made alkaline with 20% sodium hydroxide and extracted with ether. Drying and removal of the ether left an oil which was distilled to give 12.4 g. (49% over-all yield) of XXIII, b.p. 147–157° (0.3 mm.).

Anal. Calcd. for $C_{14}H_{16}N_2O$: N (basic), 6.13. Found: N, 6.16.

The hydrochloride salt of XXIII, recrystallized from isopropyl alcohol–ether, formed small white crystals, m.p. 175–177° dec.

Anal. Calcd. for $C_{14}H_{17}ClN_2O$: C, 63.53; H, 6.47; Cl, 13.40; N-methyl, 5.7. Found: C, 62.75; H, 6.37; Cl (ionic), 13.25; N-methyl, 5.0.

1-(β-Acetoxyphenethyl)-2-acetylimino-1,2-dihydropyridine (XXV).—After the initial reaction accompanied by considerable evolution of heat had subsided, a solution of 6.5 g. (0.03 mole) of XXIV in 25 ml. of acetic anhydride was heated on a steam-bath for 2.5 hours. Concentration *in vacuo* afforded a thick, viscous residue which was dissolved in dilute hydrochloric acid and made alkaline with a saturated solution of sodium carbonate to give a precipitate of 5.5 g. of tan needles, m.p. 90–93°. Recrystallization from benzene–Skellysolve B yielded 4.4 g. (49%) of XXV as fine, cream-colored needles, m.p. 104–107°.

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: N (basic), 4.69. Found: N, 4.68.

The hydrochloride salt of XXV was recrystallized from ethanol–ether to give colorless crystals, m.p. 177–179° dec.

Anal. Calcd for $C_{17}H_{19}ClN_2O_3$: C, 60.98; H, 5.72; Cl, 10.59. Found: C, 60.88; H, 5.93; Cl (ionic), 10.37.

1-(β-Hydroxyphenethyl)-2-pyridone (XXVI).—A solution of 7.7 g. (0.036 mole) of XXIV and 25 g. of potassium hydroxide pellets in 150 ml. of 50% ethanol was boiled on a steam-bath for 27 hours. (Premature work-up at the end of 3 hours resulted in recovery of starting material.) Evolution of ammonia was rapid at first, continued throughout the heating period, and slowed down toward the end. The solution was concentrated *in vacuo* to remove the alcohol and the precipitated oil dissolved in ether. The ether solution yielded a total of 5.9 g. of colorless needles, m.p. 116–121°. Recrystallization from isopropyl alcohol–Skellysolve B afforded 5.3 g. (69%) of XXVI, m.p. 124–128°.[22]

The hydrochloride salt, crystallized from ethanol–ether, melted with evolution of gas at 156–158°. The compound readily gives up hydrogen chloride on vacuum drying.

Anal. Calcd. for $C_{13}H_{14}ClNO_2$: Cl, 14.09. Found: Cl (ionic), 13.70 (dried *in vacuo* at room temperature); Cl, 8.51 (dried *in vacuo* at 60°).

Acknowledgment.—The authors are indebted to Mr. Dean F. Cortright and to Miss Mary Unroe for the basic nitrogen and ionic halogen determinations, and particularly for the ultraviolet absorption data and dissociation constants.

(22) J. A. Gautier, *Compt. rend.*, **198**, 1430 (1934), *C. A.*, **28**, 4422[1], reports m.p. 127° for this compound prepared by the alkaline ferricyanide oxidation of the hydroxyphenethylpyridinium salt. C. Alberti, *Gazz. chim. ital.*, **86**, 1181 (1956), *C. A.*, **52**, 2005*i* (1958), reports m.p. 117–118° for the compound prepared by the aluminum isopropoxide reduction of 1-phenacyl-2-pyridone.

DECATUR, ILL.

[CONTRIBUTION NO. 459 FROM THE CENTRAL RESEARCH DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS AND CO.]

