affect the reactions due to light. Pacini and McGuigan (163) calculated that, for each nicotine molecule, the loss of toxicity, the development of a yellow color, the loss of basicity, and, finally, the development of acidity require roughly 1.9×10^{-16} gram-calories of radiant energy. The yellow color is believed by Gant (63) to be due to an oxidation product of nicotinic acid and is destroyed by further irradiation. When all of the titratable basicity of nicotine has been destroyed by irradiation there still remains unaltered nicotine in the form of its nicotinate or malonate. The acidity produced by irradiation is destroyed by further irradiation, with the production of a colorless neutral product containing no nicotine. Destruction of the pyrrolidyl ring destroys the vaso-constricting power, and the resulting products have no perceptible pharmacological action; this destruction may be avoided by excluding air, light, or both.

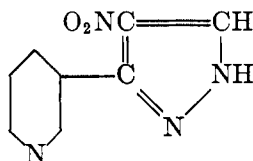
(c) *Oxidation by platinized asbestos.* The researches of Zelinskii (277) have shown that it is an easy matter to dehydrogenate a cyclohexane ring catalytically, but that a cyclopentane ring cannot be dehydrogenated in

this way. When nicotine is distilled slowly through a tube containing 2 g. of 30 per cent platinized asbestos and heated to 290–350°C., it is largely dehydrogenated to 3,2'-nicotyrine. The most favorable temperature was found to be 320°C.; isomerization did not occur, only unchanged nicotine and 3,2'-nicotyrine being obtained. After one passage of the nicotine through the tube, 73 per cent of it was transformed into 3,2'-nicotyrine; on repeating the dehydrogenation with the reaction product and with freshly platinized asbestos, an almost theoretical yield of 3,2'-nicotyrine was obtained. It thus appears that the pyrrolidyl ring can be dehydrogenated catalytically (263).

(d) *Oxidation by acids.* Nicotinic acid was first obtained by Huber (92) by oxidizing nicotine with chromic acid. Cahours and Étard (27) obtained what they called carboxypyridenic acid when nicotine was oxidized with nitric acid. Pictet and Rotschy (176) and Weidel (258) obtained nicotinic acid by oxidizing nicotine with nitric acid. In the oxidation of nicotine by nitric acid by the method of McElvain and Adams (133), Gough and King (76) found that there was formed, besides nicotinic acid, about 5 per cent of a by-product, the properties of which agreed with those of a 4-nitro-5-(3-pyridyl)pyrazole



or its tautomeric form (105).



Lund (132) determined the melting point as 220°C. and ascribed to the substance the structure of 3-nitro-5-(3-pyridyl)pyrazole, thus changing the position of the nitro group. By the oxidation of nicotine with chromic acid a well-characterized amino acid was obtained by Huber (91).

(e) *Oxidation by hydrogen peroxide.* It was shown by Pinner (183) that oxynicotine is not the primary product of the oxidation of nicotine with hydrogen peroxide, but that it is formed by condensation from an aldehyde first formed. Pinner and Wolffenstein (184) mixed nicotine with platinum sponge, then treated it with hydrogen peroxide and allowed the whole to stand for several weeks. The liquid was then evaporated at 40–50°C.

in a vacuum and extracted with alcohol. After the latter had been removed in a vacuum, the residue was allowed to remain in a desiccator until it solidified to a crystalline, deliquescent mass; the product was a base having the composition $C_{10}H_{12}N_2O$ and may be termed nicotine-*N*-oxide. Preiss (190) has shown that the action of hydrogen peroxide on nicotine solutions is strongly dependent on the hydrogen-ion concentration. The decomposition of nicotine is greatest in weakly alkaline solution, while in acid or strongly alkaline solution the substance is relatively resistant to oxidation by hydrogen peroxide. The addition of weak ammonia increases considerably the speed of oxidation of nicotine by hydrogen peroxide; the ammonia possibly exercises a catalytic action also.

(f) *Oxidation by potassium permanganate.* Laiblin (116) and Oliveri (154) obtained nicotinic acid when nicotine was oxidized by means of potassium permanganate.

(g) *Oxidation by potassium ferricyanide.* Cahours and Étard (29) prepared 3,2'-nicotyrine by oxidizing nicotine with potassium ferricyanide, but when nicotine was dissolved in dilute potash and then treated with the ferricyanide, the product was isodipyridine, $C_{10}H_{10}N_2$ (28).

(h) *Oxidation by silver oxide.* Blau (21) obtained 3,2'-nicotyrine by oxidizing nicotine with silver oxide.

2. Reduction

The reduction of nicotine by means of sodium and alcohol was first studied by Liebrecht (121) and later by Oliveri (154); both isolated a basic product which they called β,β -dipiperidyl, since they regarded nicotine as hexahydrodipyridyl. Blau (20) made a more complete investigation of the reaction and showed that Liebrecht's base was not dipiperidyl but a mixture of two amines, which he called hexahydronicotine and octahydronicotine. Pinner (179) also studied the reduction of nicotine with sodium and alcohol and reported the isolation mainly of hexahydronicotine, whereas Overhoff and Wibaut (162) obtained chiefly the octahydro compound. Windus and Marvel (265), in attempting to carry out the above synthesis, reduced nicotine with sodium and alcohol, and reduced nicotine hydrochloride with hydrogen under pressure, using the platinum oxide-platinum black catalyst of Adams and Shriner (1). They found that the reduction of nicotine by sodium and alcohol produced approximately 5 parts of hexahydronicotine to 1 part of octahydronicotine, while the catalytic reduction of the hydrochloride produced 1 part of hexahydronicotine to 3 parts of octahydronicotine.

