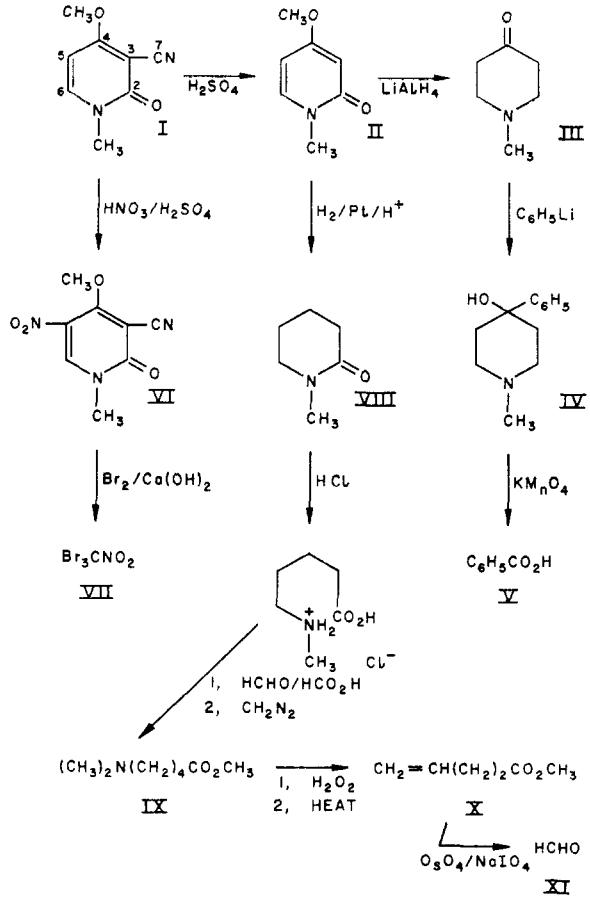

methylated with formic acid and formaldehyde and esterified with diazomethane to methyl 5-dimethylaminovalerate IX, b.p. 90° (20 mm.),[9] characterized as its methiodide (*anal.* Calcd. for $C_9H_{20}O_2NI$: C, 35.88; H, 6.69; N, 4.65; I, 42.13. Found: C, 35.89; H, 6.81; N, 4.77; I, 42.02). The N-oxide of IX when pyrolyzed yielded the methyl ester of allylacetic acid X, identified by comparison of its infrared spectrum with that of an authentic synthetic sample, b.p. 127–128° (760 mm.) (*anal.* Calcd. for $C_6H_{10}O_2$: C, 63.13; H, 8.83. Found: C, 63.3; H, 8.86). The olefin was cleaved using sodium periodate and osmium tetroxide[10] and the liberated formaldehyde XI, containing carbon 6 of ricinine, isolated as the dimedon derivative, m.p. 191–192°.[11]

The results obtained with the use of the procedures outlined above are recorded in Table I.

TABLE I

LOCATION OF RADIOACTIVITY IN RICININE

Precursor	% of activity of ricinine C-4	C-5	C-6
Acetate-2-^{14}C	0.0	0.3	Not detd.
Succinic acid-2,3-^{14}C	0.0	0.0	Not detd.
Glycerol-1-^{14}C	25.8	2.2	19.7
Glycerol-2-^{14}C	2.2	38.8	0.0

As expected[3] there is virtually no activity associated with carbons 4 and 5 of ricinine after feeding acetate-2-^{14}C and succinic acid-2,3-^{14}C. From results reported previously[2] it is clear that at least part of the glycerol is broken down to simpler units prior to incorporation. However, the fact that carbon 5 of ricinine from the glycerol-2-^{14}C experiment contains an appreciable percentage of the incorporated activity while carbon 4 and carbon 6 contain little or no activity suggests that part of the glycerol was incorporated intact into ricinine at positions 4, 5, and 6. The high activity at carbon 4 and carbon 6, and low activity at carbon 5 after the feeding of glycerol-1-^{14}C lends support to this suggestion.

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THE CORRECTED STRUCTURE OF A KETOAMIDE ARISING FROM THE METABOLISM OF (−)-NICOTINE

Sir:

During the course of studies[1] on the metabolism of (−)-nicotine, a ketonic metabolite $C_{10}H_{12}N_2O_2$ was isolated from the urine of dogs, and later from rats.[2] This compound, which has amphoteric properties, as exhibited in its behavior toward ion exchange resins, was ostensibly obtained in pure form and then hydrolyzed to a keto acid $C_9H_9NO_3$ and methylamine. The oxime of the keto acid then was subjected to a Beckmann rearrangement. The isolation of 3-pyridylacetic acid from the reaction products of this rearrangement was a crucial point in the conclusion[1] that the ketoamide had the structure of γ-(3-pyridyl)-β-oxo-N-methylbutyramide. On the basis of current data, which include both a degradation and a synthesis, the foregoing structure which arose through technical errors of a yet undetermined nature is incorrect. Since the ketoamide, now shown to be γ-(3-pyridyl)-γ-oxo-N-methylbutyramide, appears to occupy a key role as an intermediate in the mammalian degradation of the pyrrolidine ring of (−)-nicotine to γ-(3-pyridyl)-γ-oxobutyric acid,[3] γ-(3-pyridyl)-γ-hydroxybutyric acid,[4] 3-pyridylacetic acid,[5] and other substances, a summary of data necessary to the immediate correction of the erroneous formula is presented.