Synthesis of 3-Substituted 5-Hydroxy-3-pyrrolin-2-ones

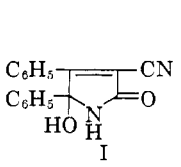
BY E. G. HOWARD, R. V. LINDSEY, JR., AND C. W. THEOBALD

RECEIVED FEBRUARY 11, 1959

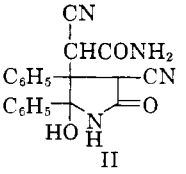
α,β-Diketones react in water at *p*H 7–10 with acetamides substituted in the α-position with strong electron-withdrawing groups to give the corresponding 3-substituted 5-hydroxy-3-pyrrolin-2-ones.

The only report of the reaction of α,β-diketones with substituted acetamides is the recent one of Jocelyn and Queen.[1] We have independently investigated this reaction under conditions different from those reported and have obtained significantly different results.

Jocelyn and Queen found that benzil reacts with cyanoacetamide in the presence of piperidine to give a pyrrolinone, I, which was converted to a substituted pyrrolidone, II, when heated with additional cyanoacetamide. Only products corresponding to II were isolated from reactions of aliphatic 1,2-



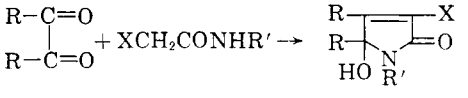
I



II

diketones and cyanoacetamide.

We have found that α,β-diketones, including aliphatic diketones, react smoothly in aqueous solutions at *p*H 7–10 at room temperature with a variety of acetamides possessing a strong electron-withdrawing group in the α-position to give 3-substituted 5-hydroxy-3-pyrrolin-2-ones.



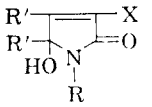
The reaction is exothermic and is characterized by loss of the yellow color of the diketone and separation of the product, usually as a white crystalline solid. Control of the *p*H is essential to avoid decomposition of the diketone and the product. Diacetyl, benzil and 1,2-cycloheptanedione all participated in this reaction. Acetamides substituted on the α-position with cyano, carbamoyl, ethoxycarbonyl, acetyl and quaternary ammonium groups were employed successfully. Phenylacetamide did not react.

In a typical example, cyanoacetamide reacted with diacetyl to give a product for which the empirical formula $C_7H_8O_2N_2$ was established by elemental analyses and molecular weight determinations. The product smoothly absorbed one mole of hydrogen with palladium catalyst, and failed to react with typical carbonyl group reagents. The absence of ketone carbonyl strongly

(1) P. C. Jocelyn and A. Queen, *J. Chem. Soc.*, 4437 (1957).

TABLE I

3-SUBSTITUTED-5-HYDROXY-3-PYRROLIN-2-ONES



X	R	R′	Yield, %	M.p., °C.	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CN	H	CH_3	61	145–147 d.	$C_7H_8N_2O_2$	55.25	55.29	5.30	5.35	18.42	18.27[b]
$COOC_2H_5$	H	CH_3	60	167–172 d.	$C_9H_{13}NO_4$	54.26	54.21	6.58	5.02	7.03	7.06[c]
CH_3CO	H	CH_3	65	153–168 d.	$C_8H_{11}NO_3$	56.79	56.81	6.56	6.64	8.28	8.36
$CONH_2$	H	CH_3	88	226–228 d.	$C_7H_{10}N_2O_3$	49.39	49.21	5.92	5.93	16.46	16.25
CN	H	$(CH_2)_3$[a]	49	158–162 d.	$C_{10}H_{12}N_2O_2$	62.48	62.63	6.30	6.34	14.58	15.49
$CONH_2$	H	$(CH_2)_3$[a]	79	211 d.	$C_{10}H_{14}N_2O_3$	57.14	57.25	6.71	6.79	13.33	13.25
CN	H	C_6H_5	80	181–183 d.	$C_{17}H_{12}N_2O_2$	73.90	74.42	4.38	4.61	10.14	10.23
$CONH_2$	H	C_6H_5	82	237 d.	$C_{17}H_{14}N_2O_3$					9.52	9.31
CN	CH_2=$CHCH_2$	C_6H_5	100	170	$C_{20}H_{16}N_2O_2$	75.93	76.01	5.10	5.10		
CN	CH_2=$CHCH_2$	CH_3	68	Liquid	$C_{10}H_{12}N_2O_2$	62.50	62.01	6.30	6.35	14.58	14.78
CN	$N(CH_3)_2$	CH_3	82	122–122.5	$C_9H_{13}N_3O_2$	55.39	55.68	6.71	6.68	21.53	21.48
CN	CH_3, C_2H_5[f]	H	64	151.5–152	$C_8H_{10}N_2O_2$	57.81	58.02	6.05	6.11	16.86	16.84
CN	*i*-C_3H_7	H	42	165–170	$C_{11}H_{16}N_2O_2$	63.43	63.90	7.74	7.72	13.46	13.27
CN	α-C_4H_3O	H	45	203–205	$C_{13}H_8N_2O_4$	60.95	61.06	3.15	3.19	10.94	10.89
$C_5H_5N^+Cl^-$	H	CH_3	42	Dec.	$C_{11}H_{13}ClN_2O_2$	51.07	51.16	5.85	6.03	10.85	10.61[d]
n-$C_{12}H_{25}N^+(CH_3)_2Cl^-$	H	CH_3	70		$C_{20}H_{39}ClN_2O_2$					7.13	7.27[e]

