[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

THE SYNTHESIS OF DIHYDROMETELOIDINE AND RELATED COMPOUNDS*

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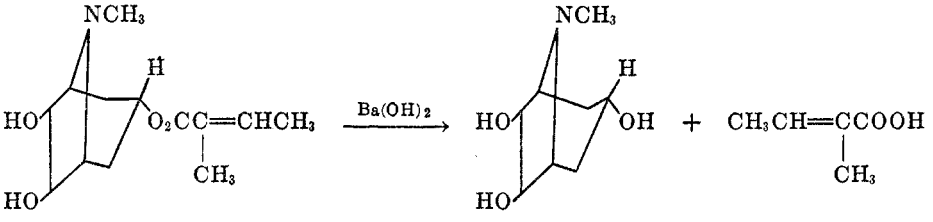
In addition to the pharmacologically important tropane alkaloids atropine and scopolamine, plants of the *Datura* genus [*D. meteloides* (1, 2), *D. ferox* (3), and *D. myoporeides* (4)] produce several less well known alkaloids. One of these, meteloidine (I), was first isolated in 1908 from *D. meteloides* by Pyman and Reynolds (1). Hydrolysis with aqueous barium hydroxide yielded tiglic acid (II) and an optically inactive base, teloidine (III), which was considered to be a 3,6,7-trihydroxytropane.



I III II

The 6,7-glycol was assumed to be *cis* to account for the optical inactivity of meteloidine. These assumptions were later confirmed by the synthesis of teloidine (5). Recent work (6) has made readily available the C_3 ketone precursor (teloidinone, IV) of meteloidine. This communication reports the complete synthesis of a compound corresponding in structure to dihydrometeloidine.

Teloidinone (IV) was converted in 89% yield to the benzylidene derivative by treatment with freshly distilled benzaldehyde in the presence of *p*-toluenesulfonic acid.

Hydrogenation of benzylideneteloidinone (V) in aqueous ethanol in the presence of Raney nickel W-4 (7) afforded a 90% yield of benzylideneteloidine (VI). This product was assigned the natural configuration on the basis of the production of teloidine (5) (III) by hydrogenolysis in glacial acetic acid or by reductive cleavage of the benzylidene group with sodium in liquid ammonia.

Benzylideneteloidine (VI) was acylated in 61% yield by treatment with α-methylbutyric anhydride in pyridine, and the benzylidene group was removed by hydrogenolysis in glacial acetic acid in the presence of a 30% palladium on carbon catalyst (8).

This series of reactions constitutes a total synthesis of what appears to be dihydrometeloidine, however, the product has not as yet been compared directly with authentic dihydrometeloidine.

* Dedicated to the late Professor W. E. Bachmann.

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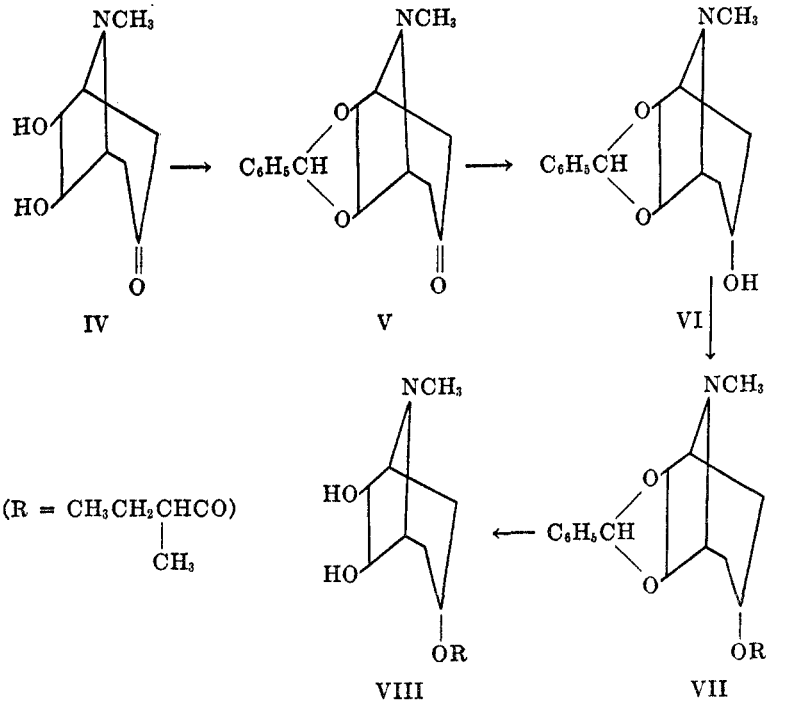
In view of the desirability of finding useful substitutes for scopolamine and because of a certain structural similarity of benzylideneteloidine to scopine, several other benzylideneacylteloideines were prepared. In addition a series of



