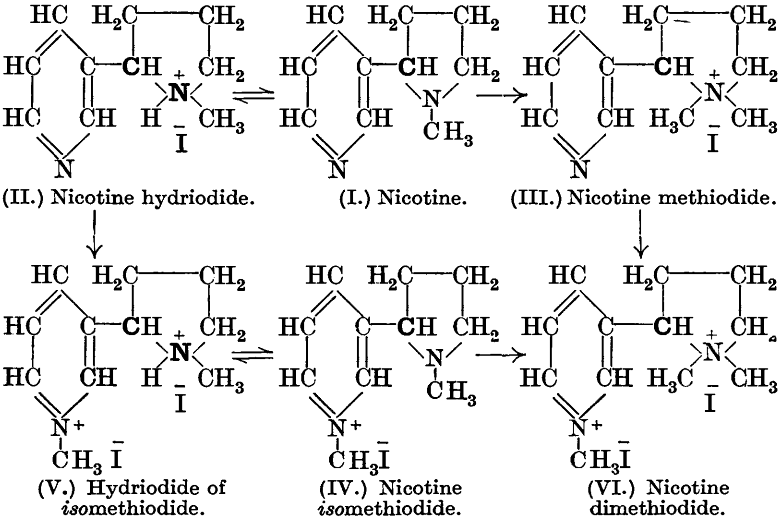
CLXXX.—*The Properties of Nicotine and its Derivatives. Part I. Molecular Extinction Coefficients.*

By THOMAS MARTIN LOWRY and WILLIAM VIVIAN LLOYD.

THE optical properties of nicotine are of interest on account of the simple structure of the compound and its exceptional optical activity. Measurements of the optical rotatory power of the base for 27 wave-lengths from 6708 to 4046 Å.U. (Lowry and Singh, *Compt. rend.*, 1925, **181**, 909) have shown that its rotatory dispersion is approximately simple, the reciprocal $1/\alpha$ tending towards a zero value at $\lambda^2 = 0{\cdot}06$, $\lambda = 2450$ Å.U. The refractive indices have also been measured for 13 wave-lengths from 7685 to 4341 (Gifford and Lowry, *Proc. Roy. Soc.*, 1927, *A*, **114**, 592) but without any attempt to correlate the data either with the rotatory dispersion or with the absorption spectrum of the base.

1. *Asymmetric Carbon and Nitrogen.*—The principal compounds investigated during the present research are formulated below:



(II.) Nicotine hydriodide. (I.) Nicotine. (III.) Nicotine methiodide.

(V.) Hydriodide of *iso*methiodide. (IV.) Nicotine *iso*methiodide. (VI.) Nicotine dimethiodide.

(i) The base (I) contains a single asymmetric carbon atom, which forms part of a saturated pyrrolidine ring; but it is also linked directly to the aromatic ring of the associated pyridyl radical and it is to this unsaturated system that we must look for an explanation of its selective absorption in the ultra-violet region and of the main characteristics of its rotatory dispersion. According to the usual conventions, nicotine does not possess an asymmetric nitrogen atom, since the tervalent nitrogen of the pyridyl ring can be formulated with a double bond, and the tervalent nitrogen of the pyrrolidine ring is generally regarded as having a planar configuration. This conclusion is based on the failure of attempts to resolve unsymmetrical amines of the type $NR_1R_2R_3$, but the alternative view, that the non-resolution of these compounds may be due to the small stability of an incomplete tetrahedron rather than to the existence of a stable planar symmetry, is not excluded, and in the case of nicotine would be expected to give rise to unequal concentrations of the *d*- and *l*-nitrogen atoms under the influence of the fixed asymmetry of the adjacent carbon atom of the base.

(ii) The salts (II), on the other hand, contain a quaternary nitrogen atom which is obviously asymmetric and is perhaps a unique example of the occurrence of an asymmetric atom other than carbon in a natural organic compound (Lowry, *Nature*, 1926, **117**, 417). In view, however, of the conditions under which salt formation takes place, it is clear that the proportion of *d*- and *l*-nitrogen atoms will be controlled in the first instance by the fixed asymmetry of the molecule; and the ready dissociation of the salts of tertiary amines makes it unlikely that these *d*- and *l*-components could be separated permanently. Even, therefore, if we suppose that the crystalline hydrochloride is really a pure *l*-C, *d*-N salt, it is probable that this would pass on dissolution into an equilibrium mixture of the *ld*- and *ll*-forms, and that this process would be too rapid even to give rise to mutarotation under normal conditions of observation.

