dation. Similarly, quinone imine 11, derived from 3,7-diOH-CPZ, lost its chloride through substitution, requiring 2 electrons for oxidation.

The importance of radical ion or quinoneimine formation to the biological activity of the hydroxylated chlorpromazines is difficult to assess, but the present results allow some insight into their possible involvement in pharmacological effects. First, radical formation from 3-OH-CPZ is very likely at physiological pH, and it is also probable that 7-OH-CPZ undergoes a similar reaction, although it was not observed explicity here. While electrochemical generation of radicals is not possible in the region denoted III in Figure 2, homogeneous generation of radicals is possible if one-electron oxidants are used. This aspect is potentially important in vivo, where 1-electron oxidants are widespread, and the concentration of radical would be sufficiently low to prevent rapid disproportionation.

The likelihood of generation and the fate of the quinone imines are also difficult to evaluate. However, significant pharmacological evidence indicates the importance of oxidation of hydroxylated CPZ metabolites to the drugs' side effects, and the oxidation products and intermediates observed electrochemically are likely to be formed in vivo, if oxidation does indeed occur.

Acknowledgment. The authors thank Dr. A. A. Manian for gifts of compounds and helpful discussions. This work was supported by NIMH through Grant No. MH 28412.

References and Notes

(1) H. N. Blount, *J. Electroanal. Chem.*, **42**, 271 (1973).
(2) J. Evans and H. Blount, *J. Org. Chem.*, **41**, 516 (1976).
(3) V. D. Parker and L. Eberson, *J. Am. Chem. Soc.*, **92**, 7488 (1970).
(4) U. Svanholm and V. D. Parker, *J. Am. Chem. Soc.*, **98**, 997 (1976).
(5) B. K. Bandlish, S. R. Mani, and H. J. Shine, *J. Org. Chem.*, **42**, 1538 (1977).
(6) J. Evans, J. Lenhard, and H. Blount, *J. Org. Chem.*, **42**, 983 (1972).
(7) J. Evans and H. Blount, *J. Org. Chem.*, **42**, 976 (1977).
(8) H. Y. Cheng, P. H. Sackett, and R. L. McCreery, *J. Am. Chem. Soc.*, **100**, 962 (1978).
(9) L. Levy, T. Tozer, L. Tuck, and D. Loveland, *J. Med. Chem.*, **15**, 989 (1972).
(10) D. Thompson, C. Veneziani, and H. Shine, *J. Heterocycl. Chem.*, **4**, 517 (1967).
(11) D. E. Green and I. S. Forrest, *J. Forensic Sci.*, **17**, 592 (1972).
(12) G. Bulow, I. Yamazaki, and L. Piette, *Biochem. Biophys. Acta*, **88**, 120 (1964).
(13) S. Ohnishi and H. McConnell, *J. Am. Chem. Soc.*, **87**, 2293 (1965).
(14) T. Akera and T. Brody, *Biochem. Pharmacol.*, **21**, 1403 (1972).
(15) T. Akera and T. Brody, *Biochem. Pharmacol.*, **25**, 1751 (1976).
(16) P. Turano, W. Turner, and A. Manian, *J. Chromatogr.*, **75**, 277 (1973).
(17) J. Buckley, M. Steenberg, H. Barry, and A. A. Manian, *J. Pharm. Sci.*, **62**, 715 (1973).
(18) H. Y. Meltzer et al., *Eur. J. Pharm.*, **41**, 431 (1977).
(19) A. Mackay, A. Healey, and J. Baker, *Br. J. Clin. Pharm.*, **1**, 425 (1974).
(20) G. Sakalis et al., *Psychopharmacologia*, **32**, 279 (1973).
(21) T. L. Perry, C. A. Culling, K. Berry, and S. Hanson, *Science*, **146**, 82 (1964).
(22) M. H. Woert, *Nature (London)*, **219**, 1054 (1968).
(23) H. R. Adams et al. in "Phenothiazines and Structurally Related Drugs", I. S. Forrest, C. J. Carr, and E. Usdin, Eds., Raven Press, 1974, p 281.
(24) R. L. McCreery, *J. Pharm. Sci.*, **66**, 357 (1977).
(25) M. Neptune and R. L. McCreery, *J. Med. Chem.*, **21**, 362 (1978).
(26) T. A. Grover, L. H. Piette, and A. A. Manian, ref. 23, p 561.
(27) R. N. Adams, "Electrochemistry at Solid Electrodes", Marcel Dekker, New York, N.Y., 1976.
(28) Z. Galus, "Fundamentals of Electrochemical Analysis", Wiley, New York, N.Y., 1976.
(29) W. M. Clark, "Oxidation Reduction Potentials of Organic Systems", Krieger, New York, N.Y., 1972.
(30) D. L. Forster et al., *J. Chem. Soc. C*, 993 (1971).
(31) Reference 27, p 336.
(32) J. F. Corbett, *J. Chem. Soc. B*, 213 (1969).
(33) L. Papouchado, G. Petrie, J. Sharp, and R. N. Adams, *J. Am. Chem. Soc.*, **90**, 5620 (1968).
(34) M. F. Marcus and M. D. Hawley, *J. Electroanal. Chem.*, **18**, 175 (1968).
(35) Reference 29, p 368.