Harlan and Hixon (81), selecting the most feasible method for the reduction of nicotine, utilized platinum oxide-platinum black and hydrogen, as used by Smith (216) on the dipyridyls, by Hamilton and Adams (79)

on the pyridine and quinoline derivatives, and by LaForge (115) for the reduction of metanicotine to dihydrometanicotine. Contrary to expectation, in the catalytic reduction of nicotine, rupture of the pyrrolidine ring takes place simultaneously with the hydrogenation of the pyridine ring. Complete reduction, with the absorption of 3.7 moles of hydrogen to each mole of nicotine hydrochloride, gives a mixture containing 25 per cent of hexahydronicotine hydrochloride and 75 per cent of octahydronicotine hydrochloride. If the reaction is interrupted at the point where 3 moles of hydrogen have been absorbed for each mole of nicotine hydrochloride (the theoretical amount for reduction to hexahydronicotine), the resulting mixture consists of 19 per cent hexahydronicotine hydrochloride, 57 per cent octahydronicotine hydrochloride, and 21 per cent unchanged nicotine hydrochloride. Hexahydronicotine is the sole product obtained by the reduction of nicotine with sodium amalgam (180).

3. *Effect of ultraviolet light*

Wakeham and Tracy (254) found that the exposure of nicotine to ultraviolet light produces a 70 to 75 per cent reduction of its toxicity in about 75 min., followed by a return almost to the original toxicity. Wakeham and Johnson (253) later found that no reasonable amount of ultraviolet irradiation will destroy the toxicity of nicotine, thus confirming the results of the earlier investigators.

4. *Effect of heat*

If nicotine vapor is passed over red-hot porcelain it is partly decomposed (about 20 per cent), yielding a gaseous mixture of hydrogen with paraffins and olefins, and a liquid product containing pyridine, picoline, collidine, and a new basic substance boiling at temperatures above 250°C. (28); the collidine boiled at 170°C. and showed a great tendency to form resinous polymerides (30).

Oliveri (154) obtained methylamine and a small proportion of nicotinic acid when nicotine was heated at 250–280°C. in a closed tube for about 24 hr.

5. *Reaction with elements*

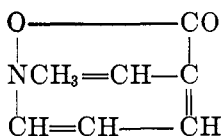
(a) *Reaction with sulfur.* Cahours and Étard (27) found that, when 5 parts of nicotine were heated to 140°C. with 1 part of sulfur, hydrogen sulfide was given off and continued to be liberated as the temperature rose to 155°C. The perfectly fluid mass assumed a chrome-green color at 160–170°C. When it was allowed to stand for some days, yellow prismatic crystals separated in abundance. These, after being purified by washing with cold alcohol and then recrystallizing from boiling alcohol, had the composition $C_{20}H_{18}N_4S$. Morton and Horvitz (143), by the dehydrogena-

tion of nicotine by sulfur in boiling toluene for 50 hr., obtained hydrogen sulfide, nicotyrine, and thiodinicotyrine.

(b) *Reaction with selenium.* When 100 parts of nicotine and 20 parts of selenium are heated together for some time at 240°C. and then briskly boiled, the condensing tube becomes filled with white lamellar crystals. When the vapor is heated nearly to redness, it is decomposed into ammonia and selenium. As soon as the crystals cease to form, the heating is discontinued, and the liquid is decanted from the undissolved selenium and distilled. Oily products pass over above 180°C., and a tarry residue is left in the retort. These products are freed from selenium by adding a solution of soda and distilling in a current of steam, the receiver being changed as soon as the distillate becomes distinctly milky. The oily substances are separated from the water by means of ether, and again distilled. In this way hydrocollidine is obtained. The other product of the action of selenium is isodipyridine; it is probable that the selenium acts on the nicotine in the same way as sulfur, removing the hydrogen as hydrogen selenide and forming isodipyridine. The hydrogen selenide then combines with unaltered nicotine, forming a hydroselenide which removes one atom of nitrogen in the form of the ammonia compound described above. When nicotine hydroselenide is subjected to dry distillation, it yields the same products as those obtained by the action of selenium on nicotine (30).

(c) *Reaction with halogens.* (i) *Iodine.* At the ordinary temperature the action of iodine on nicotine in ether or chloroform solution results in the replacement of hydrogen by iodine and the formation of periodides which are insoluble in the menstruum. The composition of these products is influenced by the relative amounts of iodine and nicotine present, as well as by the proportion of the solvent, and as these conditions are continuously varying throughout the period of reaction, various periodides of both iodonicotine hydroiodide and of nicotine hydroiodide are precipitated. Basic compounds are obtained at the same time. The results tend to support the evidence already obtained by the titration of nicotine with acids in the presence of a variety of indicators: namely, that this alkaloid normally functions as a monacid base (106).

The formation of two isomeric quaternary iodides from nicotine proves that the two nitrogen atoms of this alkaloid are both tertiary. When the isohydroxide, corresponding to the isomethiodide, is oxidized by potassium permanganate, it is converted into trigonelline (the methylbetaine of nicotinic acid).



This reaction shows that the two methiodides have the following formulas: $C_5H_4N-C_4H_7N(CH_3)_2I$ (methiodide) and $C_5H_4NCH_3I-C_4H_7NCH_3$ (isomethiodide) (174).

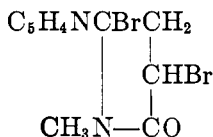
(ii) *Chlorine*. Geuthen and Hofacker (71) report the formation of a beautiful crystalline chlorine compound by the action of gaseous chlorine on nicotine hydrochloride.

(iii) *Bromine*. By the action of bromine and water on nicotine in sealed tubes at 120–150°C., Laiblin (117) obtained a crystalline compound similar to that obtained by Cahours and Étard (30), which is probably $C_{10}H_{12}Br_2N_3 \cdot HBr$. Bromonicotine is obtained by adding a mixture of 4 parts of nicotine and 5 parts of water in small quantities at a time to 12.5 g. of bromine in 7.5 cc. of water, the temperature not being allowed to rise above 50–60°C. The whole is warmed on a water bath until the oil formed is dissolved, and then 15–18 g. of water is added; on cooling a crystalline substance separates.

