bromo-16α,17α-dihydroxy-4-pregnene-3,11,20-trione (IIa) was obtained by direct crystallization. Acetylation gave the solvated 16α,21-diacetate IIb in an 8% over-all yield from Ia. The same final product IIb was obtained in 10% yield when the hydroxylation was carried out with osmic acid in benzene.[7,8] These yields are to be compared with a 28% yield obtained by hydroxylation of the parent nonhalogenated compound 21-acetoxy-4,16-pregnadiene-3,11,20-trione (Ib) with permanganate,[5b] and with a 50% yield by hydroxylation of Ic with osmic acid.[7]

The lower yields observed in the preparation of the 12α-bromo-16α,17α-diols may, in part, be ascribed to steric hindrance. Examination of a molecular model of Ia shows the axial 12α-bromine atom to be in close proximity to the rear side of the C16,17-double bond. Consequently, the bromine atom may inhibit the formation of a large osmate or permanganate complex on the rear side of the D-ring.

The assigned structure of IIb was confirmed by the reductive removal of the bromine atom with zinc in acetic acid[9] to afford in good yield the known 16α,21-diacetoxy-17α-hydroxy-4-pregnene-3,11,20-trione (IIc).[5b,7]

## EXPERIMENTAL[10]

*21-Acetoxy-12α-bromo-16α,17α-dihydroxy-4-pregnene-3,11,20-trione* (IIa). To a solution of 926 mg. of 21-acetoxy-12α-bromo-4,16-pregnadiene-3,11,20-trione (Ia) in 40 ml. of acetone at 0° was added 320 mg. of potassium permanganate dissolved in 25 ml. of 85% aqueous acetone. The mixture was stirred at 0° for 7 min. when a solution of cold saturated sodium bisulfite was added. The resulting inorganic precipitate was separated by filtration. The filtrate was concentrated and 440 mg. of white solid, m.p. 200–205°, was collected. Paper strip chromatographic analysis revealed the presence in appreciable amount of five Blue Tetrazolium reducing products.

Crystallization of this mixture from acetone–petroleum ether gave 88 mg. of crude product, m.p. 250° (dec.). Two further crystallizations from acetone gave 20 mg. of pure IIa, m.p. 263° (dec.), $[\alpha]^{25}_{D}$ +39° (*c*, 0.28, pyridine); $\nu_{max}$ 3400, 1738, 1714, 1664, 1662, and 1236 cm.$^{-1}$

*Anal.* Calcd. for $C_{23}H_{29}O_7Br$ (497.38): C, 55.54; H, 5.88; Br, 16.07. Found: C, 55.85; H, 5.95; Br, 16.21.

In another run with 1.4 g. of Ia in 60 ml. of acetone, 480 mg. of potassium permanganate in 50 ml. of 85% acetone, and 0.35 ml. of acetic acid there was obtained 180 mg. (12% yield) of IIa, m.p .261° (dec.);$\lambda^{methanol}_{max}$ 237 mμ (ε 16,400).

*16α,21-Diacetoxy-12α-bromo-17α-hydroxy-4-pregnene-3,11,20-trione* (IIb). (a) To a solution of 155 mg. of 21-acetoxy-12α-bromo-16α,17α-dihydroxy-4-pregnene-3,11,20-trione (IIa) in 6 ml. of pyridine was added 0.6 ml. of acetic anhydride. After standing at room temperature for 20 hr. the mixture was poured into ice water and filtered to afford 135 mg. of a white powder, m.p. 219–221° (dec.). Crystallization from acetone–petroleum ether gave 105 mg. of IIb, m.p. 228–229°. Further crystallization did not change the melting point; $\nu_{max}$ 3430, 1740, 1718, 1760, 1622, and 1238 cm.$^{-1}$

*Anal.* Calcd. for $C_{25}H_{31}O_8Br$ (539.42): C, 55.66; H, 5.79; Br, 14.82. Found: C, 56.46; H, 5.97; Br, 14.55.