Notes

Selective Transformations of Sugar Tosylhydrazones to Deoxy and Unsaturated Sugars[1]

Vasu Nair* and A. K. Sinhababu

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242

Received December 12, 1977

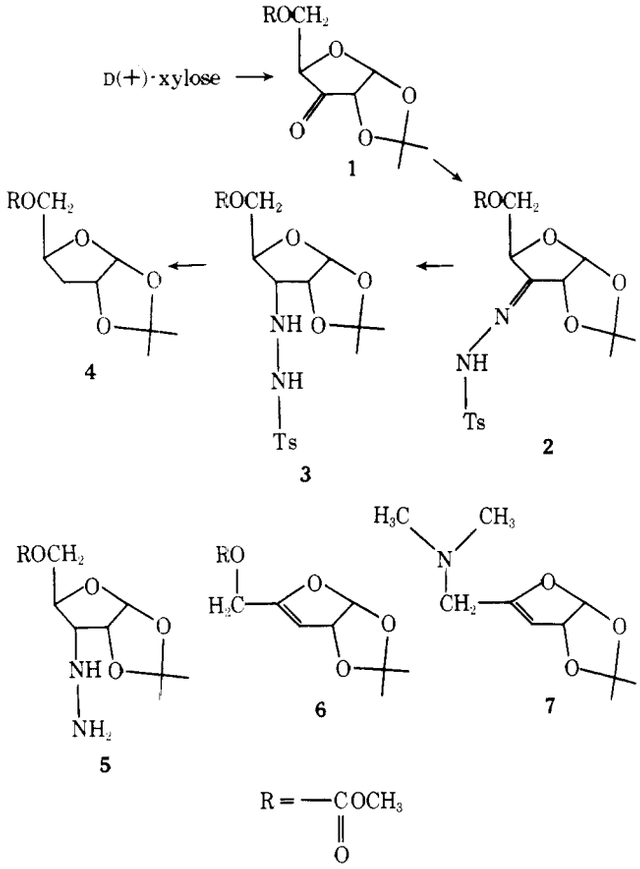
In many areas of synthesis of natural products and especially in carbohydrate chemistry, there is occasionally need for deoxygenation of a secondary hydroxyl group selectively and quantitatively. In connection with some work in our laboratory on the synthesis of nucleoside antibiotics, we needed a relatively simple, high yielding, synthetic accessibility to the naturally occurring pentose 3-deoxy-D-*erythro*-pentose.[2] The existing methods of synthesis of 3-deoxypentoses are in general cumbersome, involved procedures which have limitations due to low product yields, complexity of product mixtures, and difficulties associated with obtaining starting compounds.[2-7] The major difficulty in deoxygenation of secondary hydroxyl groups in carbohydrate chemistry arises because S_N2 processes are generally hindered at these carbons both sterically and through dipolar effects.

The availability of mild and specific oxidation methods in carbohydrate chemistry suggested the desirability of deoxygenation via keto sugars. Recent reports[8] suggest that a wide variety of aldehydes and ketones can be deoxygenated via their tosylhydrazones with sodium cyanoborohydride ($NaBH_3CN$) under acidic conditions. Noteworthy features of $NaBH_3CN$[9] which are of particular interest to carbohydrate chemistry include its acid stability[10] and its reported ability to reduce tosylhydrazones selectively to methylene derivatives without the formation of side products in the presence of a host of otherwise sensitive functional groups. These observations are significant in view of the fact that glycofuranosidulose and glycopyranosidulose derivatives can be produced in high yields, and these in turn, we have found, can be converted to the corresponding crystalline tosylhydrazones almost quantitatively. In this report we wish to describe a mild and high yielding procedure for the synthesis of protected 3-deoxy sugars from their tosylhydrazones. We also developed in the process one of the most efficient methods for the introduction of 3,4 unsaturation in furanoid sugars.[3,11]

The keto sugar 1 served as the source for our starting compound 2. This ketone can be prepared in high yield from D(+)-xylose.[12] In order that the final product be produced in

0022-3263/78/1943-5013$01.00/0

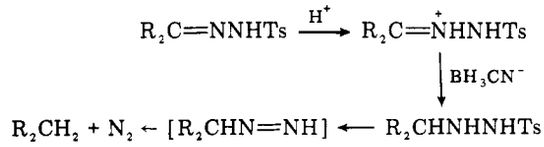
such a form that it could be utilized for further elaborations, two different protecting groups were used to mask the other hydroxyl groups of D(+)-xylose, namely, the acid-labile isopropylidene group and the base-labile carbonate protecting