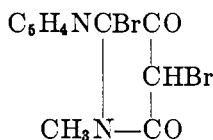
By the addition of bromine to free nicotine, large quantities of resinous products are formed. The action of bromine on a solution of nicotine in acetic or hydrobromic acid gives rise at first to an oily addition product which is undoubtedly a perbromide and from which the bromine is eliminated by treatment with sulfurous acid. In acetic acid solution the reaction quickly goes further; hydrogen bromide is formed, and the product contains the two compounds $(C_5H_4N)_2Br_2$ and $(C_5H_4N)_2Br_2O_2$; the former compound yields the well-crystallized perbromide, $(C_5H_4N)_2Br_2 \cdot HBr$, described by Huber (90) and by Cahours and Étard (29). The perbromide is obtained by adding 3.5 to 4 parts of bromine, dissolved in 4 to 5 parts of acetic acid, to a solution of nicotine in 5 to 6 parts of acetic acid. It crystallizes after 2 days in monosymmetric, chrome-red scales or flat, yellowish red needles. By treating the perbromide with ammonia the free base, dibromodihydronicotine, is obtained. Dibromodioxidyhydronicotine hydrobromide is obtained by heating nicotine with aqueous hydrobromic acid and bromine in a sealed tube for 10 to 12 hr. on a water bath. It crystallizes from water in slender white needles or in colorless, lustrous, flat prisms.

The two compounds dibromocotinine and dibromoticonine are obtained by the action of bromine on nicotine; the former is obtained as the perbromide by the addition of bromine to an aqueous solution of nicotine hydrobromide. The free base is best prepared by treating the perbromide with sulfurous acid and then adding potassium carbonate. It crystallizes from dilute alcohol in beautiful colorless prisms. The hydrochloride crystallizes in needles and turns blue on heating.

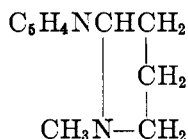
Pinner (179) assigns to dibromocotinine the constitution



and to dibromoticonine the constitution



Thence he deduces for nicotine the constitution



6. Reaction with hydrogen halides and halogen acids

With hydrogen chloride nicotine forms $\text{C}_{10}\text{H}_{14}\text{N}_2 \cdot 2\text{HCl}$, nicotine dihydrochloride. This salt forms deliquescent crystals which are very readily soluble in water and alcohol and insoluble in ether (11). It decomposes upon the evaporation of its aqueous solution (181).

Nicotine yields well-characterized tetrachloroiodides when its solution in concentrated hydrochloric acid is added to an excess of a solution of tetrachloroiodic acid. *N,N*-Dimethylnicotine bistetrachloroiodide separates from boiling glacial acetic acid in fine yellow needles, melting at 145°C . (34). Nicotine tetrachloroiodide separates quantitatively as beautiful orange prisms when a solution of nicotine in hydrochloric acid is added to a similar solution of iodine trichloride (33).

$2\text{C}_{10}\text{H}_{14}\text{N}_2 \cdot 3\text{I}_2 \cdot 2\text{HCl}$ is obtained as beautiful bright ruby-red plates by saturating a dilute alcoholic solution of nicotine iodide with hydrochloric acid. $2\text{C}_{10}\text{H}_{14}\text{N}_2 \cdot 3\text{I}_2$ is prepared by bringing together ether solutions of nicotine and iodine and evaporating the ether; it forms beautiful ruby-red crystals (90).

Nicotine dihydroiodide, $\text{C}_{10}\text{H}_{14}\text{N}_2 \cdot 2\text{HI}$, formed by the direct action of hydrogen iodide on nicotine, crystallizes in long colorless needles melting at 195°C . When boiled with nicotine in alcoholic solution it is converted into the hydroiodide, which is a pale yellow, uncrystallizable mass (174).

Étard (60) heated 5 g. of nicotine with 5 g. of red phosphorus and 60 g.

of fuming hydrogen iodide in a sealed tube at 260–270°C. for 10 hr.; hydrogen was liberated. The crystalline contents of the tube, consisting probably of a periodide, were treated with potash, and the liberated oily bases were fractionated. The products thus obtained in small quantities were hydrocollidine and hydronicotine.

7. Reaction with acids

(a) *Benzoic acid.* Nicotine is attacked with some difficulty when boiled with benzoic acid; it yields partly the racemized original material and a non-separable mixture of benzoynornicotine and benzoymetanicotine. When nicotine is gently boiled with benzoic acid two reactions take place: (i) opening of the ring and addition of an acid residue to form the compound $C_8H_4NCH(OH)CH_2CH_2CH_2NCH_3R$ ($R =$ acyl radical), which, by loss of water, gives the *N*-acylmetanicotine, and (ii) the normal formation of acylnornicotine (24).

(b) *d-Camphoric acid.* When nicotine and *d*-camphoric acid are heated together at 250°C., nicotine camphorate is formed (65).

(c) *Tartaric acid.* When a hot concentrated alcoholic solution of tartaric acid is added to nicotine, there soon separate white crystalline tufts of nicotine acid tartrate (55). The neutral salt of nicotine and *d*-tartaric acid, $C_{10}H_{14}N_2 \cdot C_4H_6O_6 \cdot 2H_2O$, crystallizes as needles. Its water of hydration does not disappear in a vacuum over concentrated sulfuric acid, but at 100°C. the salt gives off not only water of hydration but also nicotine (178). The acid salt of nicotine and *d*-tartaric acid forms prisms (from warm water) (171, 178).

(d) *Oxalic acid.* When the calculated quantity of oxalic acid is added to nicotine the normal oxalate is formed, but on the addition of excess oxalic acid to the normal salt the tetraoxalate is formed as nacreous lamellae. When the anhydrous salt is heated it melts at 110°C. and begins to decompose with violent evolution of gas at 113.5°C.; at 160°C. it yields the normal oxalate, and at 250°C. pure nicotine.

(e) *The lower fatty acids.* Gendre and Bary (68) made nicotine salts by the action of nicotine on acids such as formic, acetic, or lactic or by a double decomposition reaction between a nicotine salt and an alkali formate, acetate, or lactate. Gendre (66) obtained organic salts of nicotine by bringing nicotine and an organic acid such as caprylic acid into intimate contact. The salts dissolve in water and have insecticidal properties. Gendre and Bary (67) obtained British patent 446,368 (April 29, 1936) for the preparation of salts of nicotine from formic, acetic, lactic, etc. acids by the direct reaction between the acid and nicotine; these salts are commercially important on account of their insecticidal or anticryptogamic properties.

(f) *Acetic anhydride*. When nicotine is heated to 150°C. with acetic anhydride, it is converted into diacetylnicotine; this is a syrupy liquid which boils, with partial decomposition, at about 330°C. and is not affected by alkalis (61). When nicotine is heated with acetic anhydride at 170°C. for 10–12 hr., it forms acetylmetanicotine (182).