closely related isopropylidene compounds were synthesized, also for pharmacological testing. These esters differ from scopolamine only in the acyl groups attached at C_3 and in having a 6,7-cyclic acetal (benzylidene) or ketal (isopropylidene) instead of the 6,7-epoxide.

Benzylideneteloidine (VI) gave an acetate (IX) on treatment with acetic anhydride in pyridine. The benzylidene group was removed by hydrogenolysis to give an 86% yield of acetylteloideine (X). Acetylation of this compound with acetic anhydride in pyridine yielded a triacetate (XI) identical with that prepared from teloidine (III) itself.

Benzylidenediphenylacetylteloideine (XII) was prepared in 83% yield by treating benzylideneteloidine (VI) in anhydrous ether with diphenylketene (9).

Isopropylideneteloidinone (XIII) was prepared in 82% yield by refluxing a solution of teloidinone (IV) and *p*-toluenesulfonic acid monohydrate in acetone. Hydrogenation in aqueous ethanol in the presence of Raney nickel W-4 afforded a 94% yield of isopropylideneteloidine (XIV), m.p. 131–133°. The natural configuration was established by hydrolysis with aqueous hydrochloric acid to teloidine hydrochloride (5).

Isopropylideneacetylteloideine (XV) and isopropylidenediphenylacetylteloideine (XVI) were prepared in essentially the same manner as the corresponding

benzylidene compounds. Heating isopropylideneteloidine (XIV) with an excess of benzoyl chloride on a steam-bath for several hours resulted in a 38% yield of isopropylidenebenzoylteloideine (XVII), isolated as the hydrobromide.

Since no data were available on the action of the relatively new hydride reducing agents on oxygenated tropinones and since it has been shown that they normally do not attack acetal linkages (10) it was of interest to determine which of the two possible isomeric alcohols these reagents would produce. Sodium borohydride was chosen because of its selectivity and ease of handling.

When isopropylideneteloidinone (XIII) was reduced with sodium borohydride there was obtained a 50% yield (based on teloidinone) of compound XVIII melting at 121–123°. It was assigned the pseudo or unnatural configuration[2] by hydrolysis with aqueous hydrochloric acid to pseudoteloidine hydrochloride (5). Isopropylideneacetylpseudoteloideine was obtained in 84% yield by the usual procedure.

EXPERIMENTAL[3]

Benzylideneteloidinone (V). A solution of 3.4 g. (0.02 mole) of teloidinone (1) (IV) and 4.2 g. (0.022 mole) of *p*-toluenesulfonic acid monohydrate in 40 ml. of freshly distilled benzaldehyde was stored at room temperature for 48 hours. Ether (200 ml.) was added and the precipitated salts were removed by filtration. The precipitate was shaken with 50 ml. of *N* sodium hydroxide, and the resulting mixture was extracted with benzene. The dried (magnesium sulfate) benzene extract yielded 4.60 g. (89%) of nearly colorless V, m.p. 148–149.5°. Recrystallization from ether afforded colorless, prismatic needles. The analytical sample was sublimed at 140–150° (0.05 mm.), m.p. 150–151°.

Anal. Calc'd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40.
Found: C, 69.59; H, 6.71; N, 5.40.

The *hydrobromide* recrystallized as colorless needles from ethanol, m.p. 215–216° (dec.).

Anal. Calc'd for $C_{15}H_{18}BrNO_3 \cdot C_2H_5OH$: C, 52.88; H, 6.22; N, 3.63.
Found: C, 52.96; H, 6.45; N, 3.66.

The *p-toluenesulfonic acid* salt, m.p. 202–203° (dec.), was recrystallized from ethanol.