group. The reaction of the keto sugar **1** with *p*-toluenesulfonylhydrazine in ethanol afforded crystalline tosylhydrazone **2**, mp 174–175 °C, in 96% conversion. The reaction of **2** with $NaBH_3CN$ in DMF at 110 °C in the presence or absence of *p*-toluenesulfonic acid gave a mixture of products as determined by ^1H NMR. The ratio and complexity of products were dependent on the amount of *p*-toluenesulfonic acid used. In the absence of acid, the unsaturated sugars **6** and **7**, the hydrazine **5**, and the deoxy sugar **4** (4%) were all produced, with the unsaturated sugar **6** (40%) being the major product. In the presence of catalytic amounts of *p*-toluenesulfonic acid, the same product mixture was obtained, except that in this case the deoxy sugar **4** was the major product (20%). At relatively high concentrations of acid (pH ~3.8, $NaBH_3CN$ is unstable below pH 3), no unsaturated products were formed and the final mixture consisted of **3**, **4**, **5**, and their 5-dimethylamino derivatives. Lower reaction temperatures did not alter significantly the ratios of the products. Although the unsuitability of DMF as a solvent for selective deoxygenation was apparent, an important observation from these studies was that at lower pH values not only was the amount of unsaturated sugar minimized, but the tosylhydrazine **3** was isolated. This result, together with the demonstrated propensity of $NaBH_3CN$ to reduce iminium systems,[9] suggested the possibility of deoxygenation through the intermediacy of the tosylhydrazine. In contrast to earlier reports,[8] the tosylhydrazine formed is relatively stable under our reaction conditions (pH 3–4), and its decomposition needs then to be induced separately (Scheme I).

Thus, when the tosylhydrazone **2** in THF–CH_3OH (1:1 by volume) was treated with $NaBH_3CN$ and anhydrous HCl (pH ~3.8) at room temperature, the tosylhydrazine **3** was isolated as a crystalline solid, mp 144–147 °C dec, in quantitative

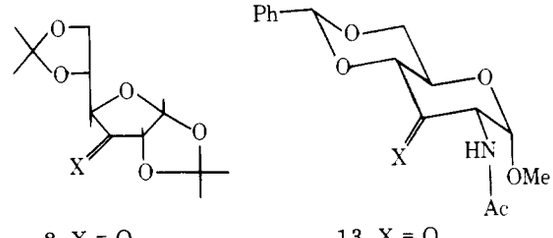
Scheme I

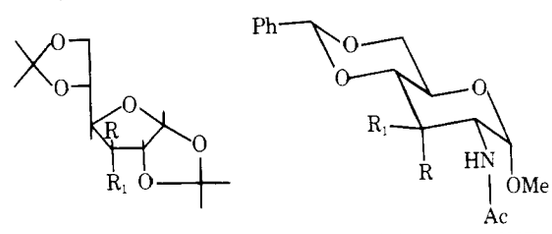


conversion. Interestingly, this reduction is stereospecific as shown by NMR studies. The ^1H NMR spectrum of **3** exhibited coupling constants $J_{1,2} = J_{2,3} \simeq 4.0$ Hz, consistent with the α stereochemistry of the hydrazine group.[13a] Its ^1H noise-decoupled PFT ^{13}C NMR spectrum showed the presence of a single compound with carbon-3 resonance at δ 64.0. The tosylhydrazine **3** can be converted to 3-deoxy-1,2-*O*-isopropylidene-5-*O*-methoxycarbonyl-α-D-*erythro*-pentofuranose (**4**), mp 70–71 °C, in quantitative yield by heating in refluxing ethanol for 5 h in the presence of sodium acetate. The identity of **4** was easily established by ^{13}C and ^1H NMR spectroscopy and elemental analysis, and by its conversion to the known 3-deoxy-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose (**4**; R = H).[13b]

To examine the generality of this deoxygenation procedure, we extended this study to glucose. The keto sugar **8** was converted to the tosylhydrazone **9** almost quantitatively. The reduction of **9** in THF–CH_3OH at pH ~3.8 with $NaBH_3CN$ proceeded stereospecifically and quantitatively to give **10**, and the latter was then converted quantitatively to the deoxy sugar **11** by treatment with sodium acetate in ethanol under reflux.

One further example was studied. The deoxy sugar **16** was of special interest because 2-amino-2,3-dideoxy sugars and related modified ones occur in a number of aminoglycoside antibiotics. For example, 2-amino-2,3-dideoxy-D-*ribo*-hexopyranose occurs in lividomycin B[14] and 2,6-diamino-2,3,6-trideoxy-D-*ribo*-hexopyranose is a component of tobramycin.[15] Although syntheses of these aminodeoxy sugars have already been described,[16–18] a superior approach to their preparation would be via 2-amino-2-deoxy-D-glucose, a commercially available starting material which has the 2-amino group in the required configuration. This scheme would involve application of our deoxygenation procedure. For example, for the synthesis of **16** the keto sugar **13** was prepared





in excellent yields from 2-amino-2-deoxy-D-glucose.[19,20] Compound **13** was found, however, to be sparingly soluble in methanol or ethanol, the most commonly employed solvents for hydrazone formation without acid catalysis,[21] and the most convenient procedure for this conversion was found to be in

DMF at 70 °C under *p*-toluenesulfonic acid catalysis. Without acid catalysis, the reaction is extremely sluggish. However, hydrolysis of the labile benzylidene protecting group cannot be completely eliminated under the conditions used for hydrazone formation. The hydrazone **14** was converted to the deoxy sugar **16** in almost quantitative yield, as expected, through the intermediacy of **15**. The stereochemistry at carbon-3 in **15** has not been established unequivocally because of considerable overlapping in the ^{1}H NMR spectrum in the region of the proton on this carbon.