(b) A solution of 575 mg. of osmic acid in 10 ml. of benzene was added to a solution of 926 mg. of the diene Ia in 25 ml. of benzene containing 0.4 ml. of pyridine. The mixture was stirred at room temperature for 7 hr. when a solution of 3.8 g. of sodium sulfite and 3.8 g. of potassium bicarbonate in 40 ml. of water and 25 ml. of methanol was added. After being stirred at room temperature overnight the mixture was filtered, and the residue was washed thoroughly with ethyl acetate. The combined filtrates were washed, dried, and filtered. Evaporation gave an intractable oil which on acetylation resisted crystallization.

The crude diacetate was subjected to partition chromatography on 150 g. of Celite[11] with a ternary system consisting of 10 parts petroleum ether (b.p. 90–100°), 3 parts dichloromethane, and one part ethylene glycol. The second hold-back volume (240 ml.) upon concentration gave 83 mg. of crystals, m.p. 225–227° (dec.). Three crystallizations from acetone–petroleum ether gave 50 mg. of pure IIb, m.p. 228–229° (dec.), $\lambda^{ethanol}_{max}$ 237 mμ (ε 13,700); $[\alpha]^{24}_{D}$ +26° (*c*, 0.99, chloroform). Infrared spectral analysis showed this product to be identical with that obtained from the potassium permanganate hydroxylation.

*16α,21-Diacetoxy-17α-hydroxy-4-pregnene-3,11,20-trione* (IIc). A mixture of 60 mg. of zinc dust and 54 mg. of the 12α-bromo-diacetate IIb in 5 ml. of glacial acetic acid was stirred at 15–20° for 20 min. It was then filtered and the separated solid was washed with several portions of ethanol. The combined filtrates were evaporated (bath temperature <40°), and the residue was extracted with ethyl acetate. The extract was washed with saturated sodium bicarbonate and saturated saline solution. The dried extract was filtered and evaporated. A single crystallization of the crude product from acetone–petroleum ether gave 36 mg. of IIc, m.p. 233–234°. The product exhibited a negative Beilstein test for halogen, and its infrared spectrum was identical with that of an authentic sample.[5b,7]

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(7) W. S. Allen and S. Bernstein, *J. Am. Chem. Soc.*, **78**, 1909 (1956).

(8) Here also the reaction mixture was complex and no attempt was made to isolate and identify the by-products.

(9) V. R. Mattox and E. C. Kendall, *J. Biol. Chem.*, **188**, 287 (1951).

(10) Melting points are uncorrected. The petroleum ether used had a b.p. 60–70°, unless otherwise specified. The infrared absorption spectra were determined in a potassium bromide disk.

(11) The adsorbent was specially treated Celite "545" which was slurried in 6*N* hydrochloric acid and allowed to stand overnight. It was then filtered and was washed with water, followed by alcohol and/or acetone. Finally, it was dried at 100°. Celite is the trade-mark of Johns-Manville Co. for diatomaceous silica products.

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## 4-(3-Pyridyl)-4-ketobutyric Acid

HARVEY N. WINGFIELD, JR.

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A synthesis of 4-3-pyridyl-4-ketobutyric acid which would give increased yields was desired, as this compound is an intermediate in the synthesis of

DL-desmethycotinine and nornicotine.[1] Previous syntheses have been by the condensation of ethyl nicotinate and diethyl succinate[1] in the presence of sodamide[2] or by the condensation of ethyl bromoacetate with ethyl nicotinoyl acetate.[3]

The present method involving the condensation of diethyl sodiomalonate with bromomethyl ketone, reduces the possibility of concurrently formed condensation products to a minimum, and gives a good yield. The intermediate bromomethyl pyridyl ketone should also be a useful intermediate for synthesis of keto alcohols, esters, substituted malonic esters, keto aldehydes, thiazoles, and similar compounds.

### EXPERIMENTAL

*Bromomethyl pyridyl ketone.* A solution of 6 g. of 3-pyridyl methyl ketone in 20 ml. of acetic acid containing 32% hydrobromic acid was cooled and a solution of 16 g. of pyridine hydrobromide perbromide[4] in 200 ml. of glacial acetic acid was added. Warming slightly and shaking intermittently brought about decolorization and the precipitation of the bromoketone hydrobromide.

The contents of the flask were cooled and 400 ml. of ether were added. After standing at 4° overnight, the precipitate was filtered off, washed well with ether, vacuum dried, and placed in an icebox in a closed container. Under these conditions the hydrobromide was stable and was used in the next step without further purification. A small sample was dissolved in hot acetic acid and precipitated with ether several times to procure a pure sample for analysis.

