The Isolation from Tobacco of 2-Hydroxy-2,6,6-trimethylcyclohexylideneacetic Acid γ-Lactone and Its Synthesis

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A C_{11} lactone has been isolated in minute quantities from the neutral fraction of the steam volatiles from tobacco, and its structure has been shown by physical methods and synthesis to be 2-hydroxy-2,6,6-trimethylcyclohexylideneacetic acid γ-lactone.

During a preliminary stage of cigarette manufacture, hogsheads of tobacco are treated with steam in order to make the tobacco leaf more pliable. The compound, $C_{11}H_{16}O_2$ (I), was obtained from the neutral oxygenated fraction of the tobacco volatiles found in the condenser water from this process. This compound has also been obtained from bright and Turkish tobaccos in yields of 2×10^{-4} and $6 \times 10^{-4}\%$, respectively.

The molecular formula of I was determined on the basis of high-resolution mass spectral data and elemental analysis. The high-resolution mass spectrum[2] afforded a molecular weight of 180.1718; the theory for $C_{11}H_{16}O_2$ is 180.1724. Combustion analyses[3] were consistent with the formula $C_{11}H_{16}O_2$. The presence of a carbonyl function and a double bond was deduced from the following data: infrared bands[4] of I at 1761 cm^{-1} (carbonyl) and 1637 cm^{-1} (double bond). No hydroxyl function was observed in the infrared spectrum. Evidence that the carbonyl function was not an aldehyde or ketone was furnished by the resistance of the carbonyl moiety toward silver oxide oxidation, 2,4-dinitrophenylhydrazone, oxime, and semicarbazone formation. Further support for this conclusion was obtained when a qualitative determination[1b] of the optical rotatory dispersion (700–300 mμ) of I failed to show any Cotton effect.

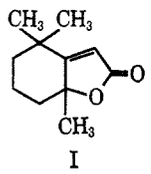
The absorption maximum,[5] in cyclohexane, at 208 mμ (log ε 4.05), is consistent with an α,β-unsaturated γ-lactone structure. Catalytic hydrogenation of I afforded a dihydro derivative II which showed no maximum in the ultraviolet spectrum and exhibited a carbonyl absorption at 1770 cm^{-1} in the infrared spectrum. A molecular weight of 182 was found for the dihydro derivative by mass spectral analysis.

The nuclear magnetic resonance spectrum[6] of I shows signals for a total of 16 protons. Three methyl groups (three three-proton singlets at τ 8.78, 8.73, and 8.50), a complex pattern in the 8.0–8.5 region, and a vinyl hydrogen (one-proton singlet at 4.48) were observed. The spectrum of the hydrogenated compound II did not show any signals in the vinyl region. Instead, a complex multiplet (about three protons), attributable to the methylene hydrogens α to the lactone carbonyl and the methine hydrogen at the ring junction, appeared at τ 7.4–8.1, the most intense peak at 7.6 accounting for ~1.3 protons. The methyl signals were somewhat displaced compared to those in I, appearing at τ 9.07, 8.94, and 8.45.

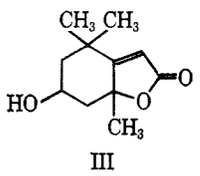
Various attempts were made to hydrolyze I without success. The compound is unchanged upon heating for several hours in methanolic potassium hydroxide, ethylene glycol–potassium hydroxide, or aqueous sulfuric acid.

Based on the physical data reported above and since the high-resolution mass spectrum afforded a strong $[M - (CH_3CO)]^+$ ion species, suggesting a saturated methylene group adjacent to the ring lactone function, two structures, I and XVI, were considered in the early stages of this investigation. Since the difficulty of isolation of I precluded degradative work, definitive evidence for the structure of the tobacco lactone was sought by the synthesis of both compounds depicted by structures I and XVI.

Compound I, which has the trimethylcyclohexanone ring of the higher terpenoids, is related to the compound loliolide (III), isolated from *Lolium perenne*[7] and



I



III

Digitalis purpurea,[8] whose structure has been recently confirmed by Horii, *et al.*[9]

Sakan and coworkers[10a] report the isolation of a lactone of structure I from the essential oil of the leaves of

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(2) Mass spectra were determined on either a Consolidated 21-103B, or, in the case of high-resolution spectra, a Consolidated 21-110 instrument. They will be reported in detail in a subsequent publication.