The persistant formation of unsaturated sugar, the Bamford–Stevens[22] product from the tosylhydrazone **2**, by the action of as weak a base as $NaBH_3CN$ ($K_b \approx 10^{-10}$)[23] in DMF or even in the presence of catalytic amounts of acid ($NaBH_3CN$, *p*-toluenesulfonic acid, DMF) is surprising. In their detailed investigation of deoxygenations via tosylhydrazones induced by $NaBH_3CN$, Hutchins and co-workers[8] observed no unsaturated products even with highly hindered tosylhydrazones. We discovered that the Bamford–Stevens product could be maximized by use of sodium acetate. Thus, when the tosylhydrazone **2** was treated with sodium acetate in DMF at 100 °C for 0.75 h, the 3,4-unsaturated sugar **6** was produced in almost quantitative yield. A similar result was observed in the conversion of the tosylhydrazone **9** into 1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enofuranose (**12**). An interesting and puzzling feature of the ^{1}H NMR spectrum of **6** was the deceptive simplicity of the appearance of the C_2 and C_3 protons. This was also found to be the case with the unsaturated sugars **7** and **12**.[24] Resolution enhancement,[25] however, showed extensive coupling of these protons. The ^{13}C NMR spectrum of **6** (in $CDCl_3$) confirmed its structure with C_3 and C_4 resonances appearing at 101.0 and 155.3 ppm, respectively.

Experimental Section

1,2-*O*-Isopropylidene-5-*O*-methoxycarbonyl-α-D-*erythro*-3-pentosulofuranose (1) was prepared as described previously.[12]

1,2-*O*-Isopropylidene-5-*O*-methoxycarbonyl-α-D-*erythro*-3-pentosulofuranose *p*-Toluenesulfonylhydrazone (2). A mixture of 1,2-*O*-isopropylidene-5-*O*-methoxycarbonyl-α-D-*erythro*-3-pentosulofuranose (24.6 g, 100 mmol) and *p*-toluenesulfonylhydrazine (20.5 g, 110 mmol) in absolute ethanol (150 mL) was heated with stirring at 70 °C for 2 h and then left overnight at room temperature. Ether (200 mL) was added, and the solid was collected by filtration and washed thoroughly with ether (4 × 50 mL). Recrystallization from a 9:1 mixture of ethanol–CH_2Cl_2 gave a white crystalline solid (39.5 g, 96%): mp 174–175 °C; $[\alpha]^{25}_D$ +259° (*c* 1, $CHCl_3$); IR ν_{max} (Nujol) 3220 (NH), 1760 (C=O), 1620 (C=N) cm^{-1}; ^{1}H NMR (60 MHz) δ Me_4Si ($CDCl_3$) 1.13 (s, 3 H), 1.35 (s, 3 H), 2.42 (s, 3 H), 3.75 (s, 3 H), 4.2–5.12 (m, 4 H), 5.95 (d, $J_{1,2}$ = 4.7 Hz, 1 H), 7.34 (d, $J \simeq$ 8.5 Hz, 2 H), 7.86 (d, $J \simeq$ 8.5 Hz, 2 H), 8.57 (s, 1 H).

Anal. Calcd for $C_{17}H_{22}N_2O_8S$: C, 49.27; H, 5.31; N, 6.76. Found: C, 49.43; H, 5.33; N, 6.76.

1,2-*O*-Isopropylidene-3-deoxy-3-(*p*-toluenesulfonylhydrazino)-5-*O*-methoxycarbonyl-α-D-ribofuranose (3). To a stirred solution of the tosylhydrazone **2** (4.14 g, 10 mmol) in a mixture of 1:1 THF–MeOH (80 mL) was added a trace of methyl orange (indicator) and sodium cyanoborohydride (630 mg, 10 mmol). Methanol saturated with hydrogen chloride was then added dropwise, keeping the color of the solution at the red-yellow transition point (orange, pH ~3.8). The mixture was stirred at room temperature for 1 h. A second portion of sodium cyanoborohydride (315 mg, 5.0 mmol) was added followed by the dropwise addition of methanol saturated with hydrogen chloride to maintain the pH at ~3.8. The mixture was then stirred for 1 h at 25 °C and at pH ~3.8. A saturated solution of $NaHCO_3$ was then added, and the mixture (pH ~7) was concentrated in vacuo at 40 °C to 10 mL. Water (60 mL) was added, and the solution was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phases were washed with 6 N HCl (1 × 30 mL), saturated aqueous $NaHCO_3$ (1 × 30 mL), and saturated aqueous NaCl (1 × 30 mL), respectively, dried over anhydrous Na_2SO_4, and then evaporated in vacuo at 40 °C to dryness to give 4.1 g (~100%) of **3** as a white crystalline solid: mp 144–146 °C dec; $[\alpha]^{25}_D$ +98.9° (*c* 1, $CHCl_3$); ^{1}H NMR δ Me_4Si ($CDCl_3$) 1.30 (s, 3 H), 1.45 (s, 3 H), 2.43 (s, 3 H), 3.0–3.30 (m, 1 H), 3.77 (s, 3 H), 3.93–4.50 (m, 4 H), 4.64 (t, $J_{1,2} = J_{1,2} = J_{2,3} \simeq$ 4.0 Hz, 1 H), 5.78 (d, $J_{1,2} \simeq$ 4.0 Hz, 1 H), 6.75 (s, 1 H), 7.36 (d, J = 8.5 Hz, 2 H), 7.90 (d, J = 8.5 Hz, 2 H); ^{13}C NMR δ Me_4Si ($CDCl_3$) 21.6, 26.3, 26.5, 54.9, 64.0, 66.4, 75.9, 77.4, 104.7, 112.5, 128.4, 129.6, 134.7, 144.2, 155.4.

