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An Alternative Degradation of Colchicine to Octahydrodemethoxydesoxydesacetamidocolchicine and Hexahydrodemethoxydesacetamidocolchicine

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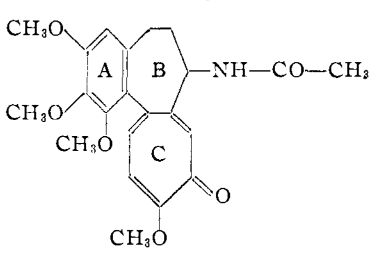
An alternative path has been found for removing the acetamido group in colchicine degradation products. The method consists in reduction with lithium aluminum hydride to the N-ethylamine, acetylation, reduction of the N-ethyl acetylated amine to the N,N-diethylamine, and degradation to the nitrogen-free compound on warming the tertiary amine with methyl iodide. Hydrogenation then led to octahydrodemethoxydesoxydesacetamidocolchicine (VII) when hexahydrodemethoxydesoxycolchicine (III) was the starting material. In an analogous manner the reaction sequence was applied to tetrahydrodemethoxycolchicine ethyleneketal (VIII) and led to a compound in which the carbonyl function in ring C is retained. This compound, hexahydrodemethoxydesacetamidocolchicine (XIII), has its carbonyl group at the same position as does colchicine.

In a recent publication[2] experiments were described, the objective of which was to degrade colchicine (I) to a less formidable compound in which the carbon skeleton of ring C was preserved.



I

Synthesis of such a compound, octahydrodemethoxydesoxydesacetamidocolchicine (VII), then would provide definitive chemical evidence for the nature of this ring.[3] A collateral objective has been the degradation of colchicine to a compound in which the carbonyl group of ring C is retained intact. Any doubt as to the specific position of the methoxyl and carbonyl groups[3] could be removed by synthesis of such a compound.

The present report describes a degradative method which has led to the preparation of the desired ketonic compound, hexahydrodemethoxydesacetamidocolchicine (XIII),[4] and also provides a more reliable path to the previously prepared octahydrodemethoxydesacetamidocolchicine (VII).

Initial attempts to apply the previous degradative method to the preparation of hexahydrodemethoxydesacetamidocolchicine (XIII) all ended in failure. Elimination of the acetamido group by heating with phosphorus pentoxide in xylene led to a complex mixture of products when employed with any compound still retaining an oxygen function in ring C, or to the dimethylmercaptole. Therefore, an alternative method was sought for eliminating the acetamido group—one that a carbonyl group, or a masked carbonyl group, could survive.

An attractive possibility for breaking the carbon–nitrogen bond at position 7 appeared to be the Hofmann degradation. Presumably, since the process could be completed without recourse to any acidic conditions, a carbonyl, protected as a ketal, would remain unaffected. To test the procedure, it was decided to apply it to hexahydrodemethoxydesoxycolchicine (III) which previously had been degraded to the octahydro compound VII by heating with phosphorus pentoxide followed by hydrogenation.

Avoiding any acidic conditions, the acetamido group of hexahydrodemethoxydesoxycolchicine (III) was first converted to the N-ethylamine (IV) by lithium aluminum hydride reduction, then acetylated with acetic anhydride in pyridine to the N-ethylacetamide (V), and again reduced with lithium aluminum hydride to the N,N-diethyl *t*-amino (VI). In each step, the yields were 90% or better.

Hofmann degradation of the tertiary amine (VI) proceeded with surprising facility. After merely heating for several hours with methyl iodide, the reaction mixture was filtered, the insoluble material was identified as diethyldimethylammonium iodide, and the filtrate was separated into an alkaline fraction (recovered tertiary amine) and a neutral fraction. Apparently the reaction proceeds, after quaternization of the tertiary amine, through elimination of diethylmethylamine and an equimolar quantity of hydrogen iodide which distributes itself between starting tertiary amine and the diethylmethylamine. Quaternization of the diethylmethylamine then leads to a precipitate of diethyldimethylammonium iodide, and formation of the soluble hydroiodide of the N,N-diethylamine (VI) prevents its further reaction with methyl iodide, resulting in some recovered starting material. Although this provides a rationalization for the nature of the products, the unexpected ease of elimination is being investigated further.

