

473. Volatile Products of Pyrolysis of Nicotine.*

By CHARLES H. JARBOE and C. JAMES ROSENE.

The pyrolysis of nicotine in an inert atmosphere at 600–900° produces a variety of heterocyclic nitrogen compounds and aromatic hydrocarbons, consideration of which permits a mechanism to be established for the primary reactions. In addition, a number of secondary products are ascribed to free-radical reactions involving cleavage and recombination.

It is well known that only a part of the nicotine present in tobacco is transported into tobacco smoke, and more than 30 bases structurally related to nicotine have been identified in smoke.¹ When nicotine is passed through heated packed reactors² the products of pyrolysis include hydrogen cyanide, methylamine, ethylamine, pyridine, 3-picoline, 3-ethylpyridine, 3-vinylpyridine, nicotinic acid, myosmine, nicotyrine; noteworthy is its catalytic pyrolysis to 3-cyanopyridine in 51.5% yield.³ Percolation through tobacco ashes at 740° has been found by Truhart *et al.*² to produce, in addition to the above compounds, nicotinamide, nornicotyrine, *N*-methylmyosmine, nornicotine, and tentatively a pyridinealdehyde and an aminopyridine. At 750° nicotine pyrolysis yields also dibenzo-*[a,j]*- and -*[a,h]*-acridine;⁴ these compounds and dibenzo-*[c,g]*carbazole have been found in cigarette smoke and are considered possible nicotine artifacts. As the conditions in these experiments were relatively uncontrolled and in many cases air was the carrier, both oxidation and thermal reactions may have been involved.

TABLE I. Pyrolysis products of nicotine.*

Compound	Retention time †		Temperature			
	"Ucon"	"Carbowax"	600°	700°	800°	900°
Pyridine	1.00	1.00	0.50	3.40	6.00	4.70
3-Picoline	1.64	1.46	1.40	4.00	2.60	0.05
3-Ethylpyridine	2.15	1.92	1.10	0.46	0.03	0.03
3-Vinylpyridine	2.82	2.42	10.00	8.00	2.60	0.03
Metanicotine	—	2.46	0.01	0.01	0.01	—
Benzonitrile	4.10	3.61	—	—	0.01	0.44
3-Cyanopyridine	5.50	5.43	0.64	1.80	1.10	0.05
Naphthalene	6.85	5.46	—	—	0.01	0.45
Compound A	—	4.24	0.11	0.10	0.13	—
3-(Buta-1,3-dienyl)pyridine	—	5.96	0.17	0.01	—	—
2-Cyanopyridine	9.40	8.31	—	—	0.01	0.01
Compound B	10.6	8.65	—	0.41	—	—
Quinoline	12.1	9.82	0.01	1.60	1.50	0.82
Nicotine	11.2	9.28	34.00	—	—	—
Isoquinoline	13.9	11.3	0.01	0.20	0.40	0.20
Nornicotyrine	—	12.0	0.01	0.01	0.01	—
Myosmine	22.2	23.0	11.00	—	—	—
1,7-Diazaindene	76.3	61.8	—	—	0.01	0.01

* Yields (% by wt.) based on initial nicotine. † Gas-liquid chromatography, with pyridine as internal standard.

In order to study the pyrolysis factor only, we have used unpacked reactors and helium as inert atmosphere. The reactor exit streams were condensed in an air-cooled receiver

* Presented before the Thirteenth Tobacco Chemists Conference, Lexington, Kentucky, October, 1959.

¹ Bentley and Berry, "The Constituents of Tobacco Smoke: An Annotated Bibliography," Tobacco Manufacturers Standing Committee, London, 1959, pp. 19–24; also First Supplement thereto, 1960, pp. 10, 11.

² Cahours and Etard, *Compt. rend.*, 1880, **90**, 275; 1887, **105**, 1079; Oliveri, *Gazzetta*, 1895, **25**, 59; Woodward, Eisner, and Haines, *J. Amer. Chem. Soc.*, 1949, **66**, 911; Truhart and DeClerq, *Bull. Assoc. franç. Étude Cancer*, 1957, **41**, 426.

³ Woodward, Badgett, and Williamson, *Ind. Eng. Chem.*, 1944, **36**, 540.

⁴ Van Duuren, Bilbao, and Joseph, *Amer. Chem. Soc.*, Meeting-in-Miniature, New York City, March, 1960.