Anal. Calcd for $C_{17}H_{24}N_2O_8S$: C, 49.04; H, 5.77; N, 6.72. Found: C, 49.07; H, 5.61; N, 6.71.

3-Deoxy-1,2-*O*-isopropylidene-5-*O*-methoxycarbonyl-α-D-*erythro*-pentofuranose (4). A mixture of the tosylhydrazine **3** (2.08 g, 5.0 mmol) and sodium acetate trihydrate (2.72 g, 20 mmol) in 60 mL of absolute ethanol was refluxed for 5 h. Ethanol was removed in vacuo, and the residue was dissolved in 50 mL of water. The aqueous solution was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with water (1 × 20 mL), dried over anhydrous Na_2SO_4, and then evaporated to dryness to give 1.16 g (~100%) of **4** as a pale yellow syrup. Column chromatography of the crude syrup on silica gel with 7:3 hexane–ether as eluent (250 mL) followed by evaporation of the eluent in vacuo gave 1.05 g (91%) of an analytically pure solid: mp 70–71 °C; $[\alpha]^{25}_D$ −1.53° (*c* 6, $CHCl_3$); ^{1}H NMR δ Me_4Si ($CDCl_3$) 1.30 (s, 3 H), 1.48 (s, 3 H), 1.60–2.27 (m, 2 H), 3.78 (s, 3 H), 3.98–4.82 (m, 4 H), 5.84 (d, $J_{1,2} \simeq$ 3.8 Hz, 1 H); ^{13}C NMR δ Me_4Si ($CDCl_3$) 26.2, 26.8, 35.0, 54.9, 68.0, 75.5, 80.4, 105.7, 111.4, 155.7.

Anal. Calcd for $C_{10}H_{16}O_6$: C, 51.72; H, 6.9. Found: C, 51.63; H, 7.07.

3-Deoxy-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose (4; R = H). To a stirred solution of 3-deoxy-1,2-*O*-isopropylidene-5-*O*-methoxycarbonyl-α-D-*erythro*-pentofuranose (610 mg, 2.6 mmol) in 10 mL of methanol was added a solution of sodium methoxide (216 mg, 4.0 mmol) in 10 mL of methanol. The reaction flask was stoppered, and the mixture was stirred at 25 °C for 16 h. The mixture was then neutralized (pH 7) with Dowex 50W-X8 (H^+ form) and filtered immediately, and the filter was washed with methanol (3 × 5 mL). The combined filtrates were evaporated in vacuo to dryness to give 435 mg (96%) of the title compound as a pale yellow solid. Recrystallization from cyclohexane gave white plates: mp 79–80 °C; $[\alpha]^{27}_D$ −10.3° (*c* 0.8, $CHCl_3$) [lit.[13b] mp 79–80 °C [$\alpha[^{20}_D$ −10° (*c* 0.8, 1,2-dichloroethane)]; ^{1}H NMR δ Me_4Si ($CDCl_3$) 1.32 (s, 3 H), 1.50 (s, 3 H), 1.73–2.10 (m, 2 H), 2.57 (broad s, OH, 1 H), 3.37–3.96 (m, 2 H), 4.13–4.53 (m, 1 H), 4.66–4.82 (m, 1 H), 5.82 (d, $J_{1,2}$ = 3.8 Hz, 1 H).

1,2-*O*-Isopropylidene-3-deoxy-3-hydrazino-5-*O*-methoxycarbonyl-α-D-ribofuranose (5). To a solution of 1,2-*O*-isopropylidene-3-deoxy-3-(*p*-toluenesulfonylhydrazino)-5-*O*-methoxycarbonyl-α-D-ribofuranose (2.91 g, 7.0 mmol) in 50 mL of *p*-dioxane was added sodium cyanoborohydride (882 mg, 14.0 mmol). The mixture was refluxed for 9 h and treated upon cooling with 100 mL of 10% aqueous NaCl solution. The mixture was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic phases were washed with saturated aqueous NaCl solution (1 × 50 mL), dried over anhydrous Na_2SO_4, and then evaporated to dryness. The syrupy residue (1.8 g) crystallized from chloroform–hexane as white crystals (1.1 g, 60%): mp 141–142 °C; ^{1}H NMR δ Me_4Si (CD_3CN) 1.40 (s, 3 H), 1.57 (s, 3 H), 2.33–2.61 (br, 1 H), 3.15–3.57 (m, 1 H), 3.80 (s, 3 H), 3.87–4.58 (m, 3 H), 4.80 (t, $J_{2,1} = J_{2,3} \simeq$ 4.0 Hz, 1 H), 5.88 (d, $J_{1,2} \simeq$ 4.0 Hz, 1 H), 6.20 (br, 2 H); ^{13}C NMR δ Me_4Si (CD_3OD) 26.7, 55.4, 62.9, 67.3, 77.4, 77.9, 106.3, 113.8, 157.0.