The neutral fraction was hydrogenated, absorbing one mole of hydrogen, and then chromatographed on alumina to give octahydrodemethoxydesoxydesacetamidocolchicine (VII) as a dimorphic compound. The lower melting form (m.p. 70–71°) was obtained from solution or sublimation, while the higher melting form (m.p. 76.4–77.5°) was obtained by cooling the melt, by heating the lower just below its melting point, or by allowing the lower to stand several weeks at room temperature.

Before this degradation procedure, which had given such satisfactory results, could be applied to the series with a carbonyl function in ring C, the apparent discrepancy between the octahydrode-

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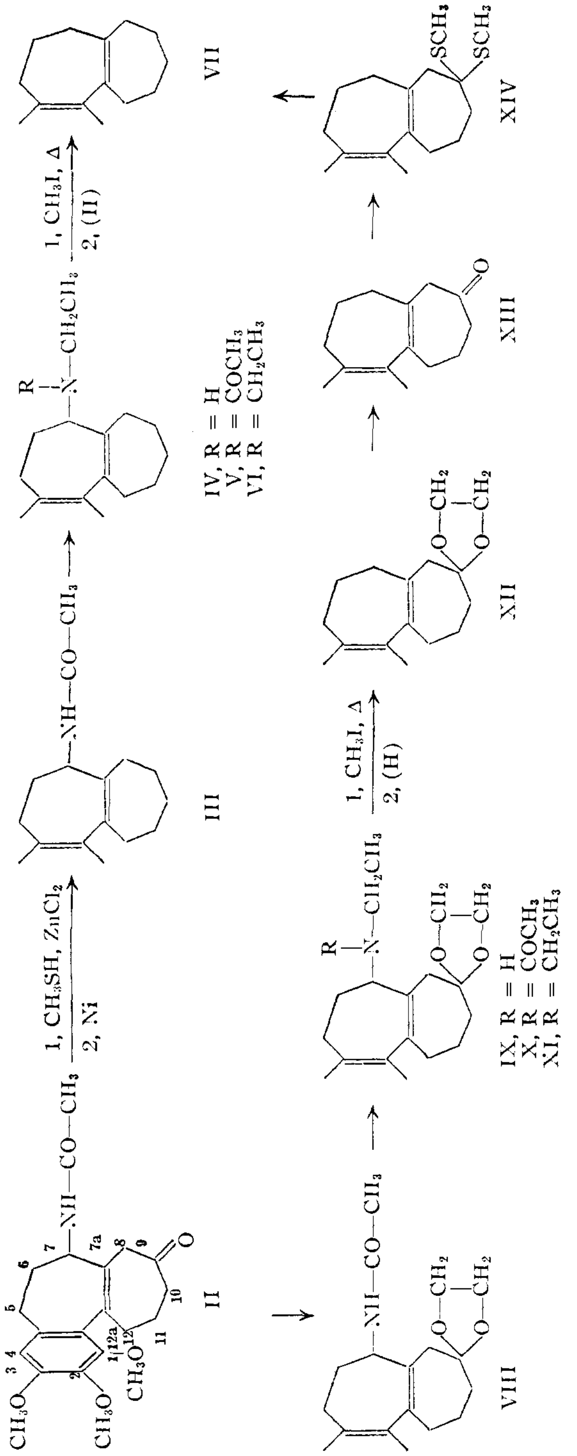
[1] National Science Foundation Fellow, 1953–1954.

[2] H. Rapoport, A. R. Williams, J. E. Campion and D. E. Pack, THIS JOURNAL, **76**, 3693 (1954)

[3] The evidence in the literature which has led to the general acceptance of structure 1 for colchicine has been reviewed in ref. 2.