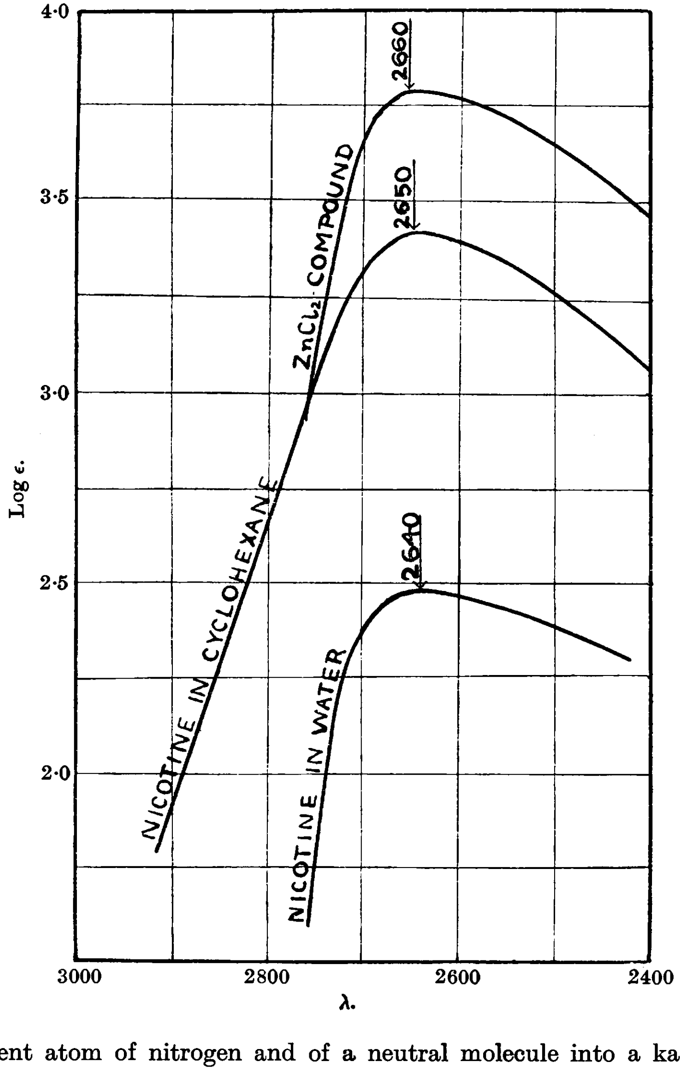
(iii) In the methiodides (III and VI) the pyrrolidine nitrogen is again quaternary, but is not asymmetric, since it is now linked to *two* methyl groups; the *iso*methiodide (IV), on the other hand, is in the same condition as nicotine, since the base contains a planar (?) atom of tervalent nitrogen which becomes quadricovalent and asymmetric in its salts (V).

2. *Molecular Extinction Coefficients.*—The absorption spectrum of nicotine has been examined by Dobbie and Fox (J., 1913, **103**, 1193), who observed a single absorption band at $1/\lambda = 3840$ ($\lambda = 2600$ Å.U.) " almost midway between the heads of the bands for α- and β-picoline " (Baly and Baker, J., 1907, **91**, 1122; Purvis, J., 1909, **95**, 296). The head of the band was at 56 mm. of *N*/5000-solution, so that $\log \varepsilon = 3$, approximately, presumably in alcoholic solution. In the present experiments, the molecular extinction coefficients of the base were measured both in water and in *cyclo*hexane, and a number of soluble salts, including three methiodides, were also examined in water. The results of the observations are plotted in Figs. 1 and 2, and the positions of the maxima are set out in Table I.

The constancy, at about 2650 Å.U., of the wave-length of maximum absorption is very striking, in view of the two-fold change of structure (namely, the conversion of a tervalent into a quinquevalent atom of nitrogen and of a neutral molecule into a kation) which accompanies the formation of the methiodides and of the salts. It can be explained, however, if we remember that in many

FIG. 1.

Absorption spectra of nicotine and its zinc chloride compound.



of its properties the ion $\overset{+}{N}H_4$ resembles the molecule CH_4 even more closely than does the molecule NH_3. The aromatic character of the pyridyl ring is therefore preserved intact in these derivatives,

FIG. 2.