Anal. Calcd for $C_{10}H_{18}N_2O_6 \cdot H_2O$: C, 42.92; H, 7.14; N, 10.00. Found: C, 42.60; H, 6.60.

3-Deoxy-1,2-*O*-isopropylidene-5-*O*-methoxycarbonyl-α-D-*glycero*-pent-3-enofuranose (6). A solution of 1,2-*O*-isopropylidene-5-*O*-methoxycarbonyl-α-D-*erythro*-3-pentosulofuranose *p*-toluenesulfonylhydrazone (1.035 g, 2.5 mmol) and sodium acetate (0.8 g) in 10 mL of dry DMF was heated at 100 °C with stirring for 40 min. After cooling to room temperature, water (20 mL) was added and the solution was extracted with CH_2Cl_2 (3 × 30 mL). All of the organic layers were combined, dried over Na_2SO_4, and then evaporated in vacuo to dryness. The crude oily residue was treated with hexane (30 mL) under reflux and the solution was collected by decantation. This process was repeated twice. All of the hexane solutions were combined, and evaporation of solvent gave 529 mg (92%) of a colorless oil. The product was essentially pure. An analytical sample was prepared by preparative layer chromatography on silica gel plates (R_f 0.6, developing solvent CH_2Cl_2): IR ν_{max} (neat) 1775 (C=O), 1690 (C=C) cm^{-1}; ^{1}H NMR δ Me_4Si ($CDCl_3$) 1.43 (s, 6 H), 3.8 (s, 3 H), 4.67 (s, 2 H), 5.23–5.34 (complex m, 2 H), 6.12 (d, $J_{1,2}$ = 5 Hz, 1 H); ^{13}C NMR δ Me_4Si ($CDCl_3$) 27.8, 28.0, 55.2, 62.0, 83.3, 101.0, 106.5, 112.5, 155.3, 155.8.

Anal. Calcd for $C_{10}H_{14}O_6$: C, 52.70; H, 6.09. Found: C, 51.85; H, 6.45.

1,2:5,6-Di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose *p*-Toluenesulfonylhydrazone (9). A mixture of 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (8)[26] (5.16 g, 20 mmol) and *p*-toluenesulfonylhydrazine (4.46 g, 24 mmol) in 30 mL of absolute ethanol was heated at 70 °C with stirring for 2 h and then left at room

temperature overnight. The mixture was filtered, and the precipitate was washed several times with ether. Recrystallization from ethanol–CH_2Cl_2 (9:1) gave a white crystalline solid (7.7 g, 91%): mp 181–183 °C dec; ^1H NMR δ Me_4Si ($CDCl_3$) 1.38 (s, 9 H), 1.60 (s, 3 H), 2.44 (s, 3 H), 3.63–4.20 (m, 3 H), 4.45–4.63 (m, 1 H), 4.86 (d of d, $J_{2,1} \simeq 4.3$ Hz, $J_{2,4} \simeq 1.3$ Hz, 1 H), 5.78 (d, $J_{1,2} \simeq 4.3$ Hz, 1 H), 7.31 (d, $J = 8.5$ Hz, 2 H), 7.82 (d, $J = 8.5$ Hz, 2 H), 10.30 (s, 1 H).

Anal. Calcd for $C_{19}H_{26}N_2O_7S$: C, 53.52; H, 6.10; N, 6.57. Found: C, 53.62; H, 6.14; N, 6.59.

1,2:5,6-Di-*O*-isopropylidene-3-deoxy-3-(*p*-toluenesulfonylhydrazino)-α-D-*ribo*-hexofuranose (10). To a solution of 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose *p*-toluenesulfonylhydrazone (**9**) (426 mg, 1.0 mmol) in 15 mL of THF–CH_3OH (1:1 by volume) was added sodium cyanoborohydride (95 mg, 1.5 mmol) and a trace of methyl orange indicator. To the stirred mixture was added methanol containing ~5% hydrogen chloride, and the color of the solution was maintained at the red-yellow transition point (orange, pH ~3.8). The mixture was stirred for 1 h at 25 °C and at pH ~3.8. Saturated aqueous $NaHCO_3$ solution was then added, and the mixture (pH ~7) was evaporated in vacuo to dryness. Water (15 mL) was added to the residue, and the solution was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with 6 N HCl (1 × 10 mL), saturated aqueous $NaHCO_3$ (1 × 10 mL), and saturated aqueous NaCl (1 × 10 mL), respectively, and were dried over anhydrous Na_2SO_4 and then evaporated in vacuo to dryness to give 420 mg (~100%) of the title compound as a white crystalline solid: mp 66–70 °C; ^1H NMR δ Me_4Si ($CDCl_3$) 1.31 (s, 3 H), 1.41 (s, 6 H), 1.47 (s, 3 H), 2.42 (s, 3 H), 2.75–3.15 (m, 1 H), 3.53–4.23 (br m, 5 H), 4.6 (t, $J_{2,1} = J_{2,3} \simeq 4.0$ Hz, 1 H), 5.70 (d, $J_{1,2} \simeq 4.0$ Hz, 1 H), 7.30 (s, obscured by C_6H_4, 1 H), 7.36 (d, $J = 8.5$ Hz, 2 H), 7.91 (d, $J = 8.5$ Hz, 2 H).

