Anal. Calcd for $C_{11}H_{10}N_5Cl$: C, 53.34; H, 4.07; N, 28.28; Cl, 14.32. Found: C, 53.39; H, 4.02; N, 28.30; Cl, 14.59.

***N*-[*p*-(Dimethylamino)phenyl]-α-(2-amino-3-cyano-5-pyrazinyl)nitrone (5).** To a suspension of 2.63 g (10.6 mmol) of the pyridinium salt **4** and 1.64 g (11.0 mmol) of *p*-dimethylaminonitrosobenzene in 50 mL of ethanol was added 8.33 g (60.4 mmol) of potassium carbonate in 30 mL of water. The reaction mixture became homogeneous, changed in color from green to brown, and the orange-brown nitrone started to separate. After 30 min of stirring at room temperature followed by ice cooling, the mixture was filtered and the collected solid was washed with water followed by ethanol and then ether and air-dried: yield 2.86 g (96%) of a dull orange powder, mp 219–222 °C (dec). Recrystallization from a large volume of acetonitrile (Norite) gave dark-orange needles: mp 227–228 °C (dec); NMR (Me_2SO) δ 2.95 (s, 6), 6.68 (d, 2), 7.72 (m, 4) (2 Ar protons + $-NH_2$), 8.15 (s, 1), 9.92 (s, 1); UV λ_{max} (acetonitrile) (log ε) 237 (4.22), 258 (sh, 3.89), 338 (4.27), 376 (4.38) nm; IR (KBr) 2230 cm^{-1} (CN).

Anal. Calcd for $C_{14}H_{14}N_6O$: C, 59.56; H, 5.00; N, 29.77. Found: C, 59.44; H, 5.06; N, 30.06.

2-Amino-3-cyano-5-formylpyrazine (2). A two-phase system containing 0.96 g (3.4 mmol) of the nitrone **5**, 60 mL of cold 6 N HCl, and 50 mL of ethyl acetate was shaken in a separatory funnel for several minutes. The organic layer was separated and the aqueous layer extracted twice with 50-mL portions of ethyl acetate. Brine (50 mL) was added to the aqueous layer, which was again extracted with 50 mL of ethyl acetate. The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, and evaporated to give 0.48 g (96%) of a light-gray powder, mp 202–204 °C (dec). Recrystallization from benzene (Norite) gave the aldehyde **2** as a colorless, microcrystalline solid: mp 206–208 °C (dec); NMR (Me_2SO) δ 8.32 (s, 2) ($-NH_2$), 8.70 (s, 1), 9.68 (s, 1); IR (KBr) 2240 cm^{-1} (CN).

Anal. Calcd for $C_6H_4N_4O$: C, 48.65; H, 2.72; N, 37.83. Found: C, 48.44; H, 2.80; N, 37.78.

2-Amino-3-cyano-5-formylpyrazine Dimethyl Acetal (6). To a suspension of 0.48 g (3.2 mmol) of the aldehyde **2** in 30 mL of dry methanol was added 1.0 g of Dowex 50W-X4 cation-exchange resin (hydrogen form). The mixture was stirred for 15 min to give a solution which, by TLC examination, contained one fluorescent component; all starting material had disappeared. After drying over 3A molecular sieves, the solvent was removed under reduced pressure to give 0.63 g (100%) of the desired acetal **6**, mp 91–93 °C. The acetal may be recrystallized from benzene/cyclohexane: NMR (Me_2SO) δ 3.35 (s, 6), 5.30 (s, 1), 7.43 (s, 2) ($-NH_2$), 8.42 (s, 1); IR (KBr) 2225 cm^{-1} (CN).

Anal. Calcd for $C_8H_{10}N_4O_2$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.40; H, 5.30; N, 29.07.