(g) *Bromoplatinic acid*. Nicotine bromoplatinate is formed by dissolving nicotine in an excess of dilute hydrobromic acid and treating the resulting solution with platinic chloride (259). Ortigosa (161) obtained nicotine platinic chloride by adding hydrochloric acid to a solution of platinic chloride in nicotine until it was neutral.

(h) *Silicotungstic acid*. North and Beal (151) obtained nicotine silicotungstate by dissolving nicotine in hydrochloric acid and then adding an excess of silicotungstic acid; the liquid, when heated to boiling and allowed to cool, gave a white crystalline product and not a salmon-colored one as described by Bertrand (16). Bertrand and Javillier (17) obtained the silicotungstate as a pinkish white salt by adding potassium silicotungstate to nicotine tartrate dissolved in water slightly acidified with hydrochloric acid (18). Heiduschka and Wolf (83) found that nicotine forms the compound $\text{SiO}_2 \cdot 12\text{WO}_3 \cdot 2\text{H}_2\text{O} \cdot 2\text{C}_{10}\text{H}_{14}\text{N}_2 \cdot x\text{H}_2\text{O}$ with silicotungstic acid and the compound $2[\text{P}(\text{W}_2\text{O}_7)_6]\text{H}_7 \cdot 3\text{C}_{10}\text{H}_{14}\text{N}_2$ with phosphotungstic acid (84). Tilici and Crestea (239) prepared the salt $2\text{C}_{10}\text{H}_{14}\text{N}_2 \cdot \text{H}_3[\text{Si}(\text{W}_2\text{O}_7)_6] \cdot x\text{H}_2\text{O}$ from nicotine and silicotungstic acid. Klyachkina, Strugatzkii, and Zilberg (108) found that nicotine combines with silicotungstic acid in the ratio of 1:2.

(i) *Nitric acid*. Nicotinic acid nitrate (pyridine-3-carboxylic acid nitrate) is prepared from nicotine and nitric acid; the salt contains one molecule of water of crystallization and melts at 190–192°C. (133).

(j) *Molybdic acid*. Nicotine ammonium molybdate is prepared by adding to 400 cc. of a 20 per cent solution of ammonium molybdate 320 cc. of a 10 per cent solution of acetic acid and 100 cc. of a 10 per cent solution of nicotine. The mixture is shaken several times and then rapidly filtered; the solid is washed successively with water, alcohol, and ether, and then dried at 48–50°C. It forms white microscopic prisms, which are insoluble in water (139).

(k) *Oleic acid, etc.* Hoyt (89) prepared nicotine oleate, coconate, and castorate by combining nicotine with dry oleic acid and with the mixed fatty acids in edible grades of coconut oil and castor oil.

(l) *Picric, picrolonic, and styphnic acids*. One mole of nicotine unites with 2 moles of picric acid to form a dipicrate, $\text{C}_{10}\text{H}_{14}\text{N}_2 \cdot 2\text{C}_6\text{H}_3\text{O}_7\text{N}_3$. This dipicrate is obtained as yellow needles, which melt at 218°C. (222); it is only slightly soluble in cold water but easily soluble in hot water (184). Nicotine picrolonate is obtained as an amorphous precipitate. Nicotine

styphnate, which is obtained as short blunt needles, melts with sublimation at 170–188°C. or at 194–195°C. (111).

(m) *β -Phenylpropionic acid*. When nicotine is boiled with β -phenylpropionic acid, the β -phenylpropionyl derivatives of nornicotine and metan nicotine are formed (24).

8. Organic derivatives

(a) *Methyl iodide*. Nicotine reacts readily with methyl iodide, producing methylnicotine, a yellow, translucent solid which dissolves in warm absolute alcohol (174, 234); its melting point is 85°C. (101). Stahlschmidt (234) prepared nicotine dimethiodide, which crystallizes in compact, light yellow prisms. Nicotine methiodide is obtained by treating nicotine with methyl iodide in mole proportions in methyl alcohol solution (174).

(b) *Ethyl iodide*. Nicotine reacts readily with ethyl iodide, yielding a yellow translucent solid which dissolves in warm absolute alcohol to form a deep brown solution (152).

(c) *Amyl iodide*. The iodide of nicotine isoamylate is prepared by heating amyl iodide and nicotine in a sealed tube on a water bath for several days (234).

(d) *Aldehydes*. (i) *Formaldehyde*. When treated with a drop of 30 per cent formaldehyde (free from formic acid) and a drop of concentrated nitric acid, nicotine gives a rose-red solution. As little as 0.5 mg. nicotine will show the reaction. Too much formaldehyde must not be added, nor must the mixture be warmed, as in either case explosive decompositions will occur (205). Reichard (199) found that, when a trace of nicotine is added to a 40 per cent solution of formaldehyde, there is immediately produced a yellow coloration which, upon the addition of a drop of concentrated sulfuric acid, changes to a color similar to that of a dilute solution of cobalt nitrate. If a trace of nicotine is mixed with one drop of 30 per cent formaldehyde, there is formed after some hours a solid residue which gives an intense rose coloration when touched with a drop of strong nitric acid; if resinous matter is present, a blood-red color appears. After some time, the color changes to green. A more permanent color is obtained when pure formic acid is used instead of formaldehyde (206).

(ii) *p-Dimethylaminobenzaldehyde*. A few crystals of *p*-dimethylaminobenzaldehyde dissolved in a drop of fuming hydrochloric acid and brought into contact with a drop of an aqueous solution of nicotine forms a pink and then a reddish-violet zone at the line of contact; finally the whole liquid becomes reddish violet. The coloration increases in intensity and is permanent for 10 to 24 hr. (247).

(e) *Pyridine and α -picoline*. In the reaction of nicotine with pyridine and α -picoline, carbon dioxide is liberated and benzylpyridinium chloride, benzylpicolinium chloride, and benzylnicotinium chloride are formed (256).

(f) *Benzyl chloride and iodide.* With benzyl chloride and nicotine, the monobenzyl- or dibenzyl-nicotinium compound is obtained, according to the proportions taken (256). A similar reaction occurs when benzyl iodide is used.