Absorption spectra of methiodides.

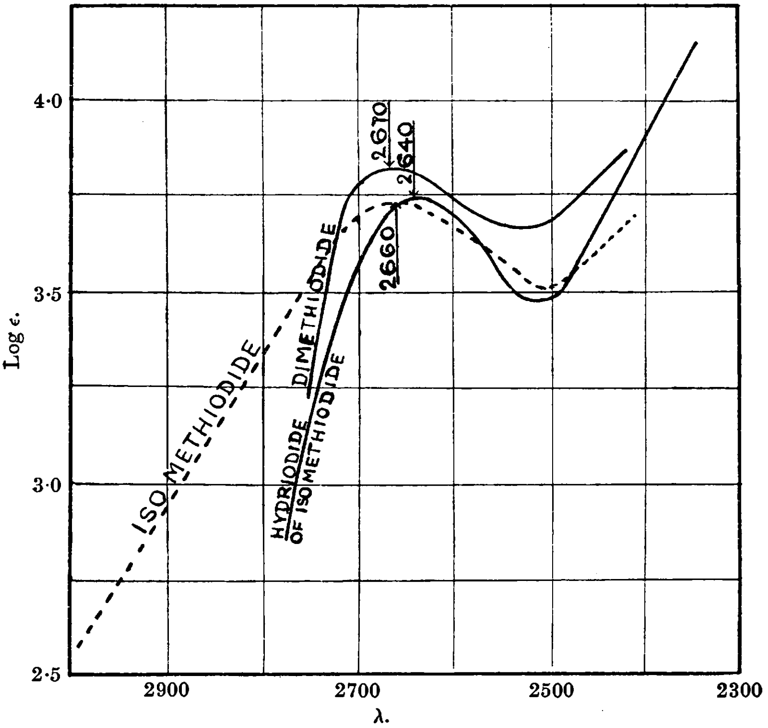
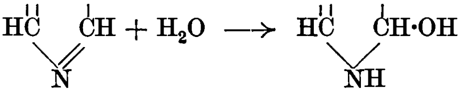


TABLE I.

Maxima in Absorption Spectra.

	Substance.	Solvent.	Log ε.	λ.
I	Nicotine	Water	2·49	2640
I	Nicotine	*cyclo*Hexane	3·43	2650
	Zinc chloride compound	Water	3·79	2660
IV	*iso*Methiodide	Water	3·74	2660
V	*iso*Methiodide hydriodide	Water	3·75	2640
VI	Dimethiodide	Water	3·83	2670

in spite of its ionic character. There is, indeed, no important contrast between the four "quaternary" compounds, for which log $\varepsilon = 3·8$ at 2660 Å.U. and the free base in *cyclo*hexane, where log $\varepsilon = 3·4$ at 2650. On the other hand, when the base is dissolved in water, the maximum falls to log $\varepsilon = 2{\cdot}5$ at 2640, and is nearly ten times less intense than in *cyclo*hexane. This cannot be due to any mere failure of the base to combine with the water, since this would make the absorption in water similar to that in *cyclo*hexane; and still less can it be explained by the formation of an ionised ammonium hydroxide, $C_{10}H_{14}N_2 + H_2O \longrightarrow [C_{10}H_{15}N_2]^+OH^-$, since the quaternary ion is three times *more* absorbent than the free base instead of ten times *less*. We are, therefore, obliged to fall back once more on the theory of Moore and Winmill (J., 1912, **101**, 1635) that aqueous solutions of weak bases contain un-ionised hydrates, and to suppose that in the case of nicotine this compound has an absorption which is at least ten times smaller than that of the free base, or may indeed not absorb at all but liberate 10% of the free base by dissociation. In view of the experiments of Decker and Kaufmann (*J. pr. Chem.*, 1911, **84**, 425) on the methyl*iso*quinolinium bases, it may be suggested that the hydrate is formed by the saturation of a double bond of the aromatic ring, giving rise to a pseudo-base from which the picoline-like structure has disappeared, leaving only two conjugated double bonds, in much the same condition as in butadiene.*



In this way we can understand why water behaves differently from inert solvents, and also from acidic hydrides which contain a more ionisable radical than hydroxyl, and which are therefore less ready to form non-ionised pseudo-salts. Since the equilibrium is evidently thrown right over to the side of the pseudo-base, the great readiness with which nicotine is oxidised is in agreement with the observation of Decker and Kaufmann that, although the " ammonium " base from *iso*quinoline methiodide is very stable, its aqueous solutions showing no change even on exposure to air for 72 hours, the isomeric " carbinol " base undergoes atmospheric oxidation very readily.