(3) Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., and by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(4) Infrared spectra were determined as thin films (liquids) and in KBr (solids) using either a Perkin-Elmer Model 21 or 221 spectrophotometer.

(5) Ultraviolet spectra were determined in cyclohexane solution using an Applied Physics Model 14 spectrophotometer in the wavelength range of 200–400 mμ.

(6) Nuclear magnetic resonance spectra were determined using Varian Associates A-60 and HA-100 instruments using $CDCl_3$ as the solvent and TMS as the reference compound.

(7) R. Hodges and A. L. Porte, *Tetrahedron*, **20**, 1463 (1964).

(8) T. Wada, *Chem. Pharm. Bull.* (Tokyo), **12** (9), 1117 (1964); **13** (1), 43 (1965).

(9) Z. Horii, T. Yagami, and M. Hanaoka, *Chem. Commun.*, **18**, 634 (1966).

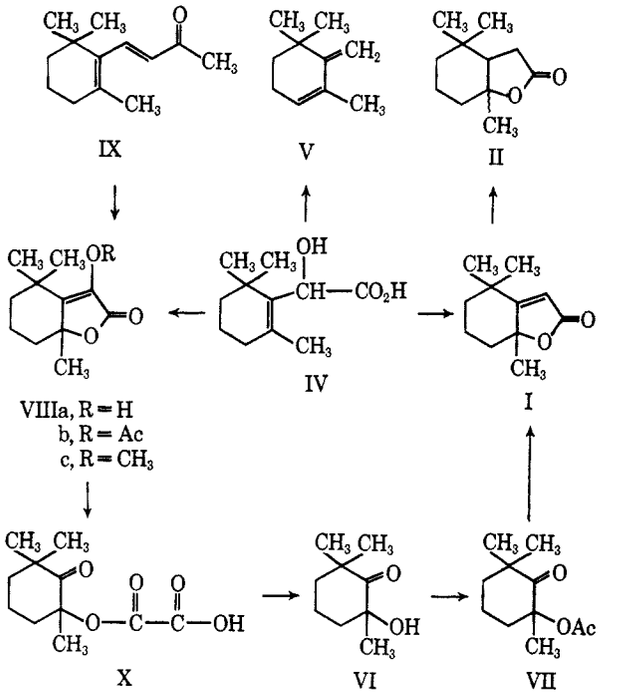
(10) (a) T. Sakan, S. Isoe, and S. B. Hyeon, *Tetrahedron Lett.*, 1623 (1967); (b) M. Mousseron-Canet, J. C. Mani, and J. P. Dalle, *Bull. Soc. Chim. Fr.*, 608 (1967); (c) J. Bricout, R. Viani, F. Müggler-Chavan, J. P. Marion, D. Reymond, and R. H. Egli, *Helv. Chim. Acta*, **50**, 1517 (1967). Since the completion of this work the three publications above appeared. The latter two, unavailable to us when the manuscript was prepared, were kindly pointed out by a reviewer. The reviewer also mentions the wide variation in the ultraviolet data and the noticeable differences in the infrared spectra reported. Correspondence with these authors establishes that the value reported by Sakan[10a] should be 214 mμ for the ultraviolet absorption. We assume both Sakan and Mousseron used ethanol as solvent as our material (I), we have since determined, has absorption maximum, in ethanol, at 214 mμ (log ε 4.03).

Actinidia polygama. Mousseron[10b] reports the isolation of I from the base-catalyzed rearrangement products obtained from the photooxidation of both β-ionone and β-cyclocitrylideneacetic acid methyl ester. The isolation of I from black tea is further reported by Bricout[10c] and coworkers. The physical property data from these publications and ours differ. The ultraviolet absorption values reported are 208, 217, and 241 mμ. These values appear widely separated for solvent differences if indeed the solvents were different. There are noticeable differences in the infrared spectra reported also. The carbonyl absorptions reported are 1745, 1750, and 1761 cm^{-1} while the double bond absorptions reported are 1625, 1630, 1637, and 1650 cm^{-1}. These values would appear to be greater than experimental error.