By a procedure patterned after the original,[1] the ketoamide was isolated from the urine of dogs after oral administration of (−)-cotinine. The colorless crystals, R_f 0.74 upon paper chromatography in the ammonia system,[6] were obtained

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from acetone and dried at 60° and 1 mm., m.p. 118.5–119.5°.[7]

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.59. Found: C, 62.59; H, 6.36; N, 14.65.

The analytical material upon hydrolysis yielded a keto acid, m.p. 161–162° after recrystallization from methanol.

Anal. Calcd. for $C_9H_9NO_3$: C, 60.32; H, 5.06; N, 7.82. Found: C, 59.92; H, 4.92; N, 7.85.

All properties of the keto acid corresponded to those of γ-(3-pyridyl)-γ-oxobutyric acid and not to those of a β-oxo compound as previously reported.[1] The keto acid, which did not upon admixture depress the melting point of an authentic sample[6,8] (m.p. 161–163°), was converted to the methyl ester, m.p. 65.5–67.5° (micro). The ester did not depress the melting point of an authentic sample,[8] m.p. 65.5–67.5°, upon admixture and gave a picrate, m.p. 126–128° (micro), which corresponded in turn to an authentic synthetic sample by melting point and mixed melting point.

Anal. Calcd. for $C_{16}H_{14}N_4O_{10}$: C, 45.50; H, 3.34; N, 13.26. Found: C, 45.55; H, 3.36; N, 13.15.

The foregoing keto ester from the metabolic ketoamide (190 mg.) was treated with an excess of hydroxylamine hydrochloride in pyridine and alcohol.[9] A chloroform solution of the resultant oximino ester was chromatographed on Florisil with acetone–benzene to obtain methyl γ-(3-pyridyl)-γ-oximinobutyrate, m.p. 70° (micro).

The oximino methyl ester in chloroform was treated with phosphorus oxychloride essentially in accordance with the previously described conditions[9] for a Beckmann rearrangement of the corresponding oximino ethyl ester. After hydrolysis and alkalinization, the reaction mixture, in contrast to our previous report,[1] contained no 3-pyridylacetic acid. The reaction mixture was extracted with chloroform to obtain 3-aminopyridine which was identified as the picrate, m.p. 199.5–200.5° (micro).

Anal. Calcd. for $C_{11}H_9N_5O_7$: C, 40.87; H, 2.81. Found: C, 40.51; H, 3.10.

The infrared absorption spectra (KBr pellet) of the foregoing and an authentic sample, m.p. 199.5 200.5° (micro), of the picric acid salt showed no essential differences. Upon admixture with the authentic sample, the melting point of the picrate derived from the degradation was not depressed.

The isolation of 3-aminopyridine *via* the Beckmann rearrangement at once pointed to a γ-position for the oxo group in the metabolic ketoamide. Confirmation of this and the demonstration that the structure is actually γ-(3-pyridyl)-γ-oxo-N-methylbutyramide was achieved through a total synthesis of the metabolite. Synthetic methyl γ-(3-pyridyl)-γ-oxobutyrate was treated with an excess of saturated aqueous methylamine overnight at room temperature. The reaction mixture was extracted with chloroform. The residue from evaporation of the chloroform was dissolved in ethyl acetate and treated with decolorizing carbon. The solution deposited crystalline γ-(3-pyridyl)-γ-oxo-N-methylbutyramide which was recrystallized from benzene to obtain the analytical sample, in low yield, m.p. 119–120°.

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.59. Found: C, 62.59; H, 6.15; N, 14.59.

The sample did not depress the melting point of the metabolic product. The infrared spectra of the natural and synthetic material in chloroform showed no essential difference.[10]

The establishment of the corrected structure of the ketoamide as the methylamide of γ-(3-pyridyl)-γ-oxobutyric acid together with its synthesis provides opportunity for additional studies on the intermediary metabolism of (−)-nicotine.

Details of the foregoing as well as an improved two-step synthesis of γ-(3-pyridyl)-γ-oxo-N-methylbutyramide will be submitted for publication shortly.

(7) This determination was made in a capillary with a heating rate of 0.5°/min., a convenient rate. Slower heating (0.1°/min. after 110°) gave a value of 112.8–113.5°. The compound was found to melt in the same range as the ketoamide obtained[1] previously from dog urine after intravenous administration of (−)-cotinine. Admixture of the two samples of the ketoamide produced no melting point depression. When melted in a capillary, the compound showed some evidence of decomposition, a yellow color, which was more pronounced at lower heating rates. The melt, which showed no tendency to become crystalline, cochromatographed with unmelted material in the ammonia system[6] and showed only one Koenig positive zone. The ketoamide melted at 120–123° on the hot stage (0.5°/min.) and resolidified on cooling.

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(10) The authors are grateful to Mr. J. Scott Osborne, Department of Research and Development, The American Tobacco Company, for the infrared determinations.

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BIOSYNTHESIS IN THE AMARYLLIDACEAE. INCORPORATION OF 3-C^{14}-TYROSINE AND PHENYLALANINE IN *NERINE BOWDENII* W. WATS.[1]

Sir:

Two recent reports have shown that 3-C^{14}-tyrosine is not incorporated into ring A and the benzylic carbon of haemanthamine (I, R = H) in either *Sprekelia formosissima*[2] or *Haemanthus natalensis*,[3] nor is this amino acid a precursor of analogous C_6–C_1 fragments in either haemanthidine (I, R = OH) or tazettine (II) in *S. formosissima*.[2] Because 3-C^{14}-phenylalanine has been reported to be incorporated into ring A and the benzylic carbon of lycorine (III),[4,5] it seemed desirable to examine the

(1) Supported in part by a research grant to Iowa State University of Science and Technology from the National Heart Institute (HE 07503-01).

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