Anal. Calcd for $C_{19}H_{28}N_2O_7S$: C, 53.27; H, 6.54; N, 6.54. Found: C, 53.09; H, 6.58; N, 6.54.

3-Deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose (11). A mixture of 1,2:5,6-di-*O*-isopropylidene-3-deoxy-3-(*p*-toluenesulfonylhydrazino)-α-D-*ribo*-hexofuranose (**10**) (428 mg, 1.0 mmol) and sodium acetate trihydrate (544 mg, 4.0 mmol) in 15 mL of absolute ethanol was refluxed for 5 h. Ethanol was removed in vacuo, and the residue was dissolved in 15 mL of water. The aqueous solution was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with saturated aqueous NaCl (1 × 10 mL), dried (Na_2SO_4), and then evaporated to dryness to give 240 mg (~100%) of 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexose as a pale yellow syrup:[27] ^1H NMR δ Me_4Si ($CDCl_3$) 1.31 (s, 3 H), 1.34 (s, 3 H), 1.41 (s, 3 H), 1.49 (s, 3 H), 1.61–2.46 (m, 2 H), 3.63–4.35 (br m, 4 H), 4.75 (t, $J_{2,1} = J_{2,3} \simeq 4.0$ Hz, 1 H), 5.83 (d, $J_{1,2} \simeq 4.0$ Hz, 1 H); $[\alpha]^{25}_D$ −7.4° (*c* 10, EtOH) [lit.[4] −7.5° (*c* 10, EtOH)].

3-Deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enofuranose (12). A mixture of 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose *p*-toluenesulfonylhydrazone (852 mg, 2.0 mmol) and sodium acetate trihydrate (1.1 g, 8.0 mmol) in 15 mL of DMF was heated with stirring at 100 °C for 1 h. Water (15 mL) was then added, and the solution was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with saturated aqueous NaCl (2 × 15 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. To the brown viscous residue was added hexane (15 mL), and the mixture was heated to reflux. The hexane solution was collected by decantation of the hot mixture. This process was repeated twice with 15-mL portions of hexane. The combined hexane solutions were evaporated to dryness to give 440 mg (91%) of the title compound as a pale yellow syrup which solidified on standing. An analytical sample was prepared by chromatography on a preparative layer silica gel plate. The plate was developed with 1:1 ether–hexane. The band with R_f 0.77 upon elution with ether followed by removal of solvent gave white solid: mp 46–48 °C (lit.[28] mp 46–48 °C); ^1H NMR δ Me_4Si ($CDCl_3$) 1.36 (s, 3 H), 1.44 (s, 9 H), 3.79–4.26 (m, 2 H), 4.57 (t, $J \simeq 6.2$ Hz, 1 H), 5.20–5.35 (m, 2 H), 6.06 (d, $J_{1,2} \simeq 5.0$ Hz, 1 H).

Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.50; H, 7.44. Found: C, 59.44; H, 7.77.

Methyl 2-Acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranosid-3-ulose *p*-Toluenesulfonylhydrazone (14). A mixture of methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranosid-3-ulose[19,20] (**13**) (642 mg, 2.0 mmol), *p*-toluenesulfonylhydrazine (744 mg, 4.0 mmol), and *p*-toluenesulfonic acid monohydrate (76 mg, 0.4 mmol), in 20 mL of dry DMF was stirred at 70–72 °C for 1 h. The solution was cooled, neutralized (pH 7–8) with aqueous $NaHCO_3$, and then evaporated in vacuo at <40 °C to dryness. Water (20 mL) was added to the solid residue and then CH_2Cl_2 (20 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic phases were washed with 6 N HCl (2 × 20 mL), saturated aqueous $NaHCO_3$ (1 × 20 mL), and saturated aqueous NaCl (1 × 20 mL), respectively, dried (Na_2SO_4), and then evaporated in vacuo to dryness to give 656 mg of pale yellow solid (67%). Recrystallization from ether–ethanol gave 580 mg of **14** as white plates: mp 179–181 °C; IR ν_{max} 3320 (NH), 1635, 1535 (amide I and II), 1605 (C=N) cm^{-1}, and no C=O near 1745 cm^{-1}; ^1H NMR δ Me_4Si ($CDCl_3$) 2.00 (s, 3 H), 2.37 (s, 3 H), 3.28 (s, 3 H), 3.70–4.70 (m, 5 H), 4.87 (d, $J_{1,2} = 3.5$ Hz, 1 H), 5.47 (s, 1 H), 6.42 (d, $J_{N,H} = 9$ Hz, 1 H), 7.25 (d, $J = 8.5$ Hz, 2 H), 7.4 (s, 5 H), 7.70 (d, $J = 8.5$ Hz, 2 H), 10.05 (s, 1 H).