[4] Of the two possible positions for the double bond in compounds II–XIV ($\Delta^{7a(12a)}$ or Δ^{12}). the $\Delta^{7a(12a)}$ position has been assigned arbitrarily as had been done previously.[2]



methoxydesoxydesacetamidocolchicine obtained from the Hofmann process (m.p. 76.4–77.5°) and that obtained when phosphorus pentoxide was used (m.p. 49–50°) had to be reconciled. Three possibilities were considered to explain the difference in the products. First, the compounds might be double bond isomers. This possibility was eliminated by the fact that they formed identical epoxides on reaction with perbenzoic acid. Second, the compounds might be polymorphs. This was rejected since the mixed melting point was 70–74° and no interconversions between forms could be induced.

A third possibility was that the phosphorus pentoxide product was impure. There had been a prior inclination toward this explanation since it had been observed that the ease of purification and the yield were extremely sensitive to the time of heating with the phosphorus pentoxide, extended times giving decreased yields of a more difficultly purified product. Also, it was observed that the consumption of perbenzoic acid varied with several samples from 80 to 100%. Although the infrared spectrum of the Hofmann product and that of the phosphorus pentoxide product were identical except for some minor variations in the regions of 1300 and 1100 cm.$^{-1}$, there were significant differences in the ultraviolet spectra.

The compounds tetrahydrodemethoxycolchicine (II),[2] hexahydrodemethoxydesoxycolchicine (III)[2] and hexahydrodemethoxydesacetamidocolchicine ethyleneketal (XII) all display ultraviolet absorption maxima and minima at essentially the same wave lengths (λ_{max}^{EtOH} 256 ± 2; λ_{min} 243 ± 2 mμ) with practically identical molar extinction coefficients (log ϵ_{max} 4.10 ± 0.01; log ϵ_{min} 3.95 ± 0.03). While both samples of octahydrodemethoxydesoxydesacetamidocolchicine (VII) are in agreement with the above compounds as to wave length, the product from the phosphorus pentoxide degradation has log ϵ_{max} 3.89 and log ϵ_{min} 3.78,[2] whereas the Hofmann product has log ϵ_{max} 4.10 and log ϵ_{min} 3.93. Since replacement of the acetamido group by hydrogen has no effect on the intensity of absorption of the styrene system, as witnessed by the comparison of compounds II, III, and XII, the octahydro compound resulting from the Hofmann degradation has the expected spectrum and undoubtedly represents purer material. The divergences (lower melting point, incomplete reaction with perbenzoic acid, and decreased absorption intensity) of the octahydro compound obtained from the phosphorus pentoxide treatment might be explained by the presence of non-absorbing, or low-absorbing, impurities formed during the relatively drastic reaction with phosphorus pentoxide and subsequent hydrogenation.

With the successful conversion of hexahydrodemethoxydesoxycolchicine (III) to the nitrogen-free compound VII *via* the Hofmann degradation, the application of this procedure to the preparation of hexahydrodemethoxydesacetamidocolchicine (XIII) was undertaken. For this purpose, tetrahydrodemethoxycolchicine (II) was first converted to its ethyleneketal (VIII) and thence to the N,N-diethylamine (XI) by successive reduction with lithium aluminum hydride, acetylation, and another reduction, the over-all yield from II to XI being 71%.

Degradation to the nitrogen-free compound proceeded with the same facility as in the previous case and the neutral material, on hydrogenation, gave hexahydrodemethoxydesacetaminocolchicine ethyleneketal (XII). *trans*-Ketalization with acetone and *p*-toluenesulfonic acid[5] was used to liberate the oily ketone XIII which formed a bisulfite addition product and was characterized as the crys-

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(5) H. Schinz and G. Schäppi, *Helv. Chim. Acta*, **30**, 1483 (1947).

talline dimethylmercaptole (XIV). With Raney nickel, the dimethylmercaptole (XIV) was desulfurized, and the octahydrodemethoxydesoxydesacetamidocolchicine (VII) formed was identical with the compound prepared from hexahydrodemethoxydesoxycolchicine *via* the Hofmann degradation.

Since the carbonyl group of tetrahydrodemethoxycolchicine (II) is undoubtedly at the same position as that of colchicine,[2] this must also be true for the carbonyl of hexahydrodemethoxydesacetamidocolchicine (XIII), and thus a degradation product has been obtained, the synthesis of which will establish the specific positions of the carbonyl and methoxyl groups in ring C of colchicine.