2,4-Diamino-6-formylpteridine Dimethyl Acetal (7). A solution of guanidine in methanol was prepared by dissolving 0.10 g (4.4 mmol) of sodium in 20 mL of dry methanol, followed by the addition of 0.42 g (4.4 mmol) of guanidine hydrochloride. This was added to a solution of 0.62 g (3.2 mmol) of the acetal **6** in 30 mL of methanol, and the mixture was heated under reflux for 18 h. It was then concentrated to a small volume under reduced pressure, cooled at −20 °C, and filtered to give 0.67 g (84%) of **7** as a light yellow powder, mp 248 °C (dec). The product was obtained in the form of bright-yellow beads, mp 254–255 °C (dec) upon recrystallization from methanol (Norite): NMR (Me_2SO) δ 3.33 (s, 6), 5.35 (s, 1), 6.67 (br s, 2), 7.57 (br s, 2), 8.72 (s, 1); UV λ_{max} (MeOH) (log ε) 261 (4.37), 284 (sh, 3.73), 368 (3.85) nm.

Anal. Calcd for $C_9H_{12}N_6O_2$: C, 45.76; H, 5.12; N, 35.58. Found: C, 45.52; H, 5.02; N, 35.81.

6-Formylpterin Dimethyl Acetal (8). A mixture of 0.52 g of 2,4-diamino-6-formylpteridine dimethyl acetal (**7**) in 20 mL of 5% aqueous sodium hydroxide was heated gently at reflux for 10 min. The resulting clear solution was filtered through sintered glass and the filtrate neutralized with acetic acid. The yellow solid which separated was collected by filtration and washed with water, ethanol, and then ether and air dried to give 0.49 g (94%) of **8** as a yellow solid, mp >330 °C. The analytical sample was prepared by recrystallization from DMF: NMR (Me_2SO) δ 3.33 (s, 6), 5.37 (s, 1), 6.93 (br s, 2), 8.63 (s, 1); UV λ_{max} (0.1 N NaOH) (log ε) 256 (4.41), 282 (sh, 3.86), 360 (3.89) nm; λ_{max} (0.1 N HCl) (log ε) 248 (4.05), 318 (3.96), 335 (sh, 3.83) nm.

Anal. Calcd for $C_9H_{11}N_5O_3$: C, 45.57; H, 4.67; N, 29.53. Found: C, 45.67; H, 4.86; N, 29.66.

6-Formylpterin (1). A mixture of 0.49 g of 6-formylpterin dimethyl acetal (**8**), 10 mL of 97% formic acid, and 1 mL of water was allowed to stand at room temperature for 30 min, poured into 15 mL of water, and neutralized with concentrated ammonium hydroxide. The yellow precipitate was collected by filtration and washed with water, ethanol, and then ether to give 0.36 g (91%) of **1** as a yellow microcrystalline solid, mp >330 °C. IR and UV spectra and TLC behavior were identical with those of an authentic sample: NMR (F_3AcOH external Me_4Si) δ 8.92 (s, 1), 9.65 (s, 1).[16]

Registry No.—**1**, 712-30-1; **2**, 64440-74-0; **3**, 40127-91-1; **4**, 64440-75-1; **5**, 64440-76-2; **6**, 64440-77-3; **7**, 64440-78-4; **8**, 59453-01-9; pyridine, 110-86-1; *p*-dimethylaminonitrosobenzene, 138-89-6; guanidine, 113-00-8.

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Preparation and Crystal Structure of 6-Acetyl-1-iodocodeine

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Received August 8, 1977

In conjunction with the development of a radioimmunoassay for morphine and related compounds[1] we were interested in preparing a sample of ring A specifically iodinated morphine. We found that the methods previously used for obtaining chloro-[2] or bromomorphine[3] or fluorocodeine[4] did not lead to the iodo derivative.