[a] R′R′. [b] Calcd. mol. wt. 152, found 148. [c] Calcd. mol. wt. 199, found 191. [d] Calcd. mol. wt. 258, found 267. [e] Calcd. Cl, 9.03, found 9.50. [f] Related positions not known.

suggested that the product was formed by a cyclization reaction, for which the following possibilities were considered: (1) direct condensation

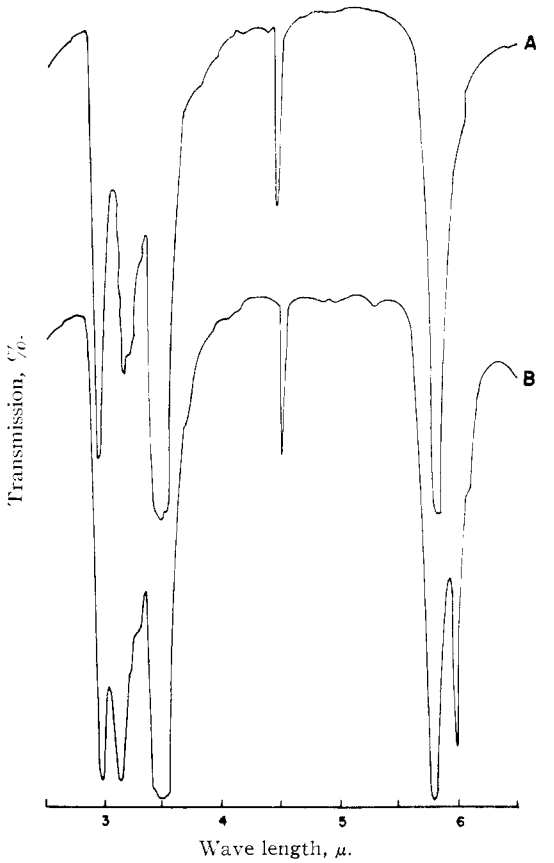
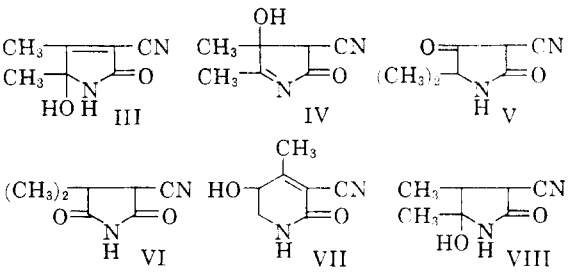


Fig. 1.—Infrared spectrum of 3-cyano-4,5-dimethyl-5-hydroxy-2-pyrrolidinone (A) and 3-cyano-4,5-dimethyl-5-hydroxy-3-pyrrolin-2-one (B).

to give III or IV, (2) participation of a rearranged diketone (benzilic acid type) to give V or its isomer VI, and (3) reaction of an enol form of the diketone to give six-membered structures such as VII.