9. Inorganic derivatives

(a) *Mercury compounds.* (i) *Mercurous chloride.* Nicotine mercurous chloride is prepared by adding a solution of nicotine hydrochloride to a saturated solution of mercurous chloride until the precipitate formed no longer dissolves (23).

(ii) *Mercurous iodide.* Nicotine iodide-mercurous iodide is formed when a solution of nicotine hydrochloride is added to a saturated solution of mercurous iodide until the precipitate formed begins to persist (23).

(iii) *Mercurous cyanide.* Nicotine mercurous chloride-cyanide is obtained when a solution of nicotine hydrochloride is added to an equal volume of a saturated solution of mercurous cyanide (23).

(iv) *Mercuric oxide.* Nicotine is heated to 240°C. and mercuric oxide is added, in small quantities at a time, until the liquid becomes thick and brown. Each addition of the oxide produces an energetic reaction; water is given off and metallic mercury forms. The product of the reaction is allowed to cool and is then dissolved in dilute hydrochloric acid. The solution is filtered, and the filtrate is treated with hydrogen sulfide. The mercuric sulfide formed is filtered off, and the dark brownish black filtrate is mixed with alkali, which produces a flocculent brown precipitate having the composition $C_{30}H_{27}N_6O_2$ or $(C_{10}H_9N_2)_3O_2$ (60).

(v) *Mercuric chloride.* Nicotine mercuric chloride, $C_{10}H_{14}N_2 \cdot HgCl_2$, is obtained by treating a solution of mercuric chloride with nicotine; it forms white crystals which are insoluble in water and ether, feebly soluble in alcohol, and decompose above 100°C. (161). The compound $C_{10}H_{14}N_2 \cdot 2HgCl_2 \cdot Hg(CN)_2$ forms prisms, which are easily soluble in hot and cold water and in alcohol without decomposition (23).

(vi) *Mercuric iodide.* Nicotine is precipitated as $C_{10}H_{14}N_2 \cdot HgI_2$ from its solution in alkali carbonate (10–15 per cent solution of potassium or sodium carbonate) by means of mercuric iodide dissolved in sodium thiosulfate (275).

(b) *Cadmium chloride.* When an alcoholic solution of nicotine hydrochloride is added to a large excess of an alcoholic solution of cadmium chloride, the compound $(C_{10}H_{14}N_2 \cdot 2HCl)_3 \cdot 7CdCl_2$ is formed; this substance crystallizes from alcohol in kidney-shaped masses. If, however, the proportions are reversed, the compound $(C_{10}H_{14}N_2 \cdot 2HCl)_2 \cdot 3CdCl_2 \cdot 2H_2O$, is obtained; it crystallizes from 50 per cent alcohol in radiant clusters of fine needles and thin plates (73).

(c) *Silver acetate and nitrate.* By the action of silver acetate on nicotine,

a basic substance is obtained which appears to be identical with a compound prepared by Cahours and Étard (38).

(d) *Sodium amide*. The action of sodium amide on nicotine in the presence of an indifferent solvent such as petrolatum or toluene leads to the formation of 2(or 6)-aminonicotine in about 18 per cent yield. After crystallization from light petroleum, it forms biaxial leaflets or plates which melt at 124–125°C. Tschitschibabin and Buchholz (245) and Tschitschibabin and Kirssanov (246) found that both isomers are produced in approximately equal amounts when nicotine is dissolved in xylene and heated with sodium or potassium amide at 135–140°C.

(e) *Gold chloride*. Varying amounts of nicotine were added to solutions of $\text{AuCl}_3 \cdot \text{HCl} \cdot 4\text{H}_2\text{O}$ (5 cc. of 0.1 per cent gold solution in 100 cc. of water), with or without added hydrochloric acid and boiling; the color of the solution was blue (32). $\text{C}_{10}\text{H}_{14}\text{N}_2 \cdot 2\text{HCl} \cdot 2\text{AuCl}_3$, was obtained; it crystallized from water as bright yellow, warty masses (181).

(f) *Potassium ferro- and ferri-cyanides*. With potassium ferrocyanide in hydrochloric acid solution nicotine yields a crystalline precipitate (42) which is characteristic enough to be used in corroborative identification tests (43). Cummings and Brown (49) prepared nicotine hydroferri-cyanide in alcoholic solution as a yellow precipitate which tends to become gummy in concentrated solution but is soluble in an excess of either reagent.

(g) *Sodium cobaltinitrite*. Sodium cobaltinitrite, when added to a neutral or slightly acidified (with acetic acid) solution of nicotine, forms greenish white needles of nicotine cobaltinitrite (167).

H. IDENTIFICATION

Kocsis and Németh (109) made use of the fluorescence of nicotine in ultraviolet light for its identification; in aqueous solutions as little as 0.1 mg. of nicotine can be thus detected. The azure-blue fluorescence is not affected by the addition of sodium or ammonium hydroxide, but it becomes a little more greenish when hydrochloric acid is added.

The most sensitive microchemical reagent is a cold saturated solution of picric acid to which 10 per cent of concentrated hydrochloric acid has been added. A yellow, amorphous precipitate, from which crystals separate in a few seconds and which is recognizable with the naked eye, is obtained with 10 μg . of nicotine. With 5 μg . of the alkaloid the precipitate is not formed; however, the same crystals generally appear, in indistinct feathery form but always of the same magnitude and arranged in groups (247).

Nicotine can be detected even in small quantities, since it is colored violet by being heated gently with a very little hydrochloric acid; the violet color becomes an intense orange on the addition of a little concentrated nitric acid (164).

From a study of the electrolytic reduction of nicotine and its salts in aqueous solution at the dropping mercury cathode, Semerano (210) established conditions for its determination; even in the presence of pyridine and ammonium bases, the alkaloid can be determined with an accuracy of 1 part in 10^7 .

Upon the dissolving of traces of nicotine in epichlorohydrin and heating to boiling, a deep red coloration is produced; about 0.00025 g. of nicotine can thus be detected (135).