In conclusion, attention may be directed to the development by the three methiodides (IV), (V), (VI), in the region beyond the absorption band, of a strong " general absorption," which is not shown by nicotine or its salts; this is perhaps associated with the methylation of the pyridyl nitrogen; but, since no observations were made with the liquid methiodide (of which the purity could not be guaranteed), this conclusion is only a provisional method

* The process of hydration might, of course, also proceed further than this (compare Jephcott, J., 1919, **115**, 104).

of summarising the data now available. Conversely, whilst the molecular extinction coefficient usually falls very steeply from the maximum on the side of longer wave-lengths, there is a wide extension of absorption towards the visible region in the cases of nicotine in *cyclo*hexane and of the *iso*methiodide in water; the common feature here is the presence of a tervalent nitrogen atom in the pyrrolidine ring. Finally, the four compounds in which the pyridyl nitrogen is ionised, whether with the help of a proton or of a methyl group, all exhibit in aqueous solutions a selective absorption which is twice as great as that of the free base in *cyclo*hexane.

EXPERIMENTAL.

Purification of Nicotine.—The nicotine was decolorised by distillation under 2 mm. pressure in an atmosphere of nitrogen. The zinc chloride salt was then prepared by mixing the colourless nicotine (100 g. in 180 c.c. of 95% alcohol) with concentrated hydrochloric acid (140 g.) and alcoholic zinc chloride (180 c.c. of a solution containing 50 g. in 100 c.c.). The resulting double salt, $C_{10}H_{14}N_2,2HCl,ZnCl_2,H_2O$, was recrystallised three or four times from an equal weight of boiling 60% alcohol, and decomposed by adding potassium hydroxide (160 g. in 190 g. of water) to the salt (100 g. in 190 g. of water). The nicotine was separated, shaken for 24 hours with solid potassium hydroxide, and distilled in a vacuum. The second fraction was stored in a bottle from which air had been removed, but was redistilled before use.

The monohydriodide of the base could not be made to crystallise, but the dihydriodide separated from alcohol in pale yellow crystals, m. p. 195°.

The monomethiodide, prepared by mixing the base with an equimolecular quantity of methyl iodide in methyl alcohol, was a yellow syrup which could not be made to crystallise. It was purified by precipitation from chloroform by addition of ether.

The *iso*methiodide was prepared by the action of methyl iodide on the monohydriodide, the hydrogen iodide which had been used to " block " the pyrrolidine nitrogen being finally removed by the action of sodium carbonate. It was recrystallised from methyl alcohol and melted at 164°; its hydriodide crystallised from alcohol as a yellow salt, m. p. 209°. Pictet established its structure by oxidation to trigonelline (*Ber.*, 1897, **30**, 2117).

The dimethiodide, prepared by the action on the base of an excess of methyl iodide in methyl alcohol, was recrystallised repeatedly from methyl alcohol and obtained as a pale yellow compound, m. p. 216°.

*cyclo*Hexane was shaken mechanically with oleum for 2 days, washed with water, shaken with calcium chloride and lime, distilled from calcium chloride and lime, and frozen eight times. It melted at 6·05°.

The water was of conductivity standard.

Acetic acid (glacial) was distilled from chromic anhydride, frozen and drained several times, and finally distilled from an all-glass apparatus with a long fractionating column. The freezing point of the pure acid was 16·71°.

Acetone was purified through the sodium iodide compound by the Shipsey–Werner method, and was distilled over phosphoric oxide.

The absorption spectra were measured with the new symmetrical form of Bellingham and Stanley's spectro-photometer, usually at a concentration of $M/10{,}000$.

Summary.

Nicotine and its derivatives show a strong absorption band at 2650 Å.U., which is twice as strong in the zinc chloride compound and in the methiodides, but is ten times weaker when the base is dissolved in water. It is therefore suggested that the aqueous solution may contain an un-ionised hydrate or pseudo-base of the type investigated by Decker in the *iso*quinoline series.

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