After standing overnight in an icebox 2.2 g. (86%) of colorless needles separated from the reaction mixture which after recrystallization from alcohol melted at 219–220° (dec.).

Anal. Calcd. for $C_7H_4ClN_3O$: C, 46.24; H, 2.22; N, 23.13. Found: C, 46.22; H, 2.38; H, 23.16.

4-Hydroxylamino-7-methoxybenzo-1,2,3-triazine (X). The 2-amino-4-methoxybenzamidoxime (VI) was prepared from 2-amino-4-methoxybenzonitrile[11] in a manner quite analogous to that described above for the amidoxime (VII). The crude VI (2 g.) was dissolved without further purification in 2*N* hydrochloric acid and sodium nitrite (0.7 g.) dissolved in water was added dropwise with ice-cooling. The benzotriazine (X) which separated (1.1 g., 62.5%) was recrystallized from glacial acetic acid and dried for analysis over potassium hydroxide at 100°; m.p. 215–216 (dec.).

Anal. Calcd. for $C_8H_8N_4O_2$: C, 49.99; H, 4.20; N, 29.15. Found: C, 49.75; H, 4.00; N, 29.23.

When the mother liquor of the diazotization of VI was kept overnight in an ice-box 0.2 g. (12.5%) of *4-hydroxy-7-methoxybenzo-1,2,3-triazine* (XI) crystallized. XI was recrystallized from water, colorless needles, m.p. 220–221° (dec.).

Anal. Calcd. for $C_8H_7N_3O_2$: N, 23.72. Found: N, 24.19.

Reduction of VIII with sodium boronhydride. A solution of $NaBH_4$ (2 g.) in methanol was added to a finely divided suspension of VIII (2 g.) in 300 ml. of methanol and refluxed for 4 hr. Addition of water precipitated 0.7 g. of 2-amino-4-chloro-benzonitrile (XII), m.p. 160–161°. XII was identified by a mixed melting point with an authentic sample.[9]

When VIII was dissolved in 2*N* NaOH, 2*N* Na_2CO_3, or dilute $NaHCO_3$ the solution became turbid after a few minutes and the nitrile XII precipitated in an almost quantitative yield.

THE OHIO STATE UNIVERSITY
RESEARCH FOUNDATION
COLUMBUS 10, OHIO

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Morphine-*N*-Methyl-C^{14}

KATHRYN S. ANDERSEN AND L. A. WOODS

Received September 18, 1958

Several years ago Rapoport *et al.*[1] reported the synthesis of morphine-*N*-methyl-C^{14} from codeine-*N*-methyl-C^{14} in a 22% yield. In order to increase the availability of labeled morphine for pharmacological studies, methods of preparation were investigated which would give a good yield of product in a one step synthesis from normorphine.

A consideration of the instability of morphine toward high temperatures, strong acids, and strong alkalies, of the ease with which the molecule is *O*-methylated, and of the susceptibility of the isolated carbon-carbon bond toward catalytic hydrogenation,[2] eliminated selection of many of the classical methods for *N*-methylation. Since Tarpey *et al.*[3] have shown in the case of 4-phenyl-4-carbethoxypiperidine that formaldehyde-C^{14}-formate reductive methylation occurs exclusively with incorporation of the *N*-methyl-C^{14} group into the molecule, this method was adapted to the synthesis of morphine-*N*-methyl-C^{14}.

The results of paper chromatography and infrared studies indicated that morphine is largely destroyed when refluxed for 4 hr. with half an equivalent of 37–38% formalin solution and two equivalents of formic acid. The infrared spectrum of the crude resinous reaction product obtained from refluxing normorphine with a 20% excess each of formalin and formic acid showed the presence of a significant quantity of morphine. Application of the findings of Wagner and co-workers[4] on the factors influencing the Wallach reaction greatly facilitated the final selection of reaction conditions. High temperatures for extended periods enhance decomposition of the product so the procedure employed entailed gentle reflux in absolute ethanol for a short period.

N-Methylation of normorphine proceeded smoothly in the case of nonlabeled material, but difficulty was encountered in the direct application of the procedure to commercially available paraformaldehyde-C^{14} because of varying amounts of impurities. To avoid the assay for percentage formaldehyde-C^{14} freed under the reaction conditions, the syntheses were carried out in two stages; first the reaction was executed in the usual manner assuming complete depolymerization, and second the crude product was recycled using a small quantity of unlabeled paraformaldehyde in order to convert all of the original starting material to morphine.

In the early stages of development of the reaction conditions, the crude product was always found to contain 3–5% normorphine. This impurity could be removed neither by recrystallization from a wide variety of solvents or solvent mixtures nor by precipitation of the bases from aqueous solution at any *p*H. Chromatography on neutral or basic alumina using a number of different solvents and solvent mixtures failed to effect the desired separation. Application of a solvent system which produced significantly different R_f values for morphine and normorphine on paper strips to a powdered cellulose column proved acceptable for the separation of the two alkaloids. Since losses on the cellulose column were greater than those in the recycling procedure, the latter method was adopted for the synthesis of the labeled material. The cellulose chromatography procedure is somewhat tedious in application to larger amounts of material but is reported here as a technique satisfactory for

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the separation of milligram quantities of normorphine and morphine.