The lowest concentration and minimum quantity of nicotine that can be detected by various reagents are as follows: mercuric chloride, 1:100, 0.00001 g.; potassium mercuric iodide, 1:500, 0.000002 g.; cadmium iodide, 1:1000, 0.000001 g.; cadmium bromide, 1:400, 0.000005 g.; cadmium chloride, 1:100, 0.00002 g.; zinc thiocyanate, 1:100, 0.00002 g.; cobalt thiocyanate, 1:100, 0.00002 g.; platonic chloride, 1:500, 0.000002 g.; auric chloride, 1:500, 0.000002 g.; iodine in potassium iodide, 1:100, 0.00001 g.; picric acid, 1:10000, 0.000001 g.; picrolonic acid, 1:100, 0.000005 g. (252).

I. TOXIC ACTION

Nicotine is one of the most violent poisons, hardly inferior to hydrocyanic acid in toxic power and rapidity of action, and probably acting upon all classes of animals. The absorption of nicotine takes place even in a few seconds from the tongue, the rectum, and the eyes, and somewhat more slowly from the stomach; it is also absorbed from the skin. In consequence of this rapidity of absorption, nicotine exhibits its toxic action very quickly, even after a few minutes. The elimination of nicotine proceeds through the lungs and kidneys. Although not really corrosive in its action, nicotine in more concentrated form, especially as the free alkaloid, acts as a local irritant. After the administration of fatal doses by mouth, inflammation of the mucous lining of the stomach does not usually occur, for the action of nicotine is too rapidly fatal. Moreover, following brief stimulation, nicotine exerts a central paralyzing action upon the brain and spinal cord, and finally, as a result of absorption, acts upon different organs, such as the heart, eyes, and intestinal tract. In acute nicotine poisoning death ensues from paralysis of the respiratory center, but probably action upon the heart always takes place, although this usually does not lead to death.

The symptoms of nicotine poisoning have been accurately determined by various experimenters who have taken from 1 to 4 mg. of this alkaloid. The symptoms are burning in the mouth and throat, increased secretion of saliva, headache, stupefaction, dizziness, indistinctness of vision and hearing, photophobia, parched throat, coldness of the extremities, emesis and enforced evacuation of the bowels, and accelerated and labored respiration. At first the pulse increases in frequency but later it changes, be-

coming at irregular intervals more or less frequent. After 45 min. the experimenters swooned and in one case for 2 hr. there were uninterrupted clonic convulsions, especially of the muscles of respiration, with trembling of the extremities and shaking of the whole body. In severe cases of poisoning the gastric symptoms predominate. The intense diarrhoea that appears may be bloody, resulting in death in a few hours. On the other hand, in severe cases, convulsions, delirium, and paralysis predominate and may prove fatal in 10–30 min. (7).

J. ANTIDOTE

Experiments conducted on guinea pigs and rabbits show that strychnine is not an effective antidote to nicotine poisoning; eserine is more effective, but the best antidote to nicotine is the alkaloid of *Nasturtium officinale*, two injections of the expressed juice of the plant completely counteracting the effect of a fatal dose of nicotine (0.025 g.) in the case of a rabbit; similar results were obtained with dogs (274).

III. LESSER ALKALOIDS OF TOBACCO

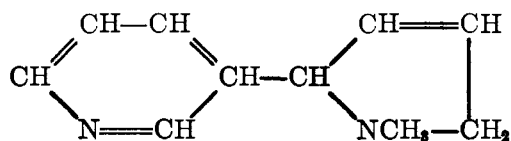
Upon the addition of a strong alkali or hydrogen peroxide, or when it was merely allowed to stand in contact with air, an aqueous tobacco extract which had previously been steam distilled and from which the nicotine had been extracted was found to yield more nicotine. This led Pinner (180) and Preiss (189) to conclude that tobacco contains a secondary alkaloid or alkaloids which, on oxidation, yield nicotine.

A. NICOTOINE, NICOTEINE, NICOTELLINE, ISONICOTEINE, AND NICOTIMINE

Noga (149) digested tobacco with water and evaporated the liquid in a vacuum. By extraction with benzene he obtained a small amount of an alkaloid which was not volatile with steam; this was fractionated into four parts, as follows: (i) nicotoine, $C_8H_{11}N$, a colorless, mobile liquid possessing a strong characteristic odor, similar to that of pyridine, and having the following constants: b.p., $208^\circ C.$; $d_4^{21^\circ}$, 0.9545, $n_D^{20^\circ}$, 1.5105. It gave the usual alkaloid reactions; with hydrochloric, sulfuric, and picric acids, and with mercuric and platonic chlorides it formed well-crystallized salts of definite melting points. The aqueous extract remaining after the removal of the nicotine and its isomer contained two alkaloids, nicotine and nicotelline, which are not volatile with steam.

(ii) Nicoteine, $C_{10}H_{12}N_2$, is a colorless liquid which is readily soluble in water and in ether; it boils at $267^\circ C.$ and does not solidify at $-79^\circ C.$ Its specific gravity is 1.0778 at $12.5^\circ/4^\circ$; n_D , 1.56021 at $14^\circ C.$; $[\alpha]_D$, -46.41° . The platinichloride forms yellow crystals and does not melt at $280^\circ C.$; the aurichloride becomes gray at $150^\circ C.$ and melts with decom-

position at 186°C.; the picrate forms large transparent prisms which melt at 165°C. The dimethiodide, $C_{10}H_{12}N_2 \cdot 2CH_3I$, is a yellow oil which cannot be made to crystallize. When the bromo derivative of the base is reduced by means of tin and hydrochloric acid a base is obtained which is volatile with steam but is neither nicotine nor nicotine; the formula



given to the base shows it to be closely allied to dihydronicotyrine (173) and dehydronicotine (183, 186) and explains the following facts: (a) nicotine on oxidation with nitric acid yields nicotinic acid; (b) it decolorizes aqueous permanganate in the presence of sulfuric acid; (c) its acid solutions respond to the tests for a pyrrole derivative.