The lactone I readily prepared starting with the known 2,6,6-trimethylcyclohexene-1-glycolic acid (IV)[11] which is obtained from 2,2,6-trimethylcyclohexanone. Treatment of the glycolic acid with aqueous sulfuric acid afforded the desired lactone I in approximately 35% yield (as determined by vpc) as well as varied amounts of the diene pyronene V.[12] Heating of the glycolic acid at 200–220° afforded the lactone in high yield without contamination by the diene component. Alternately, the lactone could be prepared from the known hydroxytrimethylcyclohexanone VI. Preparation of the acetate VII followed by base-catalyzed ring closure[13] afforded the lactone I in 13% yield. Treatment of the intermediate glycolic acid IV with chromic anhydride–pyridine mixture afforded the "hydroxyionolactone" VIIIa, which is also obtained by the permanganate oxidation[14] of β-ionone (IX). Conversion of "hydroxyionolactone" prepared from the glycolic acid into its acetate and methyl ether gave the known compounds VIIIb and VIIIc,[14b] whose physical properties were identical with materials prepared from "hydroxyionolactone" synthesized from β-ionone. Treatment of "hydroxyionolactone" VIIIa with ozone[15] afforded in high yield the expected derivative X, which, upon basic hydrolysis, afforded the known keto alcohol VI.[16] No characterizable products, however, could be obtained upon similar treatment of the lactone I under a variety of conditions. The interrelationships existing in the above synthetic procedures are depicted in Scheme I.

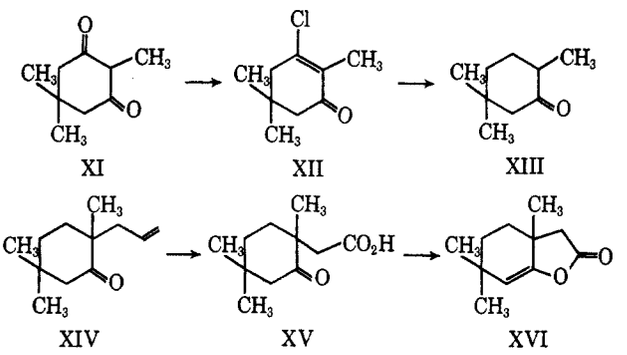
The synthesis of 1,4,4-trimethylcyclohexan-2-one-acetic acid enol lactone (XVI) was effected starting with the known 2,5,5-trimethylcyclohexane-1,3-dione (XI)[17] prepared from dimedone. Treatment of this β-diketone with phosphorus trichloride[18] gave the 3-chlorocyclohexenone XII in 67% yield. Catalytic hydrogenation of XII afforded the trimethylcyclohexanone XIII, which was further alkylated with allyl bromide to obtain 3-(1,4,4-trimethylcyclohexan-2-one)-prop-1-ene

SCHEME I



(XIV). Subsequent oxidation of XIV with ozone afforded the keto acid XV, which was converted into the enol lactone XVI upon treatment with acetic anhydride. The reaction sequence leading to the enol lactone XVI is shown in Scheme II.

SCHEME II



Experimental Section

Melting points and boiling points are not corrected. Gas chromatographic separations were effected using a F & M Model 500 chromatographic unit fitted with a 3/8 in. × 10 ft copper column containing 20% Carbowax 20M on 60–80 mesh Chromosorb P. The helium carrier gas flow was 100 ml/min and the unit was programmed from 100 to 225° at 5.6°/min.

Isolation of Lactone I from *N. Tabacum*.—Shredded leaves (2 lb) of *N. Tabacum* were extracted in a Soxhlet extractor with 3000 ml of methylene chloride. The cooled extract was dewaxed using cold acetone. After removal of solvent under reduced pressure, the residue was dissolved in ether. The ethereal solution was then extracted with cold 1 *N* hydrochloric acid followed by cold 1 *N* sodium hydroxide solution. The remaining neutral extract was washed with water and dried and the solvent was removed under reduced pressure. The residual material (10–12 g), in a minimum of hexane, was adsorbed on 300–500 g of silicic acid and eluted gradiently with acetone–hexane, with 150 ml aliquots being taken. The compound I was found in highest concentration in fraction 11 (5% acetone–95% hexane) as verified by vpc. Repeated trapping of the appropriate peak (26-min retention time under our standard conditions) on the gas chromatographic unit afforded 1–2 μl of the desired lactone

(11) J. D. Chanley, E. Chow, and H. Sobotka, *J. Amer. Chem. Soc.*, **77**, 6056 (1955), in which the compound is misnamed 2,2,6-trimethylcyclohexene-1-glycolic acid.