With positive iodine (ICl in Me_2SO), a trace of iodinated product was formed with both morphine and codeine as starting materials. With codeine, a trace of iodinated product was also formed when the conditions of tyrosine (protein) iodination were employed (chloramine T and sodium iodide in water buffered at pH 6.9).[5] Surprisingly, iodine monochloride in 0.1 N HCl with codeine produced a 67% yield of iodocodeine (**2**). This was later increased to 80–90% with the use of chloramine T and sodium iodide but again only when the reaction was carried out in 0.1 N HCl. While the reaction with codeine can be carried out quite smoothly, no readily defined reaction occurs with morphine under these conditions and iodomorphine (**5**) was therefore prepared by demethylation of iodocodeine. To avoid the possibility of deiodinaton, the demethylation was effected using boron tribromide.[6] Lastly, the preparation of iodocodeine-^{125}I (**4**) was readily accomplished using $Na^{125}I$ in the procedure shown below.

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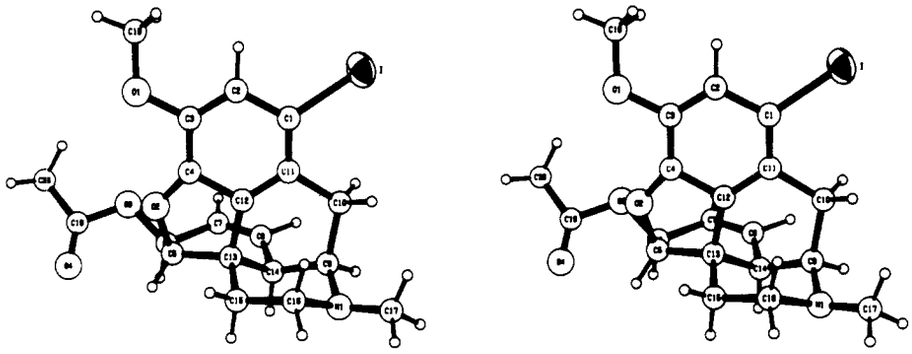
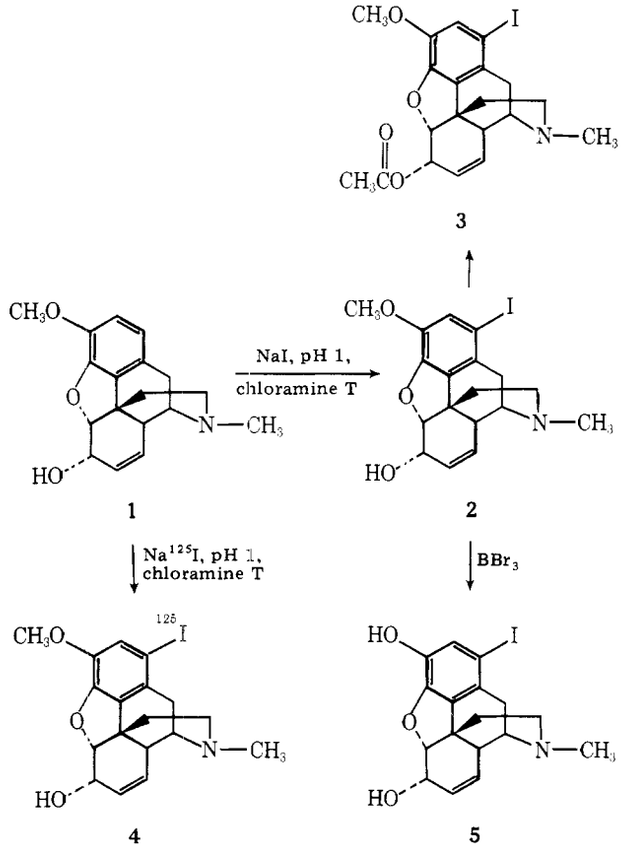


Figure 1. Stereodrawing showing the structure and conformation of **3**. The hydrogen atom positions were postulated, but they were not refined.