(iii) Isonicotine, $C_{10}H_{12}N_2$, is a colorless, viscous, oily liquid, of rather strong and very persistent odor; b.p., 293°C.; d_4^{20} , 1.0984; n_D^{20} , 1.5749. Isonicotine is optically inactive, easily soluble in organic solvents, and difficultly soluble in water and in petroleum ether. It forms well-crystallized salts with hydrochloric, sulfuric, and picric acids, with mercuric, platonic, and auric chlorides, and with methyl iodide. It is oxidized to nicotinic acid, gives the pine splint reaction, and immediately decolorizes potassium permanganate in the cold.

(iv) Nicotelline, $C_{10}H_8N_2$, is only very slightly soluble in water and ether, and is best extracted from the original aqueous solution by chloroform; upon the addition of light petroleum it crystallizes from chloroform in small white needles (m.p., 147–148°C.; b.p., slightly above 300°C.). Unlike the other alkaloids of tobacco, an aqueous solution of nicotelline is neutral to litmus. It does not appear to be a pyrrole derivative and does not decolorize potassium permanganate in the presence of sulfuric acid. Its hydrochloride is easily soluble in water and its platinichloride sparingly so; its aurichloride sinters and decomposes at about 170°C., and its mercurichloride melts at 200–201°C. Nicotelline differs from the other alkaloids of tobacco in yielding a very sparingly soluble dichromate.

The crude nicotine obtained by Pictet and Rotschy (176) by distilling a concentrated aqueous extract of tobacco leaves with steam, contains about 0.5 per cent of its weight of an isomer, nicotimine, $C_{10}H_{14}N_2$; this is a secondary base and is separated by converting it into its nitroso derivative, removing the nicotine by distilling under diminished pressure, boiling the residue with concentrated hydrochloric acid, and converting the regenerated base into its benzoyl derivative. The latter is a bright yellow oil which boils above 350°C., does not solidify at $-10^\circ C.$, and, on hydrolysis

with concentrated hydrochloric acid, yields nicotine as a colorless liquid boiling at 250–255°C. The base is easily soluble in water, is volatile with steam, and yields a white, crystalline, deliquescent hydrochloride. A study of its platinichloride, aurichloride, mercurichloride, and picrate shows that nicotine is not identical with Pinner's (181) metan nicotine.

B. ANABASINE

Anabasine, $C_{10}H_{12}O_2$, an isomer of nicotine, is colorless or pale yellow when pure and, like nicotine, darkens on standing; unlike nicotine, it is miscible with water in all proportions (278). Schmuck (207) stated that the alkaloid of *Nicotiana glauca* was not nicotine, as had been identified earlier by Juritz (99), but no identification was made. In 1929 Orekhov (156) isolated from *Anabasis aphylla* L. a new alkaloid which he named anabasine and in 1931 with Menshikov (158) suggested that it was probably β -pyridyl- α' -piperidine. Smith (219) examined a sample of *N. glauca* roots and found it to contain about 1 per cent of anabasine. A sample of the whole plant was later obtained from the same source and its identity confirmed; a further examination of samples of dried leaves showed that they too contained anabasine. Smith concluded that it is very doubtful that nicotine is present in this plant except possibly as a trace. Khmura (103, 104) found anabasine to the extent of 0.74 per cent in the young upper leaves of *N. glauca* and in a yield of 0.33 per cent for the entire plant.

In 1931 Ehrenstein (58) stated that Pietet's (172) nicotine had no existence. The fraction corresponding to nicotine was resolved into two fully individual alkaloids, which differed in boiling point by only a few degrees; the lower boiling alkaloid was recognized as nornicotine, and the higher boiling one as anabasine. Smith (218) isolated α -piperidyl- β -pyridine and coined for it the name neonicotine, but Ehrenstein (58) suggested that the substance was probably the *dl*-form of anabasine.

Späth and Mamoli (229) synthesized anabasine by condensing *l*-benzoyl-piperidone with ethyl nicotinate and submitting the product to the action of hydrochloric acid at 130°C., Δ^2 -2-(3'-pyridyl)tetrahydropyridine (anabasine) was thus obtained. This substance, on reduction, gave *dl*-anabasine, which was deracemized by Späth and Keszler (225) by the use of *l*-6,6'-dinitro-2,2'-diphenic acid to separate *l*-anabasine, $[\alpha]_D^{18}$, -82.45° ; to isolate *d*-anabasine ($[\alpha]_D^{18}$, $+62.11^\circ$) from the mother liquor, *d*-6,6'-dinitro-2,2'-diphenic acid was used.

The boiling point of anabasine has been reported as follows: 104–105°C. at 2 mm. (158); 137.5–138.5°C. at 10.5 mm. (58); 145–146°C. at 15 mm. (156); 155°C. at 19 mm. (58); 276°C. (158); 277.5–280°C. (218); 280–281°C. (72); 280–282°C. (217); 280.9°C. (147); 281°C. (219).

The following values have been given for the density of anabasine: d_4^{20} , 1.044 (156); d_{20}^{20} , 1.0455 (158), 1.046–1.048 (278), 1.0481 (147).

The specific rotation of anabasine has been reported as follows: $[\alpha]_D^{20}$, -9.1° (219); $-47^\circ 21'$, -59.66° (202); -82.2° (158); $[\alpha]_D^{15}$, -81.7° , 20.6° (in two equivalents of hydrochloric acid, $c = 1.75$) (227). According to Orekhov (156), Norkina and Narkuziev (150), and Orekhov and Men-shikov (158), the specific rotation of anabasine varies with the solvent and racemization is apt to occur during extraction.

Gorbachev (75) determined the vapor pressure of anabasine by deter-

TABLE 34
Vapor pressure of anabasine

TEMPERATURE	PRESSURE OBSERVED	TEMPERATURE	PRESSURE OBSERVED
°C.	mm.	°C.	mm.
79.0	2.5	218.6	211.5
100.0	6.0	280.6	756.8
137.1	31.6	280.9	760.0
184.2	85.4	282.4	776.1

mining the boiling points in a manostat; the experimental results were quite in agreement with the Kistyakovskii equation:

$$\log P = \log T - (2586.6/T) = 1.0143$$

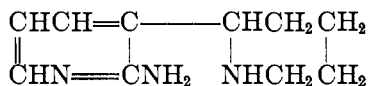
Nelson (147) obtained the vapor pressure within an accuracy of about 5 per cent up to 100°C . and to better than 0.10 per cent for the remainder of the temperature range investigated by the empirical equation

$$\log P_{\text{mm.}} = 7.2423 - (2416.14/T_K)$$

Optically active anabasine sulfate has been found to undergo racemization when heated in a sealed tube (137). It was observed that, after a dilute solution of the sulfate had been heated in a sealed tube at 200°C . for 70 hr. and the anabasine had been freed, the rotation changed to $[\alpha]_D^{20} = -25^\circ$ from presumably $[\alpha]_D^{20} = 82.2^\circ$, while after heating for 120 hr., the value of $[\alpha]_D^{20}$ was -3.0° . About 10 months after a rotation of -59.66° was found for anabasine, another sample was purified; this sample showed a rotation of $[\alpha]_D^{20} = -51.93^\circ$, thereby indicating autoracemization at room temperature.