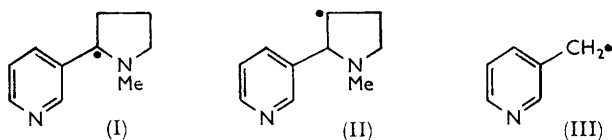
followed by a trap at -72° , and virtually all the volatile products were separated and characterized. The results are shown in the Table. Two compounds, isolated in small amounts were shown by their infrared spectra and reactivity towards cyanogen bromide and *p*-aminobenzoic acid⁵ to be 3-substituted pyridine derivatives. Compound A is an unstable liquid colouring rapidly in air and possessing an ammoniacal odour; its ultraviolet spectrum is similar to that of metanicotine and the change of spectrum in alcoholic hydrogen chloride indicates marked basicity; but its infrared spectrum shows no similarity to that of metanicotine. Compound B occurs to a measurable extent only at 700° and is indicated by its acid shift of ultraviolet maxima to be less basic than compound A; it is a moderately stable liquid, discolouring only slowly in air.

By-products were not formed at $<600^\circ$. The optical activity of nicotine before and after passage through the apparatus at 500° was little changed, indicating a high thermal stability.

In comparing these results with those of Woodward *et al.*², it is apparent that the pyrolytic environment is an important factor in determining the composition of the products: a vertical reactor: packed with quartz or activated alumina produced myosmine as the major product,² while our unpacked horizontal reactor gave almost equivalent quantities of myosmine and 3-vinylpyridine at 600° . The minor rôle of catalytic effects in the present work is further indicated by the low yield of 3-cyanopyridine, a major product when highly active catalysts are used.³

In our experiments no evidence was found for production of nornicotine, nicotyrine, *N*-methylmyosmine, nicotinamide, or nicotinic acid, all of which have been found when air was the carrier.

The nature of the compounds isolated, bond strengths, activation energies, and analogy with similar systems⁶ led to a mechanism involving formation of the radical (I) from nicotine. The radical may react by elimination to form myosmine (3-2'-pyrrolinyl-



pyridine *) or rearrange to radical (II) which is free to form metanicotine by elimination. The subsequent reactions of myosmine yield nornicotyrine,† presumably by dehydrogenation. Whether this compound is cleaved to pyridine is problematical: the possibility of this is indicated by the rising yield of pyridine and the disappearance of myosmine in reactions at 760° .

Metanicotine, because of the yield and the facility with which it undergoes elimination,⁹ must be an intermediate in the formation of 3-(buta-1,3-dienyl)pyridine. Isolation of the diene, quinoline, and isoquinoline supports the free-radical theories of Badger and Spotswood regarding the thermal synthesis of aromatic hydrocarbons like naphthalene

* Myosmine, first considered to be a Δ^2 -pyrroline derivative, was believed by Späth *et al.*⁷ to have a structure involving $\Delta^1 \longleftrightarrow \Delta^2$ -pyrroline tautomerism. Eddy *et al.*⁸ finding no N-H bond at 3300 cm.^{-1} in the infrared spectrum, favoured the pure 1-pyrrolinyl structure. Their work is supported by our studies which show a strong C=N bond stretching frequency at 1626 cm.^{-1} and the complete lack of a trisubstituted ethylene band in the $840\text{--}790 \text{ cm.}^{-1}$ region.

† The formation of nornicotyrine from myosmine suggests that at high temperatures the tautomeric equilibrium is shifted towards the Δ^2 -isomer. An alternative, less satisfactory, interpretation is that the Δ^1 -isomer is dehydrogenated to form a transient pyrrolenine which immediately assumes the structure of nornicotyrine.

⁵ Koenig, *J. prakt. Chem.*, 1904, **69**, 105.

⁶ Roberts and Szwarc, *J. Chem. Phys.*, 1948, **16**, 981; Szwarc, *ibid.*, 1949, **17**, 431; Leigh and Szwarc, *ibid.*, 1952, **20**, 403, 844.

⁷ Späth and Mamoli, *Ber.*, 1936, **69**, 757; Späth, Wenusch, and Zajic, *ibid.*, p. 393.

⁸ Eddy and Eisner, *Analyt. Chem.*, 1954, **26**, 1428.

⁹ Pinner, *Ber.*, 1914, **27**, 2866.

from 1-phenylbutadiene.¹⁰ Precedent for the thermal synthesis of such heterocyclic systems exists in the pyrolysis of anabasine to 5-methylisoquinoline.¹¹

The formation of 3-vinylpyridine in relatively large quantities at lower temperatures is evidence that under these conditions the primary reaction of 3-(buta-1,3-dienyl)pyridine is scission at the carbon-carbon single bond of the side chain rather than the alternate single bond joining the chain with the ring. This is in marked contrast to the pyrolysis of 1-phenylbutadiene where the analogous chain-scission is considered unimportant in the overall mechanism. The decrease in 3-vinylpyridine yield and the increase in that of pyridine with rise in temperature indicates either a change in the mechanism to favour cleavage adjacent to the ring or cleavage of 3-vinylpyridine. In addition to being a possible source of pyridine, 3-vinylpyridine is the most attractive source of 3-ethylpyridine and 3-picoline. These compounds would most logically arise by reduction, formation of radical (III) by disproportionation, and hydrogen abstraction to form 3-picoline.

