the separation of milligram quantities of normorphine and morphine.

EXPERIMENTAL[5]

Preparation of morphine-N-methyl-C¹⁴. 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-C¹⁴, 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-C¹⁴), contained 2–5% normorphine (*vide infra* paper chromatography) and was radiochemically pure (*vide infra* autoradiography).

Purification of morphine-N-Methyl-C¹⁴. Crude morphine-*N*-methyl-C¹⁴, 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-C¹⁴); 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-C¹⁴ (*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.

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(6) Kindly supplied by Dr. Carl Pfister, Merck and Co., Inc., Rahway, N. J.

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

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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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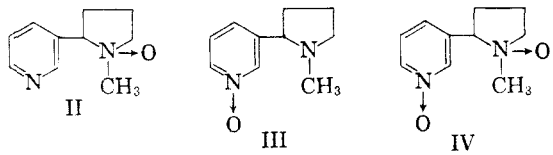
(12) It is relevant to point out that Pinner's "nicotone", which can be prepared from II by distillation, has been shown to be 2-methyl-6-(3-pyridyl)-tetrahydro-1,2-oxazine [C. H. Rayburn, W. R. Harlan, and H. R. Hanmer, *J. Am. Chem. Soc.*, **72**, 1721 (1950)]. "Pseudooxynicotine" has been shown to be 3-pyridyl-3-methylaminopropyl ketone [P. G. Haines and A. Eisner, *J. Am. Chem. Soc.*, **72**, 1719 (1950)].

found that the direct oxidation of nicotine with 10% hydrogen peroxide gives almost quantitative yields of nicotine-1′-oxide (II), characterized as its dipicrate.

Very little information is available in the literature concerning nicotine-1,1′-dioxide (IV). A nicotine dioxide was mentioned by Badgett *et al.*, but neither its source nor its nature was disclosed.[13] A nicotine dioxide was claimed by Weil[14] by the irradiation of nicotine in the presence of oxygen, but no structure was advanced for the product or for an intermediate $C_{10}H_{12}N_2$ postulated in the same reaction. Frankenburg[15] has reported the isolation of a yellow oil, $C_{10}H_{14}N_2O_2$, apparently identical with Weil's product, from fermented tobacco, but the product again was neither characterized nor was a structure assigned. Several years later, Weil patented a process for the oxidation of nicotine by irradiation in the presence of oxygen and methylene blue[16]; the product was claimed to be a dimeric compound $(C_{10}H_{14}N_2O_2)_2$ for which no structure was suggested. We have now found that nicotine-1,1′-dioxide (IV) may be readily prepared by the reaction of nicotine with 30% hydrogen peroxide or with perlauric acid. The latter procedure is particularly convenient, since the only contaminant is lauric acid which is readily removed from the reaction mixture by filtration.



II III IV

The literature contains no mention of nicotine-1-oxide (III).* This compound has now been prepared by the reduction of the dioxide (IV) with sulfur dioxide.

Since these nicotine oxides are liquids which cannot be distilled without decomposition, they were characterized as their picrates. Details of their preparation and characterization are given below.

EXPERIMENTAL[17]

Nicotine-1′-oxide (II). A mixture of 204 g. of 10% aqueous hydrogen peroxide and 32.4 g. of nicotine was allowed to stand at room temperature for 2 days, and then concentrated in a rotating film evaporator in the presence of platinum foil. The residual pale, straw-colored oil was dissolved in absolute ethanol, the solution treated with charcoal and filtered, and the filtrate concentrated again in the same manner. The resulting oil was treated with an excess of picric acid in ethanol to give 124 g. (98%) of the dipicrate of II; m.p. 168–169° dec.[18] The product was recrystallized from 65% aqueous ethanol for analysis.

Anal. Calcd. for $C_{10}H_{14}N_2O.2C_6H_3N_3O_7$: C, 41.5; H, 3.2; N, 17.6. Found: C, 41.7; H, 3.2; N, 17.5.

Nicotine-1′-oxide (II) is hygroscopic and attempted removal of traces of solvent by vacuum distillation results in extensive decomposition.

Nicotine-1,1′-dioxide (IV). Method (a). To a mixture of 954 g. of glacial acetic acid and 325 g. of nicotine contained in a 3 l. flask was added, with stirring, 590 g. of 30% hydrogen peroxide. The resulting mixture was heated in an oil bath (external temperature 50°) for 16 hr., and then for an additional 6 hr. at 80–90°. Concentration of the resulting amber-colored solution in a rotating film evaporator in the presence of platinum foil yielded 869 g. of a pale yellow viscous oil. An 87-g. aliquot of this oil was dissolved in 75 ml. of water and treated with 46 g. of picric acid in 4 l. of water to yield, after cooling, 72.9 g. of nicotine-1,1′-dioxide monopicrate. This represents an 86% conversion of I to IV. Recrystallization of the picrate from water yielded an analytical sample, m.p. 246° dec.