Experimental[6]

Tetrahydrodemethoxycolchicine (II) was prepared by catalytic hydrogenation of N,N-dimethylaminocolchicide as previously described[2] and melted at 143–144°. It was converted to the known **dimethylmercaptole**,[2] m.p. 190–192°, by treatment with methyl mercaptan and zinc chloride. Raney nickel desulfurization of the mercaptole gave **hexahydrodemethoxydesoxycolchicine** (III),[2] m.p. 183–184°.

N-Ethylhexahydrodemethoxydesoxydesacetylcolchicine (IV).—Using a Soxhlet extraction apparatus and in a nitrogen atmosphere, 460 mg. (1.28 mmoles) of hexahydrodemethoxydesoxycolchine (III) placed in the thimble was extracted continuously for 24 hours by ether from a refluxing 0.091 *M* ethereal lithium aluminum hydride solution (160 ml.). With cooling, 20 ml. of benzene followed by 15 ml. of a 30% aqueous Rochelle salt solution was added, the aqueous phase was separated and washed with three 20-ml. portions of benzene, and each organic phase in turn was washed with three 20-ml. portions of 3 *N* acetic acid. After basification, the combined acetic acid solutions were extracted with three 20-ml. portions of benzene, and the benzene solutions were washed with water, dried and evaporated to yield 406 mg. (92% yield) of N-ethylhexahydrodemethoxydesoxydesacetylcolchicine as a clear, viscous oil which was distilled onto a cold finger at 95° (0.003 mm.) for analysis; $[\alpha]^{25}\text{D}$ −190° (*c* 0.42, ethanol).

Anal. Calcd. for $C_{21}H_{31}O_3N$: C, 73.0; H, 9.1; equiv. wt., 346. Found: C, 73.4; H, 9.0; equiv. wt., 350.

N-Ethylhexahydrodemethoxydesoxycolchicine (V).—A solution of 330 mg. (0.96 mmole) of the N-ethylamine IV in 5 ml. of pyridine and 2 ml. of acetic anhydride was heated under reflux for one hour and then poured into 1 *N* aqueous ammonia. After being heated on the steam-bath for 10 minutes, the solution was extracted with three 10-ml. portions of benzene and the benzene portions were washed in turn with water, 2 *N* hydrochloric acid and again with water. Evaporation of the combined, dried benzene solutions left 336 mg. (91% yield) of crystalline residue which was recrystallized from hexane and sublimed (110° (0.008 mm.)); m.p. 129.5–130.4°; $[\alpha]^{25}\text{D}$ −175° (*c* 1.11, ethanol).

Anal. Calcd. for $C_{23}H_{33}O_4N$: C, 71.3; H, 8.6. Found: C, 71.4; H, 8.7.

N,N-Diethylhexahydrodemethoxydesoxydesacetylcolchicine (VI).—Using the procedure and apparatus described above, 1.26 g. (3.26 mmoles) of N-ethylhexahydrodemethoxydesoxycolchicine (V) was reduced with 21.6 mmoles of ethereal lithium aluminum hydride. The reaction mixture was treated in the same manner as above and 1.14 g. of a basic oil was obtained. This was subjected to the acetylation procedure described above to separate any secondary amine and the basic material again isolated as an oil (1.09 g., 90% yield) which was homogeneous to chromatography on alumina. The N,N-diethyl compound VI was distilled onto a cold finger (70° (0.03 mm.)) for analysis.

Anal. Calcd. for $C_{23}H_{35}O_3N$: C, 74.0; H, 9.4; N, 3.8; equiv. wt., 374. Found: C, 74.2; H, 9.4; N, 3.5; equiv. wt., 370.

The **picrate** was formed on addition of saturated ethanolic picric acid to VI and was recrystallized from absolute ethanol; m.p. 178–179°.

Anal. Calcd. for $C_{29}H_{38}O_{10}N_4$: C, 57.8; H, 6.4; N, 9.3. Found: C, 57.8; H, 6.4; N, 9.2.