(12) G. Ohloff, *Ann.*, **627**, 79 (1959).

(13) H. G. Lehmann, *Angew. Chem. Intern. Ed. Engl.*, **4**, 783 (1965).

(14) (a) Tieman, *Ber.*, **31**, 857 (1898); (b) C. J. W. Brooks, G. Eglinton, and D. S. Magrill, *J. Chem. Soc.*, 308 (1961).

(15) Ozone was generated using a laboratory Welsbach ozonator.

(16) C. L. Stevens and A. J. Weinheimer, *J. Amer. Chem. Soc.*, **80**, 4072 (1958).

(17) (a) T. G. Halsall and D. B. Thomas, *J. Chem. Soc.*, 2431 (1956); (b) R. D. Desai, *ibid.*, 1079 (1932); (c) E. G. Meek, J. H. Turnbull, and W. Wilson, *ibid.*, 811 (1953).

(18) R. L. Frank and H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **72**, 1645 (1950).

I from 200 μl of the crude column chromatographic fraction. The analytical sample was prepared by a second rectification of the material by vpc.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 72.90, 73.07; H, 9.16, 9.31.

2-Hydroxy-2,6,6-trimethylcyclohexylideneacetic Acid γ-Lactone (I). Procedure 1.—2,6,6-Trimethylcyclohexene-1-glycolic acid (IV, 50 μl)[11] was added to 100 ml of 50% v/v aqueous sulfuric acid and the mixture heated under reflux for 2 hr. The cooled solution was extracted with three 100-ml portions of ether. The extracts were washed with 25 ml of 5% aqueous sodium hydroxide and to neutrality with water. The solution was dried and filtered and the solvent was removed; 5-μl samples of the residue were trapped from the gas chromatographic unit. The infrared, ultraviolet, and high resolution mass spectra of the synthetic compound were identical with those of the natural product. An additional material (*ca.* 35% of the total) having a retention time of 22 min was identified as pyronene[12] by comparison of their infrared spectra.

Procedure 2.—2,6,6-Trimethylcyclohexene-1-glycolic acid (IV, 3.7 g) in an evacuated tube was heated at 219° for 1 hr in a bath of phenethyl alcohol. After cooling, the contents of the tube were dissolved in ether and the solution was washed with aqueous sodium bicarbonate, saturated sodium chloride solution, and water. The dried solution was evaporated under reduced pressure to obtain 3.0 g of a tan oil. Distillation gave 2.1 g of a colorless liquid, bp 108–109° at 800 μ, which crystallized on cooling: mp 42–43°; ir 1761 cm^{-1} (strong, α,β-unsaturated lactone carbonyl), 1637 cm^{-1} (weak, double bond).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.12; H, 8.83.

Procedure 3.—6-Hydroxy-2,2,6-trimethylcyclohexanone (VI, 292 mg)[16] was dissolved in 2 ml of isopropenyl acetate containing a crystal of *p*-toluenesulfonic acid. After the solution was allowed to stand overnight, the volatile material was removed under reduced pressure and the residue was dissolved in ether. The ethereal solution was washed with aqueous sodium bicarbonate, saturated sodium chloride solution, and water. After drying, removal of the solvent afforded 222 mg of VII as an oil: ir 1736 cm^{-1} (strong, ester function), 1712 cm^{-1} (strong, ring ketone).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.80; H, 9.23.

The keto acetate (100 mg) was dissolved in 2 ml of toluene and 50 mg of potassium *t*-butoxide added. After the mixture was allowed to stand overnight, ether was added; the mixture was washed with water. Removal of the solvent under reduced pressure afforded a clear oil (20 mg) whose major peak (~90%) on vapor phase chromatography afforded the lactone I, identified by mass, infrared and nmr analyses.

2-Hydroxy-2,6,6-trimethylcyclohexylacetic Acid γ-Lactone (II).—The hydrogenation of natural lactone I was effected using platinum oxide catalyst in glacial acetic acid and a Parr laboratory shaker at room temperature and a pressure of 20–25 lb of hydrogen for 1 hr. The product was isolated by vpc trapping. The product exhibited a molecular ion of 182 in the mass spectrum; no absorption in the ultraviolet; ir 1770 cm^{-1} (strong, lactone carbonyl), no absorption in the double-bond region.