Anal. Calcd. for $C_{10}H_{14}N_2O_2{\cdot}C_6H_3N_3O_7$: C, 45.5; H, 4.1; N, 16.5. Found: C, 45.3; H, 4.3; N, 16.2.

Although nicotine-1,1′-dioxide decomposes on attempted distillation, it can be prepared essentially free of solvents and pure enough for subsequent reactions, by heating the above viscous yellow oil at 70°/50 microns for several hours.

Method (*b*). A solution containing 32.5 g. of nicotine, 216 g. of perlauric acid[19] and 1.5 l. of petroleum ether was allowed to stand at room temperature for 40 hr. and then evaporated to dryness under reduced pressure. Treatment of the residue with water and filtration yielded 180 g. (90%) of lauric acid, while concentration of the aqueous filtrate at 40° *in vacuo* yielded a pale, straw-colored viscous oil which was shown to be essentially pure nicotine-1,1′-dioxide by conversion of an aliquot to the picrate, m.p. 246° dec. A mixture melting point determination with the product formed by method (a) showed no depression.

Nicotine-1-oxide (III). Gaseous sulfur dioxide was bubbled through a solution of 298 g. of nicotine-1,1′-dioxide in 700 ml. of water for 2.5 hr. The color of the reaction solution rapidly changed from pale yellow to red to dark brown, and the temperature rose to 65°. Occasional use of an ice bath was necessary to maintain the temperature below this point. The reaction mixture was allowed to stand overnight at room temperature and then concentrated at 30° in a rotating film evaporator to give a dark red, viscous, almost solid mass consisting largely of the sulfate of nicotine-1-oxide.

An aliquot was dissolved in water and carefully neutralized with aqueous sodium hydroxide. Evaporation below 30° under reduced pressure and addition of ethanol and ether to the residue yielded sodium sulfate, which was removed by filtration. Concentration of the filtrates then gave crude nicotine-1-oxide as an orange liquid which rapidly decomposed on attempted distillation. Treatment with picric acid in water yielded a dipicrate (66% yield based on nicotine-1,1′-dioxide), m.p. 155–156° dec., which was recrystallized from water.

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* NOTE ADDED IN PROOF: Since this paper was submitted for publication, two other papers describing the preparation and properties of the nicotine-*N*-oxides have appeared: (a) A. W. Johnson, T. J. King and J. R. Turner, *J. Chem. Soc.*, 3230 (1958); dipicrate of III, m.p. 147–148°; monopicrate of IV, m.p. >220° (b) Ya. L. Gol'dfarb and V. K. Zvorykina, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 748 (1958); dipicrate of II, m.p. 168°; dipicrate of III, m.p. 161°; monopicrate of IV, m.p. 239–240°.

(17) All melting points are corrected. We are indebted for the microanalyses to Dr. Joseph F. Alicino, Metuchen, N. J.

(18) This compound is reported to melt with decomposition at 154–158°,[4] 155–156°,[7] 168°,[8] and 169°.[9]

(19) F. P. Greenspan, R. J. Gall, and D. G. MacKellar, *J. Org. Chem.*, **20**, 215 (1955).

Anal. Calcd. for $C_{10}H_{14}N_2O_2 \cdot 2C_6H_3N_3O_7$: C, 41.5; H, 3.2; N, 17.6. Found: C, 41.6; H, 3.0; N, 17.7.

It should be pointed out that neither II, III, nor IV can be satisfactorily extracted from aqueous solution with organic solvents.

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Addition of Alkanethiolic Acids to $\Delta^{1,4,6}$-3-Oxosteroids

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Recently some selective additions to $\Delta^{1,4,6}$-3-oxosteroids have been reported. Nussbaum and coworkers[1] have reported the epoxidation of the 6,7-double bond, and Kirk and Petrow[2] recorded the addition of chlorine to the 1,2-double bond. We have observed mono- and di- additions of alkanethiolic acids to the $\Delta^{1,4,6}$-3-ketones. When 1,4,6-androstatriene-3,17-dione was heated with ethanethiolic acid, a monoadduct separated rapidly from the hot solution. The same product was obtained from a chloroform solution of equimolar amounts of triene and thiolic acid irradiated with an ultraviolet lamp. On the basis of its ultraviolet spectrum ($\lambda_{max}^{methanol}$ 287 mμ, ϵ 23,400) and of analogy to the addition of thiolic acids to $\Delta^{1,4}$-3-oxosteroids,[3] this product was assigned the structure, 1α-acetylthio-4,6-androstadiene-3,17-dione.