Table I. Crystal Data[10]

Sample	6-Acetyl-1-iodocodeine
Formula	$C_{20}H_{22}NIO_4$
Formula wt	467.30
Space group	$P2_1$
a, Å	27.127 (24)
b, Å	7.287 (8)
c, Å	9.757 (8)
β,	101.43 (4)
z	4
d_{calcd}, g cm^{-3}	1.641 g
μ(Cu Kα), cm^{-1}	137.9



We were unable to assign the position of the iodine from the NMR spectrum of **2**.[7] Accordingly, this problem was solved with a crystal structure analysis of the *O*-acetyl derivative **3**. The crystal data for **3** are given in Table I. The intensity data were measured on a Hilger-Watts diffractometer by a θ–2θ scan technique. Nickel filtered Cu Kα radiation and pulse height discrimination were used. The approximate size of the crystal used for data collection was 0.08 × 0.08 × 0.3 mm; the data were corrected for absorption. Of the 2085 accessible reflections with $\theta < 76°$, 1342 had intensities which were significantly greater than background, and these reflections were used in the analysis. The structure was solved by the heavy-atom method and was refined by full-matrix least squares. The hydrogen atoms were put in at their calculated positions. In the final refinement, the iodine atom had anisotropic thermal parameters and all other atoms had isotropic temperature factors. The hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The final unweighted and weighted discrepancy indices are $R = 0.100$ and $wR = 0.105$ for the 1342 observed reflections. A stereoscopic drawing of **3** is shown in Figure 1.

Experimental Section

Melting points are uncorrected. Infrared spectra were taken on a Digilab-FTS-14 or Beckman IR-9 or Perkin-Elmer 621 spectrophotometer. Nuclear magnetic resonance spectra were taken on a Joelco-C-60H, or Varian HA-100, or Varian XL-100 spectrometer. The mass spectra were recorded on either a Varian-CH-5 or CEC-110 instrument at an ionizing voltage at 70 eV. Ultraviolet spectra were recorded on a Carey-14 instrument. Radiochemical purity was determined on thin-layer chromatograms with a Packard 7201 radiochromatogram scanner system. All solvents were distilled prior to use.

1-Iodocodeine (2). A solution of 30 mg (0.10 mmol) of codeine (**1**) in 5 mL of 0.1 N HCl was added to a stirred mixture of 1.0 mL of 0.10 M NaI (aqueous) and 1.2 mL of 0.10 M chloramine T (aqueous) contained in a 25 mL stoppered flask. The addition was carried out with magnetic stirring and at room temperature. After 12 min, the mixture was extracted with two 5-mL portions of chloroform then basified by the addition of 0.2 mL of concentrated ammonia solution. Extraction with five 5-mL portions of chloroform which were combined, washed with 1 mL of water, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo yielded 36 mg (85%) of product which by TLC (silica gel; acetonitrile/ammonium hydroxide, 25:2) showed only 1-iodocodeine at R_f 0.41 and no codeine which has R_f 0.32 in this system. A sample crystallized from toluene–hexane (5:1)[8] had mp 116–117 °C: IR ($CHCl_3$) 3650 (free OH), 3460 (H-bonded OH); UV (ethanol) λ_{max} 217 (E 31 500), 247 (6750), 286 nm (1510); NMR ($CDCl_3$) δ 2.40 (s, 3 H, NCH_3), 3.78 (s, 3 H, OCH_3), 5.25, 5.70 (dd, 2 H, C**H**=C**H**), 7.08 (s, 1 H, aromatic); m/e 425 (calcd for $C_{18}H_{20}NIO_3$, 425). Anal. Calcd for $C_{18}H_{20}NIO_3$: C, 50.9; H, 4.7. Found: C, 51.2; H, 4.9.

1-Iodocodeine-^{125}I (4). Into a serum stoppered vial containing 5 mCi of carrier-free Na^{125}I solution[9] was injected 100 μL of 0.05 M sodium iodide solution followed by 120 μL of 0.05 M chloramine T (freshly prepared in water). After stirring for 2 min, a solution of 1.50 mg of codeine (**1**) in 250 μL of 0.1 N HCl was added. After stirring an additional 5 min, the reaction mixture was treated with 110 μL of 0.05 M sodium bisulfite solution, extracted with two 2-mL portions of chloroform, then basified with about 40 μL of concentrated ammonium hydroxide solution. The resulting mixture was extracted with five 2-mL portions of chloroform which were combined, washed with 1 mL of water, dried over anhydrous magnesium sulfate, filtered, and concentrated to a residue of about 1 mg. By TLC analysis, the sample was shown to be greater than 95% iodocodeine with radiochemical purity greater than 99%. A trace of codeine was detected. Specific activity was 0.86 mCi/mg.