Hofmann Degradation of N,N-Diethylhexahydrodemethoxydesoxydesacetylcolchicine (VI).—In a heavy-walled Pyrex tube (9 × 2.5 cm.) was placed a solution of 441 mg. (1.18 mmoles) of the diethylamine VI in 5.5 ml. of methyl iodide, and the cooled tube was flushed with nitrogen and sealed. It was then heated totally immersed in an oil-bath at 75° for 5 hours after which it was cooled and the contents filtered using five 5-ml. portions of benzene as rinse. The white, crystalline material thus obtained was examined further as described below under A. To the combined filtered tube contents and rinses was added 40 ml. of benzene, and the organic phase was washed with three 50-ml. portions of cold 3 *N* acetic acid and three 50-ml. portions of water. Examination of the organic phase for degraded material is described under B. The combined aqueous portions were made alkaline with 12 *N* potassium hydroxide, extracted with three 30-ml. portions of benzene, and the washed and dried combined benzene extracts were evaporated, leaving 126 mg. (0.34 mmole, 29%) of the recovered diethylamine VI as residue.

A. **Diethyldimethylammonium Iodide.**—The white, crystalline product obtained above, which had yellowed slightly on standing, was dissolved in absolute ethanol, warmed on the steam-bath for a few minutes with a pinch of sodium hydrosulfite, and filtered. The clear filtrate was concentrated to about 3 ml. and ether added to the warm solution until incipient crystallization, completed by cooling. Several recrystallizations from absolute ethanol–ether gave material of melting point 302–303° which on mixing with authentic diethyldimethylammonium iodide (m.p. 301–302°) melted at 301–302°.

Authentic diethyldimethylammonium iodide was prepared by heating diethylamine with methyl iodide in methanol in the presence of anhydrous potassium carbonate and was crystallized from absolute alcohol–ether, m.p. 301–302°.

Anal. Calcd. for $C_6H_{16}NI$: C, 31.5; H, 7.0; I, 55.4. Found: C, 31.4; H, 6.9; I, 54.9.

B. **Octahydrodemethoxydesoxydesacetamidocolchicine** (VII).—The benzene phase containing degraded material obtained above was washed with 50-ml. portions of 2 *N* potassium hydroxide and water, dried over sodium sulfate, filtered and evaporated under nitrogen to give 260 mg. of a yellow oil which was hydrogenated in 10 ml. of glacial acetic acid using 18 mg. of platinum oxide and 36 mg. of 5% palladized carbon as catalyst. Hydrogen absorption ceased after about one hour when 103 mole % of hydrogen had been absorbed, and the mixture was filtered, made alkaline with 4 *N* potassium hydroxide, and extracted with three 30-ml. portions of benzene. The washed, dried and evaporated benzene extracts gave 251 mg. (0.83 mmole, 70%) of residue which was digested with 25 ml. of hexane, filtered, and applied to an alumina column (20 × 1 cm., Merck). After development with hexane (200 ml.), 90% hexane–10% benzene (840 ml.) eluted 158 mg. (43% yield) of crystalline octahydrodemethoxydesoxydesacetamidocolchicine (VII) which was recrystallized from aqueous methanol and sublimed at 60° (0.04 mm.). This material is dimorphic, giving melting points of 70–71° and 76.4–77.5°, the lower melting form being obtained on sublimation and the higher by crystallization from the melt. Heating the lower melting modification for 45 minutes at 67–69° sufficed to convert it to the higher melting form; $[\alpha]^{25}_{5893,5461}$ 0° (*c* 0.5, ethanol).

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.5; H, 8.7; OCH_3, 30.8. Found: C, 75.4; H, 8.7; OCH_3, 30.4.