2-Hydroxy-2,6,6-trimethylcyclohexanone Oxalate (X).—"Hydroxyionolactone" (VIIIa, 1.50 g), prepared from β-ionone,[14] was dissolved in 50 ml of anhydrous ethyl acetate. Ozone–oxygen[15] (~3% ozone) was passed into the ice-cooled solution until an excess was indicated by the KI–H_3BO_3 trap. The solution was then transferred to the Parr bottle along with 300 mg of PtO_2 and hydrogenated overnight at 40-lb pressure. The catalyst was removed by filtration and the solution was evaporated to afford 1.45 g of an oil which crystallized on standing. Recrystallization of the solid material from ether–hexane (ice cold) gave 600 mg of 2-hydroxy-2,6,6-trimethylcyclohexanone oxalate (X), mp 103–104°, with a second crop of ~100 mg recoverable from the mother liquor. The analytical sample exhibited in the ir spectrum (Nujol) a broad band at 3700–2400 cm^{-1} (acid and hydrogen-bonded carbonyl), 1782 and 1680 cm^{-1} (strong, carbonyl functions).

Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 57.91; H, 7.29.

2-Hydroxy-2,6,6-trimethylcyclohexanone (VI).—To 10 ml of methanol containing 0.663 mg of potassium hydroxide was added 201 mg of keto ester X. After the solution was allowed to stand overnight, the mixture was filtered and extracted with cold ether. The ether solution was washed with 5% aqueous sodium hydroxide and to neutrality with water. Evaporation of the dried solution afforded 103 mg of an oil: ir 3420 cm^{-1} (strong, OH stretch), 1698 cm^{-1} (very strong, six-membered ring carbonyl), 1156 cm^{-1} (strong, *t*-hydroxyl).

Treatment of the keto alcohol with pyridine–acetic anhydride afforded the acetate VII whose infrared and mass spectra were identical with those of the compound prepared above.

Oxidation of 2,6,6-Trimethylcyclohexene-1-glycolic Acid (IV).—Chromium trioxide (87 mg) was dissolved in 5 ml of pyridine, cooled to 0° and a cooled solution of the glycolic acid (174 mg) in 3 ml of pyridine was added. The mixture was left in the refrigerator overnight and then stirred at room temperature an additional 3 hr. Water (10 ml) was added and the mixture was extracted with ether. The ether layer was extracted with 5% aqueous hydrochloric acid followed by washing with water. Evaporation of the solvent afforded a dark brown residue, which was further extracted with boiling heptane to obtain 19 mg of a solid, mp 125–130°. The infrared spectrum of this material was identical[14b] with that of material prepared from β-ionone (mp 129–131°). The acetate exhibited the following characteristics: mp 70–71°; λ_{max} 216 mμ (ε 13,300); ν_{max} 1780 cm^{-1} (broad, very strong, carbonyls) and 1680 cm^{-1} (unsaturation) [lit.[14b] mp 66–67°; λ_{max} 216.5 mμ (ε 14,000); ν_{max} 1787 cm^{-1} (very strong) and 1776 cm^{-1} (very strong), γ-lactone and enolic acetate carbonyl]. The methyl ether exhibited the following characteristics: λ_{max} 227 mμ; ν_{max} 1763 cm^{-1} (very strong, lactone carbonyl) and 1663 cm^{-1} (strong, double bond) [lit.[14b] λ_{max} 226 mμ (ε 11,000); ν_{max} 1763, 1660, 2868, and 2845 cm^{-1}].

2,5,5-Trimethyl-3-chlorocyclohex-2-en-1-one (XII).—2,5,5-Trimethylcyclohexane-1,3-dione (XI) was prepared by the methylation of dimedone.[17] The reaction of XI with phosphorus trichloride was effected under the conditions described by Frank and Hall.[18]

2,5,5-Trimethylcyclohexanone (XIII).—A solution of 2,5,5-trimethyl-3-chlorocyclohex-2-en-1-one (XII, 23.4 g) in 200 ml of glacial acetic acid containing 11.3 g of anhydrous sodium acetate was shaken with 1.5 g of 5% palladium–carbon catalyst at room temperature and 25 lb of hydrogen. The catalyst was removed by filtration and the acetic acid was removed under reduced pressure. The residue was dissolved in ether. The resultant solution was washed with dilute sodium hydroxide solution and water. After drying, the solvent was removed. Distillation of the residue afforded 15.9 g of 2,5,5-trimethylcyclohexanone: bp 51–52° (4 mm) [lit. bp 71–73° (12 mm)[17a] and 79–80° (21 mm)[19]].