Anal. Calc'd for $C_{22}H_{25}NO_6S$: C, 61.08; H, 6.06.
Found: C, 60.74; H, 5.97.

Benzylideneteloidine (VI). Benzylideneteloidinone (1.95 g., 0.0075 mole) in 200 ml. of 70% ethanol containing a quarter teaspoonful of Raney nickel W-4 (7) was shaken under hydrogen at room temperature and atmospheric pressure until hydrogen was no longer absorbed (3–6 hours). Removal of the catalyst and concentration to a small volume yielded 1.75 g. (89.5%) of colorless needles, m.p. 132–135°. The analytical sample, m.p. 163–165°, was crystallized twice from benzene-ligroin and sublimed at 120° (0.05 mm.).

Anal. Calc'd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36.
Found: C, 69.09; H, 7.36; N, 4.82.

The *picrate* was obtained as yellow needles from ethanol, m.p. 189–190° (dec.).

Anal. Calc'd for $C_{21}H_{22}N_4O_{10}$: C, 51.43; H, 4.49.
Found: C, 51.88; H, 4.49.

The *hydrobromide*, m.p. 236–237° (dec.), was recrystallized from ethanol.

Anal. Calc'd for $C_{15}H_{20}BrNO_3$: C, 52.64; H, 5.89; N, 4.10.
Found: C, 52.78; H, 6.13; N, 4.75.

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[2] Tropinone on similar treatment yielded pseudotropine, which is in agreement with the observation of R. Mirza [*Nature*, **170**, 630 (1952)] that the lithium aluminum hydride reduction of tropinone produces exclusively the pseudo isomer.

[3] All melting points are corrected. We are indebted to Dr. S. M. Nagy and his associates for the elemental and infrared analyses.

Treatment of VI with sodium in liquid ammonia. Small pieces of sodium were added to a stirred suspension of 260 mg. (1 mmole) of VI in 25 ml. of liquid ammonia (cooled in a Dry Ice-acetone bath and protected from moisture) until the blue color persisted for 1 hour. Ammonium chloride (500 mg.) was added to destroy the excess sodium, and the ammonia was removed by allowing the reaction mixture to come to room temperature. The yellow residue was washed with five 1-ml. portions of ethanol. Then 10 ml. of ether was added to the ethanol and the precipitated material was discarded. The ethanol-ether solution yielded 50 mg. of slightly brown solid, m.p. 157–160° (dec.). After one recrystallization from 1-butanol it had m.p. 166–168° (dec.) (teloidine, m.p. 168–169°) (5).

Benzylidene-α-methylbutyrylteloideine (VII). A solution of 1.0 g. (0.0038 mole) of VI and 6 ml. of α-methylbutyric anhydride[4] in 6 ml. of anhydrous pyridine was stored at room temperature for 24 hours. The reaction mixture was concentrated under reduced pressure to a brown oil, which was taken up in 25 ml. of *N* hydrochloric acid, and the solution was extracted with three 10-ml. portions of ether. The aqueous phase was basified by the addition of 6 ml. of 6 *N* sodium hydroxide, and the solution was again extracted with ether. Removal of the ether, after drying over nagnesium sulfate, and evaporative distillation of the residue at 150–160° (0.2 mm.) yielded 810 mg. (61%) of oily VII. The *hydrobromide* crystallized as colorless platelets from ethanol, m.p. 237.5–238.5° (dec.).

Anal. Calc'd for $C_{20}H_{28}BrNO_4$: C, 56.27; H, 6.62; N, 3.29.
Found: C, 55.91; H, 6.69; N, 3.76.

The *picrate* was isolated from ethanol as yellow needles, m.p. 161–162°.

Anal. Calc'd for $C_{26}H_{30}N_4O_{11}$: C, 54.30; H, 5.26; N, 9.98.
Found: C, 53.72; H, 5.11; N, 9.84.

Dihydrometeloidine (VIII). A solution of 500 mg. (1.5 mmoles) of VII in 10 ml. of glacial acetic acid containing 200 mg. of prereduced 30% palladium on carbon (8) was stirred under hydrogen at room temperature and atmospheric pressure until slightly over the theoretical amount of hydrogen had been absorbed. The catalyst was removed and the filtrate lyophilyzed. The residue was taken up in 1 ml. of water which was saturated with anhydrous sodium carbonate and extracted with chloroform. The dried (magnesium sulfate) chloroform extract yielded 355 mg. (95.5%) of VIII, m.p. 82–84°. The analytical sample crystallized as needles from benzene-petroleum ether, m.p. 96–97°.

