[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NEW HAMPSHIRE]

METHYL 1-METHYL-1,2,3,6-TETRAHYDROISONICOTINATE[1]

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The conversion of isonicotinic acid and its derivatives to 1-methylisonipecotic acid and its derivatives has been accomplished by several different series of reactions (1). In some instances incomplete reduction of the pyridine ring occurred giving dihydro- or tetrahydro-pyridines (1a, b). Unfortunately, these partially reduced compounds were not completely characterized and the comparison of the various materials is difficult. We have had occasion to repeat certain of these procedures and as a result have found errors in the literature and are able to report additional derivatives of 1-methylisonipecotic acid and 1-methyl-1,2,3,6-tetrahydroisonicotinic acid.

Supniewski and Serafinowna (1a) (referred to as SS in this paper) reported that the reduction of methyl isonicotinate methiodide (Ia) over Adams' catalyst gave either methyl 1-methylisonipecotate hydriodide (IIIa) or methyl 1-methyltetrahydroisonicotinate hydriodide (IVa) depending upon the length of reaction time with hydrogen. Repetition of this work gave two hydriodides which were separated giving A, m.p. 127–128°, and B, m.p. 153–154°, which would appear to be IVa and IIIa, respectively, on the basis of the data reported by SS.

For comparison, methyl isonicotinate (I) was reduced and methylated following the procedure Feldkamp described for the synthesis of ethyl 1-methylisonipecotate (1b). The derivatives prepared from the product of this reaction were not similar to those prepared from B but were identical with the derivatives of A. From this it was concluded that either the procedure of Feldkamp proceeded with incomplete reduction to form methyl 1-methyltetrahydroisonicotinate (IV) or SS reversed the assignment of structures for the hydriodides, A and B. (A summary of the melting points of A and B and their derivatives is given in Table I.) Recently, Grob and Renk (1d) noted a discrepancy in melting points of derivatives of methyl 1-methylisonipecotate (III) which they prepared and those reported by SS (1a), but no suggestion was made concerning an incorrect assignment of structure by the latter authors.

The quantitative conversion of the product from the reduction by the method of Feldkamp to 1-methyl-4-piperidyldiphenylcarbinol (V), which has been related to piperidine derivatives prepared by unequivocal methods (2), confirmed the incorrect structural assignment of SS. Thus A is actually methyl 1-methylisonipecotate hydriodide (IIIa) and B is methyl 1-methyltetrahydroisonicotinate hydriodide (IVa). The mistake of SS probably resulted from the

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FLOW SHEET

PtO2
H2
II
CH2O
Pd-C
III
PhLi
V
OH
Ph
Ph
NaBH4
Ia or Ib
IV
PhLi
VI
OH⁻
IIIa or A
IIIa or B
IIIb
HI
HBr
I
Ia
Ib
I⁻
Br⁻

TABLE I

DERIVATIVES OF THE REDUCTION PRODUCTS OF METHYL ISONICOTINATE[a]

Base	B.P.		HI, M.P., °C.	Picrate M.P., °C.	CH_3I, M.P., °C.	Product from Reaction with PhLi, M.P., °C.
	°C.	mm.				
III	99–100	20		147–148[d]	148–149[f]	132–133[h]
Prepared from A	83–86	7	127–128[b]	142–143[d]	150–151[f]	129–131[h]
Prepared from B	106–110	14	154–155[c]	134–135[e]	203–205 (dec.)[g]	179–180[i]
IV	96–97	7		134–135[e]	210–212 (dec.)[g]	176–178[i]

[a] In all cases of the solids, mixture melting points between derivatives of III and those of the free base prepared from A were taken and showed no depression. The same was true of derivatives prepared from IV and B. [b] Lit. m.p. 152–153° (1a). [c] Lit. m.p. 130–131° (1a). [d] Lit. m.p. 151–153° (1d). [e] The picrate crystals melt at 119–121°, but on grinding the crystals, the melting point is 134–135°. [f] Lit. m.p. 193–194° (1a), 155.5–156.5° (1d). [g] Lit. m.p. 152–153° (1a). [h] Lit. m.p. 132–132.5° (2). [i] Lit. m.p. 179–179.8° (2).