6-*O*-Acetyl-1-iodocodeine (3). A 1-g sample of 1-iodocodeine was added to a mixture of dry pyridine (1 mL) and acetic anhydride (5 mL). The resulting solution was stirred at room temperature for 20 h then concentrated in vacuo to a residual oil which was treated twice with 5 mL each of benzene which was evaporated under reduced pressure. After the addition of 10 mL of water to the residual oil, solidification occurred after stirring for about 1 h. The product was collected by filtration, washed with water, and dried under high vacuum yielding 670 mg of **3**, mp 177–179 °C. A second crop of 360 mg (total yield is 94%) was obtained from the mother liquors. A sample for x-ray crystallographic analysis, crystallized from ethyl acetate–cyclohexane–hexane, was of mp 180–181 °C: NMR ($CDCl_3$) δ 2.13 (s, 3 H, CH_3CO_2), 2.43 (s, 3 H, NCH_3), 3.82 (s, 3 H, OCH_3), 5.40, 5.62 (dd, 2 H, CH=CH), 7.06 (s, 1 H, aromatic); *m/e* 467 (calcd for $C_{20}H_{22}NO_4I$, 467).

1-Iodomorphine (5). A solution of 2.12 g (5 mmol) of **2** in 12.5 mL of chloroform was added over a 4-min period to a stirred solution of 7.5 g of BBr_3 in 80 mL of chloroform maintained at 15–20 °C. Stirring was continued for an additional 15 min after which time the mixture was poured into 50 g of cracked ice and 10 mL of concentrated ammonium hydroxide solution. After standing 0.5 h at 0 °C, the solid was collected by suction filtration and washed successively with small portions of cold chloroform and water then dried to a constant weight of 1.14 g (54%): mp 215 °C dec; IR (KBr) 3500 (b, phenolic OH), 3350, 3255 (H-bonded OH); UV (methanol) λ_{max} 216 (E 27 070), inflection 245 (6450), inflection 288 (2100), max 293 nm (2160); NMR ($CDCl_3$ + Me_2SO) δ 2.30 (s, 3 H, NCH_3), 4.13 (m, 1 H, CHOH), 5.30, 5.53 (dd, 2 H, –CH=CH–), 7.00 (s, 1 H aromatic); *m/e* 411 (calcd for $C_{17}H_{18}NIO_3$, 411). A sample recrystallized from 0.1 N HCl was of mp 217 °C dec. Anal. Calcd for $C_{17}H_{18}NIO_3 \cdot HCl \cdot \frac{1}{2}H_2O$: C, 44.7; H, 4.3; N, 3.1; Cl, 7.8; I, 27.8. Found: C, 44.7; H, 4.9; N, 3.2; Cl, 7.5; I, 27.5.

Acknowledgment. We thank Dr. R. P. W. Scott and his staff in our Physical Chemistry Department, in particular, Dr. W. Benz for mass spectra, Dr. F. Scheidl for microanalyses, Dr. V. Toome for UV spectra, Mr. S. Traiman for IR spectra, and Dr. T. Williams for NMR spectra.

Registry No.—1, 76-57-3; **2**, 64739-74-8; **3**, 64754-11-6; **4**, 64739-75-9; **5**, 64739-76-0; **5**-HCl, 64739-77-1; NaI, 7681-82-5; $Na^{125}I$, 24359-64-6; acetic anhydride, 108-24-7.

Supplementary Material Available: Atomic and anisotropic thermal parameters for **3** (2 page). Ordering information can be found on any current masthead page.

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(10) See supplementary material paragraph.