EXPERIMENTAL[5]

Preparation of morphine-N-methyl-C^{14}. Normorphine,[6] (195 mg. 0.72 mmole), m.p. 275–277° (dec.), 8.5 cc. of absolute ethanol, 25.4 mg. (0.85 mmole, *ca.* 1.2 mc./mmole) of paraformaldehyde-C^{14}, and 0.85 cc. (16 mmoles) of 87–90% formic acid were heated under gentle reflux for 90 min. The alcohol and excess formic acid were removed at reduced pressure under nitrogen with a final heating period of 5 min. at 110°. The residue was dissolved in 3.5 cc. of 0.25*N* hydrochloric acid and the crude product precipitated by addition of *N* sodium hydroxide to *p*H 9. After 2 hr. at 0°, the crystals were removed by centrifugation, washed with 1.0 cc. of ice-cold water in two portions and dried *in vacuo*. The crude product weighed 167 mg. (76% from normorphine, 64% from paraformaldehyde-C^{14}), contained 2–5% normorphine (*vide infra* paper chromatography) and was radiochemically pure (*vide infra* autoradiography).

Purification of morphine-N-Methyl-C^{14}. Crude morphine-*N*-methyl-C^{14}, 331 mg. (1.2 mmoles) in 10.0 cc. of absolute ethanol was treated as above with 20.0 mg. (0.67 mmole) of unlabeled paraformaldehyde and 1.0 cc. (19 mmoles) of 87–90% formic acid. After precipitation from water, the pale yellow crystals weighed 300 mg., contained no normorphine and were radiochemically pure. The product dissolved in 3.0 cc. of absolute methanol was applied to a column (400 × 9 mm.) containing 5.0 g. of neutral alumina.[7] Elution was effected with 80 cc. of absolute methanol. After removal of the solvent in the absence of light at reduced pressure under nitrogen, the residue was dissolved in acid and precipitated as previously. The fine white crystals weighed 255 mg. (59% from normorphine, 50% from paraformaldehyde-C^{14}); m.p. 251–253° (dec.) [Kempf[8] reported a m.p. 253–254 (dec.), cor.], specific activity 0.6 mc/mmole. The picrate was recrystallized from absolute ethanol, m.p. 161–163° (dec.). [lit. 163–165° (dec.), corr.[9]]. The mixture melting point with an authentic sample showed no depression.

Chromatography. Paper chromatography on Whatman #1 paper strips was carried out at 25.0 ± 0.5° using the organic layer separated at 20.0 ± 1.0° from a combination of benzene, methyl alcohol, isoamyl alcohol, water, pyridine mixed in the volume ratios of 9:6:3:2:1. This solvent system resulted in R_f values of 0.64 ± 0.02 for morphine and 0.40 ± 0.03 for normorphine. The color of the spots was developed by spraying with Schwartz Laboratories Diazo Blue B, 50 mg. dissolved in 15 cc. of 0.25*N* *p*H 9 borate buffer. A yellow coloration appeared for normorphine and orange for morphine. In 0.1 mg. samples, 1% normorphine was readily detectable. A butanol–acetic acid–water system (1-butanol saturated at 25° with 4% aqueous acetic acid) was also used.

Column chromatography was carried out on a powdered cellulose column (300 × 20 mm.) employing the above five-solvent system used for the paper strips. In a typical run, a 60-mg. sample containing 3–5% normorphine was applied to a prewashed column in 5 cc. of solvent. After a forerun of 40 cc., uncontaminated morphine appeared in the next four 5-cc. eluates (80% yield) followed by pure normorphine. Twice this load was successfully applied to a 600 × 20 mm. column.

Autoradiography. Paper chromatograms of crude and of pure morphine-*N*-methyl-C^{14} (*ca.* 0.1 mg.) using both the five solvent system and the butanol–acetic acid–water system were exposed to Kodak No-Screen Medical x-ray film for 24-hr. periods. The film was developed in open trays with D-19 developer for 5 min. at 25° and fixed with F-10 fixer. In all instances, only one spot appeared on the film. The R_f value corresponded exactly to that of an authentic sample of morphine.

Acknowledgment. This work was made possible, in part, by U. S. Public Health Service Grant B-625 and by Michigan Memorial Pheonix Project Grants 101 and 116.

DEPARTMENT OF PHARMACOLOGY
UNIVERSITY OF MICHIGAN MEDICAL SCHOOL
ANN ARBOR, MICH.

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Pyridine-1-oxides. IV. Nicotine-1-oxide, Nicotine-1′-oxide, and Nicotine-1,1′-dioxide[1,2]

EDWARD C. TAYLOR AND N. E. BOYER[3]

Received September 2, 1958

Although nicotine (I) is an important alkaloid available commercially in large quantities, its *N*-oxides have not been thoroughly characterized. We report in this paper the preparation and characterization of nicotine-1′-oxide (II), nicotine-1-oxide (III), and nicotine-1,1′-dioxide (IV).

Nicotine-1′-oxide (II) was first prepared in poor yield by Pinner[4–6] by direct oxidation of nicotine with dilute hydrogen peroxide, but it was referred to as Pinner's "oxynicotine" in the absence of knowledge of its structure. Its correct structure was later advanced,[7] other methods for its preparation have been reported[8,9] and a number of reactions of II have been discussed, including its reduction to nicotine.[9–12] We have now

(1) For the previous paper in this series, see E. C. Taylor, A. J. Crovetti, and N. E. Boyer, *J. Am. Chem. Soc.*, **79**, 3549 (1957).

(2) This work was supported in part by grants from the National Science Foundation and from the Smith, Kline and French Foundation.

(3) Present address: Research Department, Hooker Chemical Corporation, Niagara Falls, N. Y.

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