fact that the formation of methyl 1-methyltetrahydroisonicotinate hydriodide (IVa or B) is independent of the length of reaction time but results from poisoning of the catalyst. Thus the reduction of crude methyl isonicotinate methiodide (Ia) over previously used Adams' catalyst gives a very slow reduction leading only to B. The reduction of methyl isonicotinate methobromide (Ib) gives only methyl 1-methylisonipecotate hydrobromide (IIIb).

The reduction of methiodides of pyridine derivatives by sodium or potassium borohydride has been reported (3) to yield 1-methyltetrahydropyridine derivatives. This method of reduction was applied to the methiodide (Ia) and methobromide (Ib) of methyl isonicotinate and yielded in both cases methyl 1-methyltetrahydroisonicotinate (IV) identical with the free base prepared from B.

The recent publication by Leonard (4) offered an excellent basis for the assignment of the position of the double bond in IV. The ultraviolet absorption spectrum of a tertiary vinyl amine gives a maximum in the region 225–230 mμ while the absorption of the allyl or saturated amine shows no bathochromic shift. Furthermore, α,β-unsaturated esters have been shown to absorb from 212–215 mμ with an extinction coefficient of 5,000–10,000 (5). The ultraviolet absorption spectrum of IV ($\lambda_{max.}$ 214 mμ, $\epsilon_{max.}$ 7.86×10^3) clearly indicates the appropriate assignment of structure as methyl 1-methyl-1,2,3,6-tetrahydroisonicotinate (see Fig. 1).

The reduction of methyl nicotinate methiodide (VII) with potassium borohydride in strong base has been reported (3) to give arecoline (methyl 1-methyl-1,2,5,6-tetrahydronicotinate). When VII was treated with sodium borohydride in methanol, an unsaturated ester (VIII) was obtained yielding derivatives which indicated that the product was arecoline. Examination of the absorption spectrum of VIII disclosed a single maximum at 214 mμ, $\epsilon_{max.}$ 1.06×10^4, consistent with α,β-unsaturated esters. Tertiary β-aminocrotonic esters have been shown to absorb at 275 mμ (6), and methyl 2-methyl-1,4,5,6-tetrahydronicotinate was found to have an absorption at 290 mμ with an extinction coefficient of 20,000 (7). Therefore, VIII is identical with arecoline and the double bond is in the 3,4-position.