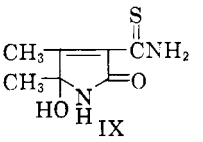
Compound VI was eliminated since it is reported[2] to melt at 116°, whereas our product melted at 145–147°. Of the remaining 5-membered structures, I is clearly favored on the basis of infrared studies.[3] The infrared spectrum showed a sharp, strong –NH band at 2.98 μ as well as a broad, strong –OH band at 3.14 μ. A strong carbonyl band occurred at 5.79 μ. This shift from the normal carbonyl position is in keeping for a conjugated γ-lactam. That the nitrile group is conjugated is shown[4] by the position of its absorption band at 4.51 μ compared with that at 4.47 μ for the hydrogenated product VIII. Finally, the intensity of the absorption for the carbon–carbon double bond reflects the asymmetrical polar substitution, and the location of the band at 5.98 μ indicates the absence of vinyl hydrogen. Six-membered ring structures such as VII were eliminated on the basis that benzil,[1] which cannot enolize, gave the same type of products as were obtained from diacetyl, as shown by both chemical and infrared studies.

The pyrrolinones are highly reactive compounds. Strong acids such as hydrogen chloride or sulfuric acid converted III under anhydrous conditions into a refractory isomeric solid of unknown structure. The addition of hydrogen sulfide to the cyano group of III gave the corresponding thiocarbamoylpyrrolinone, IX. Alcoholic solutions of

(2) F. Dickens, L. Harton and J. F. Thorpe, *J. Chem. Soc.*, **125**, 1840 (1924).

(3) We wish to acknowledge the help of Prof. Richard C. Lord in interpreting the infrared spectra of the compounds reported herein.

(4) R. E. Kitson and N. E. Griffith, *Anal. Chem.*, **24**, 334 (1952).



IX

III reacted with aromatic diamines to give golden colored precipitates. The one from *o*-phenylenediamine reacted with diacetyl in water to give 2,3-dimethylquinoxaline.[5] This result suggests that these products are simple addition complexes.

Experimental[6]

Materials.—1,2-Cycloheptanedione was prepared by selenium dioxide oxidation of cycloheptanone,[7a] conveniently obtained by pyrolysis of suberic acid.[7b] Acetoacetamide was prepared from ammonium carbonate and diketene.[8] Ethyl malonamate was obtained by thermal decomposition of the imino-ester hydrochloride from ethyl cyanoacetate, ethyl alcohol and hydrogen chloride.[9] The addition of chloroacetamide to pyridine gave carbamoylmethylpyridinium chloride.[10]

Dimethyldodecylcarbamoylmethylammonium chloride was prepared by warming a benzene solution of dimethyl dodecylamine and chloroacetamide. It was recrystallized from petroleum ether, m.p. 56°.

Anal. Calcd. for $C_{16}H_{35}ClON_2$: Cl, 11.55; N, 9.13. Found: Cl, 11.34; N, 9.55.

3-Cyano-4,5-dimethyl-5-hydroxy-3-pyrrolin-2-one (III).—The synthesis of this compound is given as a typical example of the method by which the products listed in Table I were obtained. To a mixture of 16.8 g. (0.2 mole) of cyanoacetamide, 17.2 g. of freshly distilled diacetyl and 25 ml. of water was added six drops of 10% sodium hydroxide. This was the minimum amount necessary to cause reaction. The temperature rose rapidly to 50° and cooling was applied to prevent any further temperature rise. After the mixture had been allowed to stand for one hour, 9.0 g. of solid was collected by filtration. The mother liquor was allowed to stand overnight and was cooled in an ice-bath to obtain an additional 6.0 g. of solid; total yield 15 g. (53%) of crude product. Both fractions were very soluble in water. The product melted at 145–147° dec. after recrystallization from nitromethane.

Anal. Calcd. for $C_7H_6O_2N_2$: C, 55.25; H, 5.30; N, 18.42; mol. wt., 152. Found: C, 55.29; H, 5.35; N, 18.27; mol. wt., 148.

In those examples in which the reactants were insoluble in water, *e.g.*, benzil, mixtures of ethyl alcohol and water were used as the reaction medium.