While it is legitimate to discuss these products of pyrolysis in terms of free-radical reactions, it is possible to account for some of them by ion-controlled mechanisms. However, the occurrence of benzonitrile, 2- and 3-cyanopyridine, naphthalene, 1,7-diazaindene, quinoline, and isoquinoline can only be explained on the basis of free-radical reactions as studied by Badger and his co-workers^{10,12} and of the types reviewed by Mapstone.¹³ The isolation of 1,7-diazaindene is of particular interest as it allows the possibility of thermally initiated cyclization involving a three-atom rather than a four-atom side chain as in formation of quinoline, isoquinoline, and naphthalene.

EXPERIMENTAL

Nicotine.—The nicotine used in these studies was of reagent grade, fractionally distilled just before use; it had b. p. 240—242°/722 mm., $[\alpha]_D^{20} - 161^\circ 35'$ (lit., $[\alpha]_D^{20} - 166^\circ 39'$). Analysis by gas-liquid chromatography demonstrated no impurities.

Pyrolyses.—Nicotine (50 g.) was vapourized by flash-distillation (0.1 g./min.) at 280° into a helium stream (0.05 cu. ft./hr.) and passed through a 2.2 × 30 cm. "Vycor" silica tube mounted in a horizontal electric combustion furnace controlled by a variable transformer. The apparatus was purged with helium (1 cu. ft./hr. for 10 min.) before use. The tube was fitted with ancillary heaters at the entrance and exit to prevent condensation and was wrapped with asbestos tape at the furnace junctions. Temperatures were controlled by a platinum/platinum-rhodium thermocouple inserted into a centre well in the reaction tube. Gradient measurements showed that uniform temperatures were maintained throughout a 150 c.c. volume of the tube. The outlet was fitted to an air-cooled receiver followed by a trap cooled in carbon dioxide-propan-2-ol. For results see the Table. Nicotine pyrolysed at 500° was quantitatively recovered, with $[\alpha]_D^{20} - 151^\circ 49'$.

Gas-Liquid Chromatography of Products.—This was performed with a Wilkins "Aerograph" instrument. Operating parameters were: 200 mA filament current (hot-wire thermal conductivity cell), column temperature 200°; helium flow 0.06 cu. ft./hr. The columns were 0.25 in. × 8 ft. packed with 30—60 mesh C-22 acid-washed firebrick containing a 30% loading of "Carbowax 20 M" or "Ucon" (substituted polyethylene glycol). For completeness of separation the "Carbowax" columns were preferred. Quantitative measurements were made either by standard solutions for reference or by the peak-area technique.¹⁴

For preparative work the volatile part of the total product was removed by fractional distillation at atmospheric pressure and then subjected to gas-liquid chromatography through a 0.50 in. × 5 ft. "Ucon" column. The fractions were collected by direct condensation in m. p. capillaries. The majority of products were identified by the m. p.s of their picrates¹⁵ and

¹⁰ Badger and Spotswood, *J.*, 1959, 1635.

¹¹ Dubinin and Chelintsev, *J. Gen. Chem. (U.S.S.R.)*, 1946, 16, 105.

¹² Badger, Buttery, Kimber, Lewis, Moritz, and Napier, *J.*, 1958, 2449; Badger and Kimber, *J.*, 1958, 2453, 2455; 1960, 266, 2746; Badger and Buttery, *J.*, 1958, 2458, 2463.

¹³ Mapstone, *Proc. Roy. Soc. New South Wales*, 1948, 82, 96.

¹⁴ Phillips, "Gas Chromatography," Butterworths, London, 1956, p. 63.

¹⁵ Cheronis and Entrikin, "Semimicro Qualitative Organic Analysis," T. Y. Crowell Company, New York, 1947, p. 315.

mixed m. p.s, ultraviolet spectra (Beckman, model DK-2, ratio recording spectrophotometer, MeOH solutions), and infrared spectra (Beckman model IR-5 and Perkin-Elmer model 221 infrared spectrophotometers). Ancillary details are as follows.

Pyridine: picrate, twice crystallized from 95% ethanol, m. p. and mixed m. p. 167°, ultraviolet and infrared spectra.