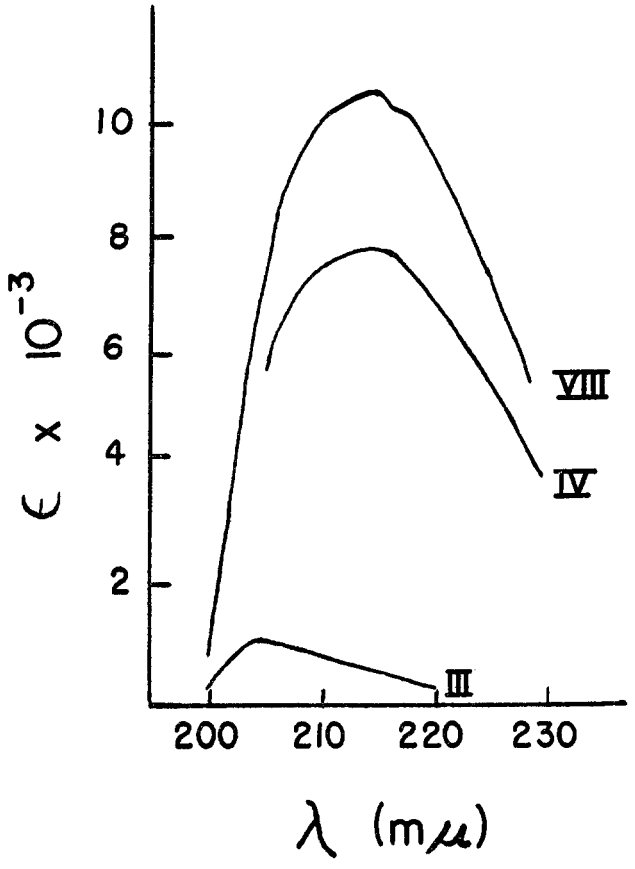

FIG. 1. THE ULTRAVIOLET ABSORPTION SPECTRA OF METHYL 1-METHYLISONIPECOTATE (III), methyl 1-methyl-1,2,3,6-tetrahydroisonicotinate (IV), and arecoline (methyl 1-methyl-1,2,5,6-tetrahydronicotinate) (VIII) in ethyl alcohol.

EXPERIMENTAL[3]

Preparation of methyl isonicotinate methobromide (Ib). The methobromide of I precipitated in 95% yield over a period of 21 hrs. from a solution of 0.17 mole of methyl isonicotinate (I) and 0.36 mole of methyl bromide in 100 ml. of methanol. After recrystallization from chloroform, Ib melted at 163–165° (dec.).

Anal. Calc'd for $C_8H_{10}BrNO_2$: Br. 34.44. Found: Br. 34.26.

Reduction of the quaternary salts of methyl isonicotinate (Ia or Ib) *over Adams' catalyst.* A solution of 10 g. of Ia or Ib in 100 ml. of methanol was shaken with 0.2 g. of platinum oxide under 2–3 atm. of hydrogen. After the pressure of hydrogen remained constant during a period of 1 hr., the solution was filtered and the solvent was removed from the filtrate by evaporation under reduced pressure. The residual solid from the reduction of the methiodide (Ia) was fractionally recrystallized from methanol-ether to give 1.4 g. (14%) of methyl 1-methylisonipecotate hydriodide (IIIa or A), m.p. 127.5–128.0°, and 1.5 g. (15%) of methyl 1-methyl-1,2,3,6-tetrahydroisonicotinate hydriodide (IVa or B), m.p. 154.5–155.5°.

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Conversion of IIIa to III by the usual methods yielded an oil, b.p. 83–86° at 7 mm., n_D^{25} 1.4590. The *methiodide* and *picrate* of III melted 150–151° and 142–143° respectively after recrystallization from ethanol.

Anal. Calc'd for $C_9H_{18}INO_2$: C, 36.13; H, 6.06.
Found: C, 36.49; H, 6.15.

Anal. Calc'd for $C_{14}H_{18}N_4O_9$: C, 43.56; H, 4.70.
Found: C, 43.77; H, 4.75.

The residual solid from the reduction of methyl isonicotinate methobromide (Ib), after recrystallization from methanol-ether, gave 8.9 g. (90%) of methyl 1-methylisonipecotate hydrobromide (IIIb), m.p. 137–138°.

Anal. Calc'd for $C_8H_{16}BrNO_2$: Br, 33.56. Found: Br. 33.46.

The *methiodide* and *picrate* derivatives of IIIb were identical with those from IIIa above.

The solid remaining from the reduction of 20 g. of crude Ia in 90 ml. of methanol over previously used platinum catalyst gave 14.4 g. (71%) of methyl 1-methyl-1,2,3,6-tetrahydroisonicotinate hydriodide (IVa or B), m.p. 148–156°. An aqueous solution of IVa was neutralized with potassium carbonate to give methyl 1-methyl-1,2,3,6-tetrahydroisonicotinate (IV) which was distilled at 14 mm. collecting three fractions: b.p. 104–105°, n_D^{25} 1.4736; b.p. 105–106°, n_D^{25} 1.4764; and b.p. 106–110°, n_D^{25} 1.4788.

The *methiodide* and *picrate* of IV were prepared and melted at 203–205° and 134–135° respectively after recrystallization from methanol.

Anal. Calc'd for (*picrate*) $C_{14}H_{16}N_4O_9$: C, 43.70; H, 4.20.
Found: C, 44.20; H, 4.47.