In the cases of 17β-acetoxy-1,4,6-androstatrien-3-one, 17α,21-dihydroxy-1,4,6-pregnatriene-3,11,20-trione 21-acetate, and 11β,17α,21-trihydroxy-1,4,6-pregnatriene-3,20-dione 21-acetate, the products isolated were di-adducts (exhibiting maxima in the 240 mμ region characteristic of Δ^4-3-ketones). Again by analogy to monoadditions,[3] these compounds were assigned the 1α,7α-diacylthio structures.

EXPERIMENTAL[4]

1α-Acetylthio-4,6-androstadiene-3,17-dione. 1,4,6-Androstatriene-3,17-dione,[5] 2.00 g., was dissolved in 5.0 ml. of ethanethiolic acid and irradiated and heated with an ultraviolet light for 1 hr. During this time crystals formed. They were separated by filtration, washed with ether, and crystallized from methylene chloride-methanol. In this way 1.00 g. of 1α-acetylthio-4,6-androstadiene-3,17-dione, m.p. 229–229.5° (dec.), was obtained.

Anal. Calcd. for $C_{21}H_{26}O_3S$: C, 70.36; H, 7.31. Found: C, 70.38; H, 7.33. Ultraviolet spectrum: $\lambda_{max}^{methanol}$ 287 mμ, ϵ 23,400. $[\alpha]_D$ +68°.

1α,7α-Dithiol-11β,17α,21-trihydroxy-4-pregnene-3,20-dione 21-acetate 1,7-dipropionate. 11β,17α,21-Trihydroxy-1,4,6-pregnatriene-3,20-dione 21-acetate,[6] 0.87 g., dissolved in 1.0 ml. of propanethiolic acid, was heated on the steam bath for several hours. Most of the excess thiolic acid was removed under vacuum and the residue was chromatographed on silica gel. The column was washed with benzene and mixtures of 5 and 10% ethyl acetate in benzene. Then the column was eluted with 15% ethyl acetate in benzene and the eluants were concentrated to yield 0.20 g. of 1α,7α-dithiol-11β,17α,21-trihydroxy-4-pregnene-3,20-dione 21-acetate 1,7-dipropionate as a glass.

Anal: Calcd. for $C_{29}H_{40}O_8S_2$: C, 59.97; H, 6.94. Found: C, 59.91; H, 7.05. Ultraviolet spectrum $\lambda_{max}^{methanol}$ 239 mμ, ϵ 21,200; $[\alpha]_D$ +37°.

1α,7α-Dithiol-17β-hydroxy-4-androsten-3-one triacetate. 17β-Acetoxy-1,4,6-androstatrien-3-one,[5] 1.93 g., was mixed with 2.0 ml. of ethanethiolic acid and heated and irradiated with an ultraviolet light for 45 min. Some of the excess thiolic acid was distilled under vacuum, ether was added to the residue, and the solid which formed was separated by filtration. Two crystallizations of this material from acetone-ether yielded 0.91 g. of 1α,7α-dithiol-17β-hydroxy-4-androsten-3-one triacetate, m.p. 199–200° (dec.).

Anal. Calcd. for $C_{25}H_{34}O_5S_2$: C, 62.73; H, 7.16. Found: C, 62.68; H, 7.46. Ultraviolet spectrum: $\lambda_{max}^{methanol}$ 237.5 mμ, ϵ 20,100; $[\alpha]_D$ −46°.

1α,7α-Dithiol-17α,21-dihydroxy-4-pregnene-3,11,20-trione 1,7,21-triacetate. 17α,21-Dihydroxy-1,4,6-pregnatriene-3,11,-20-trione 21-acetate,[6] 0.54 g., was dissolved in 1.0 ml. of ethanethiolic acid and heated and irradiated with an ultraviolet light for 1 hr. Then part of the excess acid was removed under vacuum and ether was added. The solid which formed was separated by filtration and crystallized from acetone-ether to yield 0.38 g. of 1α,7α-dithiol-17α,21-dihydroxy-4-pregnene-3,11,20-trione 1,7,21-triacetate, m.p. 190–191° (dec.).

Anal. Calcd. for $C_{27}H_{34}O_8S_2$: C, 58.89; H, 6.22. Found: C, 59.05; 58.72; H, 6.70, 6.53. Ultraviolet spectrum: $\lambda_{max}^{methanol}$ 235.5 mμ, ϵ 18,500; $[\alpha]_D$ +80°.

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(4) We wish to thank Dr. R. T. Dillon and his staff of the Analytical Division for the microanalyses and optical determinations reported. The rotations were taken in chloroform at 24 ± 1°. The melting points were taken on a Fisher-Johns melting point apparatus.

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Synthesis of 1,2,4,5-Tetrachlorobenzene-1-Cl^{36}

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1,2,4,5-Tetrachlorobenzene has been under investigation in this laboratory for use as an agricultural chemical. The compound, labeled with chlorine-36, was desired for residue determinations using an isotope dilution procedure. Since it had not previously been prepared the synthesis was undertaken employing the Sandmeyer reaction.