3-Picoline: picrate, twice crystallized from 95% ethanol, m. p. and mixed m. p. 150°, ultraviolet and infrared spectra.

3-Ethylpyridine: picrate, m. p. 126°, once crystallized from 95% ethanol. The infrared spectrum was in agreement with that in the literature.¹⁶

Metanicoline: monopicate, crystallized from 95% ethanol, m. p. 161° (Found: N, 17.9. Calc. for $C_{16}H_{17}N_5O_7$: N, 17.9%).

3-Vinylpyridine: picrate, crystallized from 95% ethanol, m. p. and mixed m. p. 143—144°, infrared and ultraviolet spectra.

3-(Buta-1,3-dienyl)pyridine: picrate, twice crystallized from 95% ethanol, m. p. 153—154° (lit.,⁹ 151°) (Found: N, 15.6. Calc. for $C_{15}H_{12}N_4O_7$: N, 15.5%), λ_{max} . 231 $m\mu$, infl. 265 $m\mu$; in alcoholic hydrogen chloride the maxima shifted to 259 $m\mu$, and the inflection disappeared; infrared (KBr pellet) maxima at 3012, 2941, 2857, 1675, 1653, 1575, 1563, 1473, 1439, 1412, 1204, 962, 825, 770, and 706 cm^{-1} .

3-Cyanopyridine: This compound crystallized in the capillary on emerging from the chromatograph. Identified by infrared and ultraviolet spectra, m. p. and mixed m. p. 49—50° after crystallization from hexane.

Naphthalene: crystallized in the capillary tube during collection, m. p. and mixed m. p. 79—80°.

2-Cyanopyridine: identified by retention time, ultraviolet and infrared spectra.

Quinoline: picrate, crystallized from 95% ethanol, m. p. and mixed m. p. 201—203°.

Isoquinoline: infrared and ultraviolet spectra.

Nornicotyrine: ultraviolet and infrared spectra and picrate, m. p. 198—200°, thrice crystallized from methanol (Found: N, 18.6. Calc. for $C_{15}H_{11}N_5O_7$: N, 18.8%).

Myosmine: ultraviolet and infrared spectra and picrate, m. p. 185° (Woodward *et al.*² give 183—184°) after crystallization from 95% ethanol.

Benzonitrile: the gross product from the 900° reaction was fractionated (0.5 mm.) through a 1.0 × 32.0 cm. column packed with glass helices. The fraction distilling at 50—80° was collected, dissolved in ether, and extracted with 6N-sulphuric acid. After evaporation, the residue was hydrolysed by refluxing 10% aqueous sodium hydroxide until no further ammonia evolved. Acidification of the solution gave benzoic acid, m. p. 120—121° after two crystallizations from water.

1,7-Diazaindene: crystallized in the capillary during collection, m. p. and mixed m. p. 105—106° after crystallization from hexane; picrate, m. p. 236—237° (from methanol) (Found: C, 45.0; H, 2.6; N, 20.2. Calc. for $C_{13}H_9N_5O_7$: C, 44.7; H, 2.7; N, 19.9%).

Compound "A": λ_{max} . 246 $m\mu$ infl., 299 $m\mu$; in alcoholic hydrochloric acid λ_{max} . 224, 257, and (infl.) 298 $m\mu$. ν_{max} . (in CCl_4) 3017, 2941, 2857, 1660, 1634, 1575, 1563, 1471, 1408, 1022, 915, 825, 792, 705, and 675 cm^{-1} . Chromatography (ascending) on Whatman No. 1 paper with t-pentyl alcohol-0.2M-sodium acetate (1:1) gave R_F 0.25. A yellow Koenigs reaction product resulted with cyanogen bromide and *p*-aminobenzoic acid.

Compound "B": λ_{max} . 222 and 287 $m\mu$; in alcoholic hydrogen chloride λ_{max} . 225 and 292 $m\mu$; ν_{max} . (KBr pellet) 3049, 2924, 2222, 1724, 1590, 1565, 1511, 1433, 1404, 1434, 1308, 1295, 1241, 1206, 1081, 893, 793, 769, and 717 cm^{-1} . Chromatography as above gave R_F 0.23. A yellow Koenigs reaction product was found.

The authors thank Mr. Walter Erwin for technical assistance.

RESEARCH LABORATORIES, BROWN & WILLIAMSON TOBACCO CORPORATION,
1600 WEST HILL STREET, LOUISVILLE 1,
KENTUCKY, U.S.A.

[Received, October 24th, 1960.]

¹⁶ Shindo and Ikekawa, *Pharm. Bull. (Japan)*, 1957, **4**, 192.