Anal. Calc'd for $C_{13}H_{23}NO_4$: C, 60.62; H, 9.01.
Found: C, 60.14; H, 9.54.

The *hydrobromide* crystallized as platelets from ethanol-ether, m.p. 216–217° (dec.).

Anal. Calc'd for $C_{13}H_{24}BrNO_4$: C, 46.16; H, 7.15.
Found: C, 46.32; H, 6.98.

Benzylideneacetylteloideine (IX). A solution of 1.0 g. (0.0038 mole) of benzylideneteloidine (VI) in 6 ml. of anhydrous pyridine and 4 ml. of acetic anhydride was stored at room temperature for 24 hours. Removal of the pyridine and excess acetic anhydride under reduced pressure and evaporative distillation of the residue at 140–150° (0.1 mm.) yielded 0.93 g. (80%) of IX, m.p. 109–110°. Two recrystallizations from aqueous ethanol and another sublimation raised the m.p. to 110.5–111.5°.

Anal. Calc'd for $C_{17}H_{21}NO_4$: C, 67.30; H, 6.98; N, 4.62.
Found: C, 67.51; H, 7.28; N, 4.75.

The *hydrobromide* formed colorless needles from ethanol, m.p. 276–277° (dec.).

Anal. Calc'd for $C_{17}H_{22}BrNO_4$: C, 53.13; H, 5.77; N, 3.65.
Found: C, 53.25; H, 5.95; N, 3.04.

Acetylteloideine (X). Hydrogenolysis of 500 mg. (0.0017 mole) of IX according to the procedure for dihydrometeloidine (VIII) yielded 305 mg. (85%) of X, m.p. 172–173° (dec.). The analytical sample was recrystallized twice from ethanol-ether and sublimed, m.p. 178.5–179.5° (dec.).

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[4] α-Methylbutyric anhydride was prepared according to W. J. Hickinbottom, *Reactions of Organic Compounds*, Longmans, Green and Co., New York, 1948, p. 227.

Anal. Calc'd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.95; N, 6.50.
Found: C, 55.64; H, 7.56; N, 5.76.

The *hydrobromide*, m.p. 207–208° (dec.), was recrystallized from ethanol.

Anal. Calc'd for $C_{10}H_{18}BrNO_4$: C, 40.60; H, 6.13; N, 4.73.
Found: C, 40.82; H, 6.31; N, 4.95.

Teloidine triacetate (XI). (*A*) *from teloidine.* Teloidine was acetylated according to the procedure for benzylideneacetylteloideine (IX) in 65% yield, m.p. 74–77°. After recrystallization from tetrahydrofuran-petroleum ether the m.p. was 84.5–85.5°.

Anal. Calc'd for $C_{14}H_{21}NO_6$: C, 56.17; H, 7.07; N, 4.68.
Found: C, 56.08; H, 7.11; N, 4.43.

(*B*) *from acetylteloideine* (X). Compound X (75 mg., 0.25 mmole) was acetylated according to the procedure for benzylideneacetylteloideine (IX). The distillate crystallized when seeded with material from (*A*), m.p. 84–85°. A mixture of the products prepared by procedures (*A*) and (*B*) had m.p. 84–85° (undepressed).

Benzylidenediphenylacetylteloideine (XII). To a suspension of 260 mg. (1 mmole) of benzylideneteloidine (VI) in 10 ml. of anhydrous ether was added 220 mg. (0.2 ml., 1.14 mmoles) of diphenylketene (9). After storage for 20 hours at room temperature, the ether was removed, and the residue was dissolved in 2 ml. of acetone and neutralized with 40% aqueous hydrobromic acid. After storage at 5° overnight there was obtained 360 mg. (83%) of hydrobromide, m.p. 222–224° (dec.). The analytical sample crystallized as colorless platelets, m.p. 256–257° (dec.), from 99% ethanol.

Anal. Calc'd for $C_{29}H_{30}BrNO_4$: C, 64.92; H, 5.64; N, 2.61.
Found: C, 65.03; H, 5.98; N, 2.83.