On hydrogenation in the presence of platonic oxide, anabasine yields a mixture of bases including *l*-2,3-dipiperidyl (m.p., $66\text{--}68^\circ\text{C}$.; b.p., $113\text{--}114^\circ\text{C}$. at 5 mm.; $[\alpha]_D^{20}$, -5.0° (alcohol) (157)). When anabasine is heated

with silver acetate or refluxed with zinc dust, six atoms of hydrogen are lost; a bipyridyl is formed (158). Treatment of anabesine in boiling xylene with sodium amide gives about 5 per cent of aminoanabesine,



which melts at 111°C. (138).

When anabesine is heated with formaldehyde and formic acid, *N*-methyl-anabesine is obtained readily and in good yield (159); it can also be prepared by refluxing anabesine with 40 per cent formaldehyde or by treating the alkaloid with magnesium and methyl iodide in absolute ether (160). Anabesine, when treated with potassium permanganate, gives nicotinic acid in good yield (158).

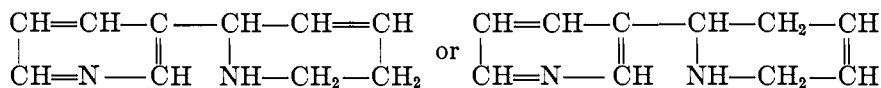
Sokolov (221) has shown that fluorosilicic acid is an excellent reagent for the distinguishing of nicotine from anabesine; the latter is precipitated as anabesine fluorosilicate in the presence of nicotine.

Anabesine stimulates and finally paralyzes the cervical sympathetic ganglia and in a concentration of 1:1,000,000 causes a flow of adrenaline from the isolated adrenal gland. The activity ratio of nicotine to anabesine for constriction of the vessels of a rabbit's ear is 1.5:1, for the rise of arterial pressure in a cat it is 2.55:1; and for respiratory stimulation it is 4:1 (5). The results of Sargin's (202) experiments indicate that anabesine is very similar to nicotine in its action; it changes the blood pressure and affects the intestines and uterus in much the same way as does nicotine.

C. *L*-ANATABINE, C₁₀H₁₂O₂

Späth and Kesztlér (226), in a continuation of the study of the concomitant bases of tobacco undertaken by Späth and Zajic (233), examined a fraction boiling at 120–140°C. at 1 mm. This was further fractionated and the products were converted into dipicrates, one of which had a melting point of 195–196°C. and yielded a base having a specific rotation, $[\alpha]_D$, of -141° . This substance, on purification, yielded a base which had the following properties: b.p., 145–146°C. at 10 mm.; $[\alpha]_D^{17^\circ}$, -177.8° ; $d_4^{19^\circ}$, 1.091; $n_D^{20^\circ}$, 1.5676. The name anatabine was suggested for this substance to indicate its origin from tobacco. On dehydrogenation with palladium sponge under mild conditions, *l*-anatabine yields 2,3'-dipyridyl. The supposition that anatabine contains a non-hydrogenated and a partially hydrogenated pyridine ring was confirmed by its catalytic hydrogenation to *l*-anabesine by means of palladium sponge in acetic acid. The optical rotation of *l*-anatabine and the fact that in its benzylation no opening of the ring and addition of water occur, exclude positions adjacent

to the secondary nitrogen atom for the double bond of the partly hydrogenated ring and leave the possible structure as:



Reactions take place which show the possibility of both formulas or either one. Anatabine shows certain similarities to the tobacco base which Ehrenstein (58) erroneously thought was *l*-anabasine.

D. NICOTYRINE

By steam distilling finely ground Brazil tobacco, Wenusch (261) obtained nicotyrine. It is not clear whether this substance preëxists in the plant or is produced in the fermentation process. If it is purely a fermentation product, it is derived from nicotine, because the Brazil tobacco is free from reducing substances.

E. *l*-NORNICOTINE

l-Nornicotine was found by Smith (220) in *Nicotiana sylvestris* to the extent of about 95 per cent of the total alkaloid content. After the cautious oxidation of *l*-nicotine with potassium permanganate and the removal of the more strongly basic portions from the product by fractional extraction with hydrochloric acid, followed by distillation with steam *in vacuo* (whereby nicotine is volatilized), the residue is transformed into the dipicrate, from which, after repeated crystallization, *l*-nornicotine is isolated. Its specific rotation, $[\alpha]_D^{20} = -76.1^\circ$, is raised to -83.2° after further purification through the perchlorate. When *l*-nicotine is treated with silver oxide and the product, dissolved in ether, is treated with aqueous sodium chloride containing hydrochloric acid, there is obtained a very strongly basic fraction from which *l*-nornicotine ($[\alpha]_D^{20} = -88.8^\circ$) is isolated. Its specific gravity is 1.07, and its melting point is 191–192°C. (230, 233).

IV. ALKALOIDS OF TOBACCO SMOKE

The following alkaloids, apart from the normal alkaloidal constituents of tobacco, have been isolated by Wenusch and Schoeller (quoted by Späth, Wenusch, and Zajic (237)) from tobacco smoke: (1) bases volatile with steam,—myosmine, obeline, α -socratine, β -socratine, and γ -socratine; (2) bases not volatile with steam,—anodmine, lathreine, and lohitam. These bases are obtainable only in minute quantities, and only one of them, myosmine, $\text{C}_9\text{H}_{10}\text{N}_2$, has been fully investigated.

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