The products were usually recrystallized from water, alcohol or nitromethane. The products containing quaternary ammonium groups did not precipitate from the reaction media and were isolated by first neutralizing the mixture and then removing the water under reduced pressure. In the case of 3-(dimethyldodecylammonium)-5-hydroxy-4,5-dimethyl-3-pyrrolin-2-one chloride, crystallization could not be induced. The product was purified by dissolving in benzene, filtering to remove traces of sodium chloride, and drying by vacuum distillation to give a taffy-like product. The one liquid product, 1-allyl-4,5-dimethyl-3-cyano-5-hydroxy-3-pyrrolin-2-one, could not be distilled without decomposition. The product formed as an oily precipitate which was analyzed directly.

4,5-Dimethyl-3-thiocarbamoyl-5-hydroxy-3-pyrrolin-2-one (IX).—Hydrogen sulfide was passed through a mixture of 15.2 g. (0.1 mole) of 3-cyano-4,5-dimethyl-5-hydroxy-3-pyrrolin-2-one (III), 50 ml. of absolute ethyl alcohol and 2 g. of triethanolamine for 10 hours at 26–30°. After the mixture had been allowed to stand for two days, 13 g. of yellow product was collected. A sample was recrystallized from nitromethane, m.p. 172–173° with decomposition beginning at 155°.

Anal. Calcd. for $C_7H_{10}N_2O_2S$: C, 45.14; H, 5.41; N, 15.05; S, 17.22. Found: C, 45.57; H, 5.41; N, 15.28; S, 17.18.

This substance gave a bright yellow solution in dilute hydrochloric acid.

Addition Complex between 3-Cyano-4,5-dimethyl-5-hydroxy-3-pyrrolin-2-one and *o*-Phenylenediamine.—When a mixture of 7.6 g. (0.05 mole) of the pyrrolinone, 5.4 g. (0.05 mole) of *o*-phenylenediamine, and 25 ml. of absolute alcohol was warmed, 11 g. of a gold-colored solid precipitated, m.p. 121–122°.

Anal. Calcd. for $C_{13}H_{61}O_2N_4$: C, 59.99; H, 6.20; N, 21.53. Found: C, 60.45; H, 6.26; N, 21.41.

A sample of this material was shown by X-ray diffraction to differ markedly from the starting materials; hence, it was not a physical mixture of the two components. An aqueous solution of this substance reacted with diacetyl to give 2,3-dimethylquinoxaline, indicating that the *o*-phenylenediamine was only loosely held in the complex. A similar complex formed between *p*-phenylenediamine and the pyrrolinone melted at 172–174° with decomposition beginning at 165°.

3-Cyano-4,5-dimethyl-5-hydroxy-2-pyrrolidinone.—A solution of 50 g. of 3-cyano-4,5-dimethyl-5-dihydroxy-3-pyrrolin-2-one in 100 ml. of methanol was hydrogenated at room temperature with 1 g. of 5% palladium-on-charcoal catalyst under 1500 lb./sq. in. hydrogen pressure. The catalyst was removed by filtration and the filtrate was allowed to stand, whereupon 33 g. of product precipitated. After recrystallization from absolute ethyl alcohol, the material melted at 139.5–141.5° with no evidence of decomposition.

Anal. Calcd. for $C_7H_{10}O_2N_2$: C, 54.53; H, 6.54; N, 18.18. Found: C, 54.66; H, 6.59; N, 18.69.

3-Ethoxycarbonyl-4,5-dimethyl-5-hydroxy-2-pyrrolidinone.—The method used was the same as above. The reaction mixture was filtered and evaporated to dryness under 1 mm. pressure at 50°. From 66.3 g. of starting material, 64 g. of viscous product was obtained.

Anal. Calcd. for $C_9H_{15}O_4N$: N, 6.98. Found: N, 6.99.