Octahydrodemethoxydesoxydesacetamidocolchicine epoxide was prepared using perbenzoic acid as previously described.[2] After 100 mole % of per acid was consumed in one hour, oxidation virtually ceased, and an 88% yield of epoxide was isolated by chromatography. It was recrystallized from hexane and melted at 115–116° alone and on mixing with epoxide (m.p. 116–117°) previously prepared.[2]

Tetrahydrodemethoxycolchicine Ethyleneketal (VIII).—Several small crystals of *p*-toluenesulfonic acid monohydrate and 3.2 ml. of ethylene glycol were added to a solution of 1.62 g. (4.3 mmoles) of tetrahydrodemethoxycolchicine (II) in 250 ml. of benzene, and the solution was heated under reflux for 18 hours with continuous removal of water. After

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[6] All melting points are corrected and those above 200° were taken in evacuated capillaries; microanalyses were performed by the Microchemical Laboratory, University of California, Berkeley.

being washed with 25-ml. portions of 1 *M* sodium bicarbonate and water, the dried benzene solution was evaporated, and the residue was crystallized from aqueous methanol, yielding 1.64 g. (91%) of the ethyleneketal VIII; m.p. 213–214°, $[\alpha]^{25}\text{D}$ −118° (*c* 1.0, ethanol).

Anal. Calcd. for $C_{23}H_{31}O_6N$: C, 66.2; H, 7.5. Found: C, 66.2; H, 7.6.

N-Ethyltetrahydrodemethoxydesacetylcolchicine Ethyleneketal (IX).—To a solution of 980 mg. (2.3 mmoles) of tetrahydrodemethoxycolchicine ethyleneketal (VIII) in 40 ml. of tetrahydrofuran in a nitrogen atmosphere was added dropwise 5 ml. of a 1.71 *M* ethereal lithium aluminum hydride solution, and the mixture was heated under reflux for 18 hours. The tetrahydrofuran then was evaporated, 50 ml. of benzene was added, and the basic fraction was recovered from the reaction mixture in the manner described above for the corresponding desoxy compound IV. A total of 830 mg., 88% yield, of oily secondary amine IX was obtained; $[\alpha]^{25}\text{D}$ −131° (*c* 0.99, ethanol).

Anal. Calcd. for $C_{23}H_{33}O_5N$: C, 68.5; H, 8.2; equiv. wt., 404. Found: C, 68.7; H, 8.2; equiv. wt., 412.

The **N-α-naphthylthiourea** derivative of IX was prepared in ethanol and recrystallized from ethanol; m.p. 153–154°; $[\alpha]^{25}\text{D}$ −75.4° (*c* 0.25, ethanol).

Anal. Calcd. for $C_{34}H_{40}O_5N_2S$: C, 69.5; H, 6.9. Found: C, 69.6; H, 7.0.

N-Ethyltetrahydrodemethoxycolchicine Ethyleneketal (X).—Acetylation of the N-ethylamine IX and isolation of neutral material was carried out as described above in the preparation of the N-ethyltetrahydrodemethoxycolchicine (V), except that 3 *N* acetic acid washes were substituted for the hydrochloric acid previously used. The yield of acetylated N-ethylamine X was 96%, m.p. 105–107° after crystallization from aqueous methanol. After several recrystallizations, the analytical sample melted at 109–111°, $[\alpha]^{25}\text{D}$ −170° (*c* 0.79, ethanol).

Anal. Calcd. for $C_{25}H_{35}O_6N$: C, 67.4; H, 7.9. Found: C, 67.1; H, 7.8.

N,N-Diethyltetrahydrodemethoxydesacetylcolchicine Ethyleneketal (XI).—Using the same reaction conditions and isolation procedure as described above in the preparation of compound IV, a crystalline residue of N,N-diethylamine XI, m.p. 155–157°, was obtained in 92% yield. Several crystallizations from hexane gave material of m.p. 160–161°.

Anal. Calcd. for $C_{25}H_{37}O_5N$: C, 69.6; H, 8.6. Found: C, 69.3; H, 8.7.