Reduction of the quaternary salts (Ia or Ib) *of methyl isonicotinate with sodium borohydride.* To a solution of 10.8 g. of methyl isonicotinate methiodide (Ia) or methobromide (Ib) in 200 ml. of absolute methanol 6.0 g. of sodium borohydride was added in small portions. The vigorous reaction was moderated by external cooling. After being stirred at room temperature for 0.5 hr., the methanol solution was concentrated by removal of 150 ml. of methanol by distillation under reduced pressure. The remaining solution was diluted with water, saturated with solid sodium carbonate, and extracted with ether. After drying over potassium carbonate, the ether was removed and the residual oil was fractionally distilled under 7 mm. of pressure. Methyl 1-methyl-1,2,3,6-tetrahydroisonicotinate (IV) was collected in three fractions: b.p. 95–96°, n_D^{28} 1.4766; b.p. 96–97°, n_D^{28} 1.4776; and b.p. 97–100°, n_D^{28} 1.4786, in yields of 70–75% from the methiodide Ia or the methobromide Ib. IV darkened rapidly on standing, and, after 2 months, a sample of IV on redistillation gave about one-half of the material unchanged.

Anal. Calc'd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44.
Found: C, 61.96; H, 8.68.

The *picrate* and *methiodide* were prepared from IV by the usual procedures and were purified by recrystallization from alcohol to give solids, m.p. 134–135° and 210–212°, respectively.

Anal. Calc'd for (*methiodide*) $C_9H_{16}INO_2$: C, 36.38; H, 5.43.
Found: C, 36.73; H, 5.59.

Reduction of methyl isonicotinate (I) *over Adams' catalyst.* Following the method of Feldkamp (1b) 15.0 g. of methyl iosnicotinate (I) was hydrogenated giving 11.08 g. of methyl isonipecotate, (II), b.p. 107–110° at 22 mm., n_D^{25} 1.4635. The product slowly solidified on exposure to air, apparently due to reaction with carbon dioxide.

The *hydrochloride* of methyl isonipecotate melted at 160–161°, lit. m.p. 169° (dec.) (8). The *picrate* was prepared and melted at 111–112°.

Anal. Calc'd for (*picrate*) $C_{13}H_{16}N_4O_9$: C, 41.94; H, 4.33.
Found: C, 41.89; H, 4.24.

Reductive methylation of methyl isonipecotate following the procedure of Feldkamp (1b) gave methyl 1-methylisonipecotate (III), b.p. 99–100° at 20 mm. The *picrate* and *methiodide* derivatives were prepared and melted at 147–148° and 148–149° respectively.

Reduction of methyl nicotinate methiodide (VII). To a cooled solution of 10.8 g. of VII in 200 ml. of methanol, 6.0 g. of sodium borohydride was added in portions. The solution was

stirred for 15 minutes, and about 160 ml. of solvent was removed under reduced pressure. Water was added to the residue and the amine was salted out with potassium carbonate and extracted with ether. The ethereal solution was dried over potassium carbonate and distilled yielding 2.14 g. (36%) of methyl 1-methyl-1,2,5,6-tetrahydronicotinate (arecoline), b.p. 95–100° at 10 mm., n_D^{28} 1.4778.

The *methiodide* and *picrate*, after recrystallization from ethanol, melted 167–170° and 110–112°, respectively; lit. m.p. 173–174° (9) and 112° (10). These derivatives did not depress the melting points of derivatives prepared from an authentic sample of arecoline.

SUMMARY

Methyl 1-methyl-1,2,3,6-tetrahydroisonicotinate (IV) has been obtained from the partial reduction of methyl isonicotinate methiodide with either sodium borohydride or used Adams' catalyst. The complete characterization of the compound is described. The reduction of methyl isonicotinate to methyl 1-methylisonipecotate (III) can best be effected by the use of platinum oxide at high pressure followed by reductive methylation.

The ultraviolet spectrum of IV shows a marked resemblance to that of arecoline, obtained by the reduction of methyl nicotinate methiodide with sodium borohydride.

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