The *methiodide*, m.p. 205–206° (dec.), was recrystallized from ethanol.

Anal. Calc'd for $C_{30}H_{32}INO_4$: C, 60.30; H, 5.40; N, 2.35.
Found: C, 60.14; H, 5.58; N, 2.54.

Isopropylideneteloidinone (XIII). A solution of 3.4 g. (0.02 mole) of teloidinone (IV) and 4.2 g. (0.022 mole) of *p*-toluenesulfonic acid monohydrate in 500 ml. of acetone was heated under reflux for 24 hours. Aqueous sodium hydroxide (100 ml. of 0.5 *N*) was added to the cooled reaction mixture, and the excess acetone was removed under reduced pressure. The aqueous concentrate was extracted continuously with ether for three days. Removal of the ether and sublimation of the residue at 40° (0.01 mm.) yielded 3.63 g. (82.3%) of XIII as colorless needles, m.p. 89–90°.

Anal. Calc'd for $C_{11}H_{17}NO_3$: C, 62.53; H, 8.09; N, 6.63.
Found: C, 62.47; H, 8.02; N, 6.52.

The *picrate* crystallized as yellow needles from ethanol, m.p. 214–215°; the *hydrobromide*, recrystallized from the same solvent, had m.p. 241.5–242.5° (dec.). The *methiodide* was obtained from aqueous ethanol as colorless prisms, m.p. 227–228° (dec.).

Anal. Calc'd for $C_{12}H_{20}INO_3$: C, 40.80; H, 5.67; N, 3.97.
Found: C, 40.71; H, 5.72; N, 4.05.

Isopropylideneteloidine (XIV). Compound XIII was hydrogenated in 94.3% yield as described by the procedure for benzylideneteloidine (VI). The analytical sample was recrystallized from benzene, m.p. 131–133°.

Anal. Calc'd for $C_{11}H_{19}NO_3$: C, 61.94; H, 8.98; N, 6.57.
Found: C, 61.99; H, 9.06; N, 6.70.

The *hydrobromide*, m.p. 195.5–196.5°, crystallized from ethanol-ether as colorless needles.

Anal. Calc'd for $C_{11}H_{20}BrNO_3$: C, 42.31; H, 7.10; N, 4.49.
Found: C, 42.37; H, 7.22; N, 4.13.

Hydrolysis of XIV to teloidine hydrochloride. Compound XIV (215 mg., 1 mmole) was heated on a steam-bath for 15 minutes with 10 ml. of *N* hydrochloric acid. The reaction mixture was concentrated to dryness under reduced pressure and the residue was recrystallized three times from ethanol, m.p. 307–308° (dec.), (teloidine m.p. "above 300°," pseudoteloidine m.p. 265–266°) (5).

Isopropylideneacetylteloideine (XV). Compound XV was prepared in 77% yield by es-

sentially the same procedure as for benzylideneacetylteloideine (IX). The analytical sample formed colorless prismatic needles from ligroin, m.p. 73.5–75°.

Anal. Calc'd for $C_{13}H_{21}NO_4$: C, 61.15; H, 8.29; N, 5.49.
Found: C, 60.89; H, 8.31; N, 5.44.

The *picrate*, m.p. 213–214°, was prepared in ethanol as yellow needles; the *hydrochloride*, m.p. 289–290° (dec.), crystallized as prisms from the same solvent.

Anal. Calc'd for $C_{13}H_{22}ClNO_4$: C, 53.51; H, 7.60; N, 4.80.
Found: C, 53.57; H, 7.68; N, 5.08.

The *hydrobromide*, m.p. 295–296° (dec.), was isolated from ethanol as needles.

Anal. Calc'd for $C_{13}H_{22}BrNO_4$: C, 46.43; H, 6.60; N, 4.17.
Found: C, 46.20; H, 6.86; N, 4.31.

Isopropylidenediphenylacetylteloideine (XVI). Compound XVI was prepared in 88% yield by a procedure similar to that for the corresponding benzylidene compound (XII). A *hydrobromide*, m.p. 165–166.5°, was recrystallized from ethanol-ether.

Anal. Calc'd for $C_{25}H_{30}BrNO_4$: C, 61.47; H, 6.19; N, 2.87.
Found: C, 61.57; H, 6.47; N, 3.55.