Rearrangement of *N*-Chloro-*N*-acetyl-1-aminoadamantane by Aluminum Chloride[1]

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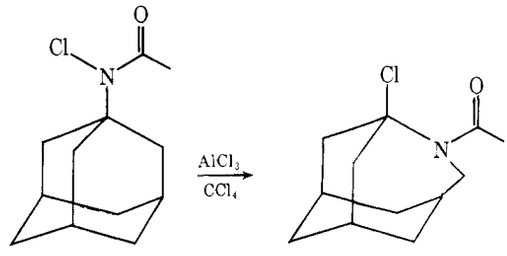
Received August 23, 1977

In 1971 it was reported that *N*-chloro-*N*-acetyl-1-aminoadamantane (**1**) rearranges to 3-chloro-*N*-acetyl-4-azahomoadamantane (**2**) in carbon tetrachloride with aluminum chloride catalyst,[2] eq 1. The authors assigned the structure on the basis of elemental analysis, IR, NMR, Beilstein test,



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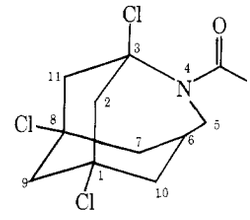

3

and chemical behavior (dehalogenation). On repeating this work, the product that we have obtained from the rearrangement is 1,3,8-trichloro-*N*-acetyl-4-azahomoadamantane (**3**). Determination of the structure was accomplished by means of elemental analysis, IR, ^1H and ^{13}C NMR, and mass spectrometry. The ^{13}C NMR spectrum contained nine peaks (as expected based on symmetry of the molecule); however, the downfield position and off-resonance decoupling splitting pattern suggested that both bridgehead carbons, 1 and 8, are quaternary. In our investigations[3] involving the ^{13}C NMR spectra of 3-substituted 4-azahomoadamantanes, a typical range for chemical shift of bridgeheads 1 and 8 is δ 26 to 28. Off-resonance decoupling shows a doublet which is characteristic of tertiary carbon atoms. In work with related models, the chemical shift for C–Cl carbon in 1-chloroadamantane is δ 67.25, for 1,3-dichloroadamantane it is δ 66.57, and for 1,3,5-trichloroadamantane it is δ 64.5[4] which is very close to the value of δ 64.97 for **3**. Mass spectrometry revealed molecular ions at *m/e* 295, 297, and 299 in about 3:3:1 ratio, as expected for the trichloro compound. The difference in melting points of the two preparations, in addition to other data,[5] suggests that the prior preparation may be a mixture derived from varying degrees of chlorination.

Investigation of reaction variables revealed (TLC and NMR) that either lowering the temperature or shortening the time below 24 h produced a complex mixture containing some starting material together with unidentified products (possibly containing a lower degree of chlorination). If the reaction is carried out for less than 4 h, most of the starting material is recovered. Reaction times of over 40 h produced good yields of product which could be easily purified by column chromatography on silica and recrystallization. The same product was obtained at 40 and 68 h but at lower yield for the shorter time.

The formation of compound **3** can be rationalized mechanistically on the basis of two known reactions: (1) the rearrangement of *N,N*-dichloro-1-aminoadamantane to the azahomoadamantyl system,[6] apparently via electron-deficient nitrogen, and (2) chlorination of C–H bonds by the alkyl halide–aluminum chloride combination. The CCl_4–$AlCl_3$ system has been used for 1,3-dichlorination of adamantane.[7] The specificity of chlorination (carbons 1 and 8, but not 6) can be rationalized by the inductive effect of amide nitrogen and by the "cage effect" (cation stabilization by unshared electrons on nitrogen).[8]

Experimental Section

Infrared spectra were obtained on a Beckman IR-8 instrument (KBr disks); ^1H NMR spectra on a Varian T60-A spectrometer and ^{13}C NMR on a Varian CFT-20 spectrometer ($CDCl_3$ as solvent and

0022-3263/78/1943-0739$01.00/0