Hexahydrodemethoxydesacetamidocolchicine Ethyleneketal (XII).—Hofmann degradation of N,N-diethyltetrahydrodemethoxydesacetylcolchicine ethyleneketal (XI) was carried out exactly as described for the analogous desoxy compound VI and diethyldimethylammonium iodide and recovered tertiary amine XI (42%) were obtained. The neutral fraction, after hydrogenation, was applied to an alumina (Merck) column in 25% benzene–75% hexane, and elution with 50% benzene–hexane gave a 39% yield of a homogeneous fraction, m.p. 93–95° after crystallization from hexane. Further crystallization and drying gave the nitrogen-free ketal, XII, of m.p. 95–96°, $[\alpha]^{25}_{5893,\ 5461}$ 0° (*c* 1.01, ethanol).

Anal. Calcd. for $C_{21}H_{28}O_5$: C, 70.0; H, 7.8. Found: C, 69.9; H, 7.9.

Hexahydrodemethoxydesacetamidocolchicine (XIII).—After boiling a solution of 49.7 mg. (0.14 mmole) of the ketal XII and 2 mg. of *p*-toluenesulfonic acid monohydrate in 25 ml. of dry acetone for two hours, 5 ml. of *M* sodium bicarbonate was added to the cold solution and the acetone was removed at reduced pressure. The residue was then distributed between benzene and water, and the oil left on evaporation of the benzene was shaken overnight with 35 ml. of 20% aqueous sodium bisulfite. Washing the bisulfite solution with benzene (2 × 25 ml.) and evaporation of the benzene after washing with bicarbonate solution, water and drying left 19.1 mg. of recovered material. The bisulfite solution was made alkaline with potassium carbonate and extracted with three 25-ml. portions of benzene, the washed and dried benzene extract was concentrated, and the residual oily ketone was distilled onto a cold finger at 75° (5 μ); yield 23.6 mg., 54%.

Anal. Calcd. for $C_{19}H_{24}O_4$: C, 72.1; H, 7.7. Found: C, 71.8; H, 8.0.

Hexahydrodemethoxydesacetamidocolchicine Dimethylmercaptole (XIV).—A solution of 52 mg. (0.16 mmole) of hexahydrodemethoxydesacetamidocolchicine (XIII) in 10 ml. of benzene was added to a heavy-walled glass tube containing 50 mg. of fused zinc chloride and 50 mg. of anhydrous sodium sulfate. After evaporation of the benzene and addition of 10 ml. of methyl mercaptan, the sealed tube was shaken at room temperature for one hour and then allowed to stand for 24 hours. The tube was now opened, the methyl mercaptan was evaporated, and to the residue was added 30 ml. of water and 30 ml. of benzene. The benzene solution, after being washed with two 30-ml. portions of 1 *N* sodium hydroxide, was dried and evaporated, and the residue was applied to an alumina (Merck) column (1 × 19 cm.) in benzene–hexane (1:3). With benzene–hexane (1:1), 43 mg. (67%) of the dimethylmercaptole was eluted, and recrystallization from hexane gave material, m.p. 104–105° after sublimation at 90° (4 μ).

Anal. Calcd. for $C_{21}H_{30}O_3S_2$: C, 63.9; H, 7.7; S, 16.3. Found: C, 63.7; H, 7.5; S, 16.6.

Octahydrodemethoxydesoxydesacetamidocolchicine (VII) by Desulfurization of the Mercaptole (XIV).—After heating under reflux in a nitrogen atmosphere for 15 hours a solution of 47 mg. (0.12 mmole) of the dimethylmercaptole XIV in 35 ml. of 90% ethanol with 1.2 g. of Raney nickel,[7] the solution was filtered and the nickel was digested with two 30-ml. portions of benzene. Evaporation of the combined filtrate and digests and application of the residue to an alumina (Merck) column (1 × 20 cm.) in hexane followed by elution with benzene–hexane (1:1) gave crystalline octahydrodemethoxydesoxydesacetamidocolchicine. This was sublimed at 52° (5 μ) and gave 26 mg. (72%) of material of m.p. 74.0–75.6°. The mixed m.p. with material (m.p. 76.4–77.5°) from the Hofmann degradation of N,N-diethylhexahydrodemethoxydesoxydesacetylcolchicine (VI) was 74.6–76.5° and the ultraviolet and infrared absorption spectra of the two products were identical.

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[7] R. Mozingo, *Org. Syntheses*, **21**, 15 (1941).