The *methiodide*, m.p. 211–212°, was obtained as colorless needles from ethanol.

Anal. Calc'd for $C_{26}H_{32}INO_4$: C, 56.83; H, 5.87; N, 2.55.
Found: C, 57.06; H, 5.89; N, 2.16.

Isopropylidenebenzoylteloideine (XVII). Isopropylideneteloidine (XIV, 215 mg., 1 mmole) was heated on a steam-bath for 2 hours with 785 mg. (0.5 ml., 5.6 mmole) of benzoyl chloride. The reaction mixture was dissolved in 3 ml. of *N* hydrochloric acid and extracted with four 5-ml. portions of ether. The aqueous phase was basified by the addition of 2 ml. of 6 *N* sodium hydroxide and again extracted with ether. After drying over anhydrous magnesium sulfate, the ether solution was saturated with gaseous hydrogen bromide, causing separation of the oily hydrobromide. Recrystallization from ethanol-ether yielded 300 mg. (38%) of XVII hydrobromide, m.p. 264–265° (dec.).

Anal. Calc'd for $C_{18}H_{24}BrNO_4$: C, 54.32; H, 6.03; N, 3.52.
Found: C, 54.47; H, 6.19; N, 3.47.

Isopropylidenepseudoteloidine (XVIII). A solution of 3.4 g. (0.02 mole) of teloidinone (IV) and 4.2 g. (0.022 mole) of *p*-toluenesulfonic acid monohydrate in 500 ml. of acetone was heated under reflux for 24 hours. Aqueous sodium hydroxide (100 ml. of 0.5 *N*) was added, and the excess acetone was removed under reduced pressure. To the aqueous concentrate was added 1.50 g. (0.04 mole) of sodium borohydride. After 1 hour at room temperature, the reaction mixture was extracted continuously with methylene chloride for 24 hours. Concentration of the methylene chloride and sublimation of the residue at 120–130° (1 mm.) yielded 2.00 g. (50%) of colorless prisms, m.p. 112–123°. Recrystallization from benzene-ether raised the m.p. to 121–123°. The m.p. of a mixture with isopropylideneteloidine (XIV) was 104–115° (depressed).

Anal. Calc'd for $C_{11}H_{19}NO_3$: C, 61.94; H, 8.98; N, 6.57.
Found: C, 61.90; H, 9.13; N, 6.32.

The *hydrochloride*, m.p. 250–251° (dec.), was crystallized from ethanol-ether. The *hydrobromide* crystallized as colorless prisms from the same solvent, m.p. 249–250° (dec.).

Anal. Calc'd for $C_{11}H_{20}BrNO_3$: C, 44.90; H, 6.85.
Found: C, 45.10; H, 6.87.

Hydrolysis of XVIII to pseudoteloidine hydrochloride. Compound XVIII (215 mg., 1 mmole) was heated on a steam-bath for 15 minutes with 10 ml. of *N* hydrochloric acid. The reaction mixture was concentrated to dryness under reduced pressure and the residue was recrystallized from ethanol to yield 150 mg. (87%) of pseudoteloidine hydrochloride, m.p. 265–266° (dec.), [lit. 265–266° (dec.) (5)].

Isopropylideneacetylpseudoteloideine (XIX). Compound XIX was prepared in 83.7% yield by a procedure similar to that outlined for benzylideneacetylteloideine (IX). The analytical sample, m.p. 125–126.5°, was recrystallized from ether.

Anal. Calc'd for $C_{13}H_{21}NO_4$: C, 61.15; H, 8.29; N, 5.49.
Found: C, 61.52; H, 8.50; N, 5.62.

SUMMARY

A compound corresponding to the generally accepted structure of the dihydro derivative of meteloidine, one of the natural oxygenated tropane alkaloids, has been synthesized. Teloidinone was converted to the corresponding benzylidene derivative, which was reduced to benzylideneteloidine. Acylation with α-methylbutyric anhydride and removal of the benzylidene group by hydrogenolysis yielded dihydrometeloidine. Teloidinone also was converted to the isopropylidene derivative, which was reduced to the two possible stereoisomeric alcohols. Acylation of these alcohols yielded a group of esters of interest as scopolamine analogs.

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