3-(1,4,4-Trimethylcyclohexan-2-one)prop-1-ene (XIV).—2,5,5-Trimethylcyclohexanone (XIII, 20.5 g) in 50 ml of dry ether was added to an ether suspension of lithamide (prepared from 1.06 g of lithium and 500 ml of anhydrous ammonia followed by replacement of the ammonia with 300 ml of dry ethyl ether). The mixture was heated at the reflux temperature for 3 hr, cooled to 0° and allyl bromide (18 g in 40 ml ether) was added in one portion. The mixture was heated at the reflux temperature for 3 hr, cooled and water was added to dissolve the precipitated salts. The ether layer was washed with water and dried. Removal of the solvent under reduced pressure afforded a residual oil (25.0 g) which was vacuum distilled to obtain 10.6 g of XIV: bp 86–89° (4.5 mm); ir 1718 cm^{-1} (strong, ketone) and 1647 cm^{-1} (unsaturation).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.95; H, 11.18. Found: C, 79.81, 79.71; H, 11.30, 11.06.

The thiosemicarbazone derivative had mp 124–125°.

Anal. Calcd for $C_{13}H_{23}N_3O$: C, 61.62; H, 9.15; N, 16.58; S, 12.66. Found: C, 61.49; H, 9.08; N, 16.37; S, 12.85.

1,4,4-Trimethylcyclohexan-2-oneacetic Acid (XV).—3-(1,4,4-Trimethylcyclohexan-2-one)prop-1-ene (XIV, 8.0 g) was dissolved in 250 ml of methylene chloride, the solution was cooled to −60 to −65° and a 3% ozone–oxygen mixture was passed through the solution for 15 min. Glacial acetic acid (175 ml) was added to the warmed (30°) solution and the methylene dichloride was removed under diminished pressure. The acetic acid solution of the ozonide was added over 20 min to a cooled solution (0°) of 150 ml of water, 1 ml of concentrated sulfuric acid, and 10 ml of 29% hydrogen peroxide. The oxidizing mixture was heated at the reflux temperature for 1.5 hr and then allowed to stand overnight at room temperature. The

(19) F. Sondheimer and S. Wolfe, *Can. J. Chem.*, **37**, 1870 (1959).

mixture was evaporated to dryness under reduced pressure. The residue was extracted with ether and the ether solution was extracted with two 30-ml portions of 5% sodium hydroxide. The combined base extract was neutralized in the cold with 5% hydrochloric acid and reextracted into ether. The ether solution was washed with water and dried. Removal of the solvent under reduced pressure afforded 7.7 g of an oil. Low-boiling material was distilled to 128° (0.2 mm) and the residue (5.0 g) was crystallized from ether to obtain XV: mp 71–77°; ir 3700–2400 cm^{-1} (broad band, acid hydroxyl) and 1721 cm^{-1} (strong, ketone); analytical sample, mp 77–78°.

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.42; H, 9.05.

The thiosemicarbazone derivative had mp 185–186°.

Anal. Calcd for $C_{12}H_{21}N_3SO_2$: C, 53.11; H, 7.80; N, 15.48; S, 11.82. Found: C, 53.35; H, 7.62; N, 15.32; S, 11.63.

1,4,4-Trimethylcyclohexan-2-oneacetic Acid Enol Lactone (XVI).—1,4,4-Trimethylcyclohexan-2-oneacetic acid (XV, 200 mg) was heated for 12 hr in 5 ml of acetic anhydride containing 100 mg of anhydrous potassium acetate. The solution was cooled and water was added. The resultant acetic acid solution was extracted with ether; the combined ether extracts were washed with saturated sodium bicarbonate and water. Removal of the solvent under reduced pressure afforded 165 mg of an oil. The analytical sample was obtained by adsorption of the material on Florisil (30:1) followed by elution with benzene: ir 1802 cm^{-1} (strong, lactone carbonyl), 1701 cm^{-1} (unsaturation); mp 44.5–45°.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.11; H, 8.88.