Reaction of 3-Cyano-4,5-dimethyl-5-hydroxy-3-pyrrolin-2-one with Anhydrous Sulfuric Acid.—A solution of 3.06 g. (0.02 mole) of 3-cyano-4,5-dimethyl-5-hydroxy-3-pyrrolin-2-one in 25 ml. of acetic anhydride was cooled to 5° and a drop of concentrated sulfuric acid was added. The temperature rose rapidly to 12°, and a pale pink solid precipitated, weight 1.6 g. Addition of ether to the filtrate caused 1.2 g. more of product to precipitate. The product was dissolved in dimethylformamide, treated with decolorizing charcoal, filtered, and reprecipitated by the addition of benzene to the filtrate. The solid gradually decomposed without melting when heated above 180°.

Anal. Calcd. for $C_7H_8O_2N_2$: N, 18.42. Found: N, 18.40.

The same product was obtained by treating the pyrrolone in ether with dry hydrogen chloride.

3-Cyano-5-methyl-4-phenyl-5-hydroxy-3-pyrrolin-2-one.—To a solution of 5.7 g. (0.068 mole) of cyanoacetamide and 10 g. (0.068 mole) of 1-phenyl-1,2-diketopropane in a mixture of 20 ml. of ethyl alcohol and 30 ml. of water was added 10 drops of 10% aqueous sodium hydroxide. The temperature rose from room temperature to 38° and on cooling, 3.0 g. of product crystallized, m.p. 150–160°. After recrystallization from methanol, it weighed 1.5 g. (10%), m.p. 154–155°.

Anal. Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.29; H, 4.71; N, 13.08. Found: C, 67.00; H, 4.84; N, 12.88.

Structure assignment is based on the similarity of ultraviolet absorption spectra taken in ethyl alcohol of 3-cyano-5-methyl-4-phenyl-5-hydroxy-3-pyrrolin-2-one (λ_{max} 290 mμ, ε 9,630) and of 3-cyano-4,5-diphenyl-5-hydroxy-3-pyrrolin-2-one (λ_{max} 290 mμ, ε 9,150). The pyrrolinones with alkyl groups in the four position absorb at shorter wave lengths, a typical example being 3-cyano-4,5-dimethyl-5-hydroxy-3-pyrrolin-2-one (λ_{max} 218 mμ, ε 11,800).

Cyanoacetodimethyl Hydrazide.—A mixture of 22.6 g. (0.2 mole) of ethyl cyanoacetate and 12 g. (0.2 mole) of

(5) S. Gabriel and A. Sonn, *Ber.*, **40**, 4852 (1907).

(6) We are indebted to Dr. E. H. Man who prepared some of the compounds.

(7) (a) M. Godchot and G. Cauquil, *Compt. rend.*, **202**, 326 (1936); (b) I. Vogel, *J. Chem. Soc.*, 2033 (1928).

(8) W. Muller, U. S. Patent 2,615,917.

(9) B. M. Gupta, *J. Chem. Soc.*, **119**, 303 (1921).

(10) A. H. Cook, J. Downer and B. Hornung, *ibid.*, 502 (1941).

1,1-dimethylhydrazine was stored at room temperature for one week. There resulted 20 g. of crude solid which, after recrystallization from methanol, melted at 116–6.5°.

Anal. Calcd. for $C_5H_9N_3O$: C, 47.23; H, 7.13; N, 33.05. Found: C, 47.83; H, 7.27; N, 32.93.

WILMINGTON 98, DELA.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA]

The Biogenesis of the Nicotiana Alkaloids. VIII. The Metabolism of Nicotine in *N. tabacum*[1]

BY EDWARD LEETE AND VIRGINIA M. BELL

RECEIVED MARCH 25, 1959

In order to investigate the metabolism of nicotine in the intact tobacco plant, methyl-C^{14} nicotine and nicotine-2,5-C^{14} were fed, in separate experiments, to *N. tabacum* plants. Nicotine was isolated from the plants at various times, from one to seven weeks after administration of the tracers. The recovered nicotine was radioactive in each case and systematic degradation indicated that there had been no randomisation of activity. The average recovery of the 2,5-labeled nicotine was about 6%, whereas the recovery of the methyl labeled nicotine was only about 1%, indicating extensive metabolic breakdown of the radioactive alkaloids. Radioactive choline was isolated from a plant which had been fed methyl labeled nicotine and degradation indicated that 90% of the activity was located on the methyl groups of the choline. Nicotine thus acts as a methyl donor in the tobacco plant.