*Anal.* Calcd. for $C_7H_7NOBr_2$: Br, 56.94. Found: Br, 56.98, 57.00. The yield of crude material was nearly quantitative.

*4-(3-Pyridyl)-4-ketobutyric acid.* To a solution of 0.2 mole of diethyl sodiomalonate in an excess of malonic ester as a solvent was gradually added 0.1 mole bromomethyl-3-pyridyl ketone, stirring continuously. If, after part of the ketone has been added, the reaction remains sluggish, about 20 ml. of ethanol may be added. Care was taken to prevent a rise in temperature.

After about 12 hr. stirring, while in an ice bath, the temperature was permitted to rise to about 25° and stirring continued for another 12 hr. The salt formed was removed by filtration and the filtrate made acid with hydrochloric acid and refluxed to hydrolyze the ester. After 16 hr. the solution was cooled, extracted with ether once, and evaporated to near dryness in a rotating film evaporator. The solution was brought to a *p*H of 5.7 and allowed to crystallize at 4°. The yield averaged about 60% of crude material based on the bromoketone used.

*Anal.* Calcd. for $C_9H_9NO_3$: C, 60.33; H, 5.08. Found: C, 60.32, 60.55; H, 5.13, 5.20.

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DEPARTMENT OF RESEARCH AND DEVELOPMENT
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[4] C. Djerassi and C. Scholz, *J. Am. Chem. Soc.*, **70**, 417 (1948).

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## The Structure of the Trimethylsilyl Derivative of Methyl Cyanoacetate

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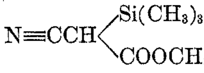
A recent note[1] corrects the structure which two of us had assigned to the trimethylsilyl derivative of ethyl acetoacetate. Since we presented the original paper,[2] we have had occasion ourselves to reexamine by spectral methods one other product which we had disclosed there. We had withheld publication pending a more complete clarification; however, none of us at present is working in this field, and it seems appropriate now to present what data we have.

Our original assignment was based primarily on the reaction of trimethylchlorosilane with methyl cyanoacetate.[3] The reported reactions of alkylating agents with cyanoacetic esters have, as far as we know, been observed to give only C-alkylation,[4] and our assignment of C-silylation to give structure I seemed to be a proper deduction. However, examination of the infrared spectrum of the carefully distilled compound showed strong absorption bands at 1623 cm.$^{-1}$ and at 2222 cm.$^{-1}$ The band at 2222 cm.$^{-1}$ is very likely displaced and strengthened absorption attributable to C≡N in a conjugated position.[5] The band at 1623 cm.$^{-1}$ is attributed to the absorption due to a carbon-carbon double bond in conjugation with the nitrile group. A relatively small absorption at 1761 cm.$^{-1}$, which progressively disappeared in successive fractions, is attributed to methyl cyanoacetate contaminant; otherwise no major carbonyl peak was apparent. Two strong bands at 850 cm.$^{-1}$ and 1250 cm.$^{-1}$ correspond to $Si(CH_3)_3$ absorption. There was no absorption in the reported range for normal Si—O stretching vibrations, but there were strong bands at 965 cm.$^{-1}$ and 1105 cm.$^{-1}$, either of which could be so assigned, in view of the evidently unusual structure.[6] A weak band at 3100 cm.$^{-1}$ is a



$$N{\equiv}CCH\begin{matrix}\diagup Si(CH_3)_3\\ \diagdown COOCH_3\end{matrix}$$

I

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[2] M. J. Hurwitz, P. L. de Benneville, and R. A. Yoncoskie, Abstracts of Papers, 131st National Meeting, American Chemical Society, Miami, Fla., 1957, p. 52–160.

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[4] A. C. Cope, H. L. Holmes, and H. O. House, *Org. Reactions*, IX, 109 (1957).

[5] L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd ed., Methuen & Co., Lt., London, Eng., 1957, p. 264.

[6] Bellamy (footnote 5, p. 340) suggests 1090–1020 cm.$^{-1}$ for normal Si—O absorption. West (footnote 1) reports "near 1000 cm.$^{-1}$" for Si—O in a more closely related structure.