The nmr spectrum showed the following: three methyl singlets at τ 9.01 (3 H), 8.93 (3 H), and 8.80 (3 H); singlets at τ 7.63 (2 H) and 5.03 (1 H); and two multiplets centered at τ 8.41 (2 H) and 8.31 (2 H).

Registry No.—I, 15356-74-8; II, 16778-27-1; VI, 7500-42-7; VII, 16797-54-9; X, 16797-55-0; XIV, 16778-23-7; thiosemicarbazene derivative of XIV, 16778-24-8; XV, 16778-25-9; thiosemicarbazene derivative of XV, 16797-44-7; XVI, 16778-26-0.

Pyrimidine Nucleosides. I. The Synthesis of 6-Methylcytidine, 6-Methyluridine, and Related 6-Methylpyrimidine Nucleosides[1]

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The first successful synthesis of 6-methylpyrimidine nucleosides has been realized. 6-Methylcytidine (VIII) and 6-methyl-2′-deoxycytidine (XI) have now been prepared by direct utilization of 6-methylcytosine (IV) *via* silylation and subsequent treatment with the appropriate acetohalo sugar in acetonitrile. Conversion of 6-methylcytidine into 6-methyluridine (IX) has been achieved in 65% yield. This direct glycosidation procedure applied to 6-methyluracil gave 6-methyl-3-β-D-ribofuranosyluracil (IIa) as the major product. Utilization of this general method has resulted in preparation of 5,6-dimethyluridine (XIII). A new route to the synthesis of 6-methylcytosine (IV) is reported.

Although thymidine, 5-methyl-2′-deoxycytidine,[2] 5-methylcytidine,[3,4] and 5-methyluridine[4,5] have been isolated from various sources of nucleic acid and each has been synthesized chemically[6,7] the corresponding 6-methylpyrimidine nucleosides are unknown. Various unsuccessful attempts to prepare N_1-glycosyl derivatives of 6-methyluracil have been recorded[8,9] and date back to the work of Fischer.[10] The only direct N_1-glycosidation of a 6-substituted uracil, cytosine, or thymine derivative disclosed in the literature is the preparation of orotidine reported by Curran and Angier[11] by coupling the mercury derivative of *n*-butyl orotate. In this latter instance the yield reported was very low and 3-β-D-ribofuranosylorotic acid was the main product.[11]

Newmark and Goodman[8] utilized 6-methyl-2,4-diethoxypyrimidine and 6-methyl-2-ethylthio-4-ethoxypyrimidine in an unsuccessful attempt to prepare 6-methylpyrimidine *N*-glycosides by the Hilbert–Johnson method.

Recent success in utilizing trimethylsilyloxypyrimidine derivatives[12,13] in a *modified* Hilbert–Johnson procedure[14] suggested a reinvestigation of the problem of the synthesis of 6-methylpyrimidine nucleosides. The readily available 6-methyluracil was converted into 6-methyl-2,4-bis(trimethylsilyloxy)pyrimidine (I) with hexamethyldisilazane.[12] Treatment of I with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide in acetonitrile gave a 16% yield of crystalline 3-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-6-methyluracil (II). Treatment of II with sodium methoxide gave a 66% yield of 3-β-D-ribofuranosyl-6-methyluracil (IIa) (see Scheme I).

Assignment of glycosidation at N_3 was made on the basis of the significant bathochromic shift of 25 mμ in basic solution accompanied by a substantial increase in ϵ_{max} which is characteristic of N_3-substituted uracils.[15–17]

Treatment of I with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide under similar conditions yielded after fractionation a homogeneous syrup, 3-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-6-methyluracil (III) which exhibited a coupling constant $J_{1',2'}$ of less than 1 cps for $H_{1'}$ which established the anomeric config-

(1) This work was supported by Research Grants CA-08109 and CA-08109-02 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) J. W. Littlefield and D. B. Dunn, *Nature*, **181**, 254 (1958); see also C. A. Dekker and D. T. Elmore, *J. Chem. Soc.*, 2864 (1951).

(3) J. W. Littlefield and D. B. Dunn, *Biochem. J.*, **70**, 642 (1958).

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