The administration of ornithine-2-C^{14} to the roots of an intact *N. tabacum* plant produces nicotine labeled on the 2-and 5-carbons of the pyrrolidine ring.[2] By allowing the tobacco to grow for considerable lengths of time (up to 9 weeks) after administration of the ornithine, we found that there was very little decrease in the total radioactivity located in the nicotine.[3] These results suggested that there was no gross metabolic breakdown of nicotine in the healthy living plant. However, it was considered likely that the N-methyl group of nicotine would be in equilibrium with methyl acceptors such as ethanolamine or homocysteine. In order to test this hypothesis we have fed methyl-C^{14}-nicotine to *N. tabacum* plants, and then the nicotine was reisolated and assayed for activity 1, 3, 5 and 7 weeks after administration of the tracer. The methyl labeled nicotine was obtained by the reaction of *l*-nornicotine (isolated from *N. glutinosa*) with methyl iodide-C^{14}. The results are summarized in Table I, and it is seen that only about 1% of the administered nicotine was recovered from the plant. There was no significant difference in the specific activity of the nicotine isolated at different times after feeding the tracer. The small differences in the percentage recovery of activity, which were observed, were probably due to unavoidable variations in the individual plants. In view of the large loss of radioactive carbon from the nicotine, it was of interest to see whether there had been any randomization of activity. The method which has been previously used for the determination of activity on the methyl group of nicotine has been that of Brown and Byerrum.[4] This involves heating nicotine with hydriodic acid to yield methyl iodide which is absorbed in triethylamine to form the quaternary salt which is assayed. Since the accuracy of the counting is usually no better than 4%, this method of degradation fails to establish whether a small amount of activity is present in the rest of the nicotine molecule. Therefore in the present work we have demethylated the radioactive nicotine with silver hydroxide and isolated the resultant nornicotine by chromatography. The nornicotine was completely inactive, indicating that there had been no randomization of activity. In order to discover whether the methyl group of nicotine was transferred to methyl acceptors, choline was isolated from the plant harvested one week after feeding the radioactive nicotine. It was indeed radioactive and degradation indicated that 90% of the activity was located on the methyl groups.

Biosynthetic nicotine-2,5-C^{14} also was fed to a group of tobacco plants to serve as a control in our study of the lability of the N-methyl group. Rather surprisingly, we found that there was considerable metabolism of this ring labeled nicotine; however, it was not as extensive as with the methyl labeled nicotine. Again there was no significant change in the amount of activity recovered in the nicotine, isolated at various times after feeding the tracer (see Table I). Systematic degradation of the reisolated nicotine indicated that all the activity was still located on the 2- and 5-carbons of the pyrrolidine ring.

The high initial loss of activity from both labeled nicotines, with little subsequent decrease in the activity after one week, is compatible with the hypothesis that metabolism of the radioactive nicotine occurs in the roots, which are the main site of nicotine synthesis in *N. tabacum*, and then little further metabolism occurs after the nicotine has been translocated to the leaves, in agreement with our previous findings.[3] The significantly higher recovery of the ring labeled nicotine is presumably a measure of the greater stability of the pyrrolidine ring to metabolic breakdown.

Tso and Jeffrey[5] have recently studied the fate of N^{15}-labeled tobacco alkaloids in *N. glauca* and *rustica*. They also found that there was extensive metabolism of nicotine when it was fed to the roots

(1) Part VII: E. Leete, *Chemistry and Industry*, 1477 (1958). This work was presented at the 135th meeting of the American Chemical Society, Boston, April 1959; and was supported in part by research grant M-2662 from the National Institute of Mental Health, Public Health Service.

(2) E. Leete and K. J. Siegfried, THIS JOURNAL, **79**, 4529 (1957).

(3) E. Leete, *ibid.*, **80**, 2162 (1958).

(4) S. A. Brown and R. U. Byerrum, *ibid.*, **74**, 1523 (1952).

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