Anal. Calcd for $C_{23}H_{27}N_3O_7S$: C, 56.44; H, 5.32; N, 8.58. Found: C, 56.11; H, 5.46; N, 8.27.

Methyl 2-Acetamido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-*ribo*-hexopyranoside (16). To a stirred solution of the tosylhydrazone **14** (489 mg, 1.0 mmol) in a mixture of 1:1 THF–CH_3OH (12 mL) was added sodium cyanoborohydride (63 mg, 1.0 mmol) and a trace of methyl orange. Methanol saturated with hydrogen chloride was then added dropwise, keeping the color of the solution at the red-yellow transition point (orange, pH ~3.8). The mixture was stirred at ~25 °C at this pH for 1.5 h. A second portion of sodium cyanoborohydride (63 mg, 1.0 mmol) was added followed by methanol saturated with hydrogen chloride to maintain the pH at 3.8. The mixture was then stirred for 1.5 h at ~25 °C at pH ~3.8. The mixture was neutralized (pH ~7) with aqueous $NaHCO_3$ and then evaporated in vacuo to dryness. To the residue was added water (20 mL), followed by CH_2Cl_2 (20 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were washed with 6 N HCl (1 × 20 mL), saturated aqueous $NaHCO_3$ (1 × 20 mL), and saturated aqueous NaCl (1 × 20 mL), respectively, dried (Na_2SO_4), and then evaporated in vacuo to dryness to give 480 mg (98%) of **15** as a white solid which was utilized in the next step without further purification: ^1H NMR δ Me_4Si ($CDCl_3$) 1.93 (s, 3 H), 2.38 (s, 3 H), 2.77–3.36 (m, partly obscured by the OCH_3 signal, 1 H), 3.27 (s, 3 H), 3.62–4.32 (m, 5 H), 4.57 (d, $J_{1,2} = 3.5$ Hz, 1 H), 4.65–4.83 (broad, 1 H), 5.45 (s, 1 H), 6.5 (d, $J_{N,H} = 9$ Hz, 1 H), 6.96 (s, 1 H), 7.27 (d, $J = 8.5$ Hz, 2 H), 7.4 (s, 5 H), 7.72 (d, $J = 8.5$ Hz, 2 H).

A mixture of the tosylhydrazine **15** (491 mg, 1.0 mmol) and sodium acetate trihydrate (544 mg, 4.0 mmol) in 10 mL of absolute ethanol was refluxed for 5 h. Ethanol was removed in vacuo, and water (15 mL) was added to the residue. The aqueous mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with saturated aqueous NaCl (1 × 20 mL), dried (Na_2SO_4), and then evaporated in vacuo to dryness to give 300 mg (98%) of the deoxy sugar **16** as a light yellow solid. Recrystallization from ether–ethyl acetate gave a white solid (292 mg): mp 244–245 °C (subl); $[\alpha]^{24}_D$ +54.0° (*c* 1, $CHCl_3$) [lit.[18] mp 245 °C (subl), $[\alpha]_D$ +55.5° (*c* 0.95); lit.[16] mp 263–264 °C, $[\alpha]_D$ +52° (*c* 1.0); lit.[17] mp 224 °C (subl), $[\alpha]_D$ +53.7° (*c* 1.0)]; ^1H NMR δ Me_4Si ($CDCl_3$) 1.78–2.27 (m, partly hidden under $COCH_3$, 2 H), 1.95 (s, 3 H), 3.40 (s, 3 H), 3.53–4.47 (m, 5 H), 4.58 (d, $J_{1,2} = 3.5$ Hz, 1 H), 5.51 (s, 1 H), 5.63–5.95 (broad d, $J_{N,H} = 9$ Hz, 1 H), 7.2–7.8 (m, 5 H); ^{13}C NMR δ Me_4Si ($CDCl_3$) 22.3, 29.8, 46.4, 53.9, 63.0, 68.2, 75.4, 96.7, 100.7, 125.1, 127.3, 128.0, 136.4, 168.4.

Acknowledgment. We thank the National Science Foundation (CHE 76-05511) and the University of Iowa for a Faculty Development Award and an Old Gold Fellowship (to V.N.).

Registry No.—**1**, 62789-42-8; **2**, 68014-59-5; **3**, 68014-60-8; **4** (R = C(=O)OMe), 68014-61-9; **4**, (R = H), 3396-71-2; **5**, 68014-62-0; **6**, 68014-63-1; **8**, 2847-00-9; **9**, 18265-29-7; **10**, 68014-64-2; **11**, 4613-62-1; **12**, 2774-28-9; **13**, 4288-74-8; **14**, 68014-65-3; **15**, 68014-66-4; **16**, 22595-95-5.

References and Notes

(1) Presented in part at the 175th National Meeting of the American Chemical Society, Anaheim, Calif., March, 1978.
(2) S. Hanessian, *Adv. Carbohydr. Chem.*, **21**, 143 (1966).
(3) *Carbohydr. Chem.*, **1–8** (1967–1974).
(4) Š. Kučar, J. Zámocky and Š. Bauer, *Collect. Czech. Chem. Commun.*, **40**, 457 (1975).
(5) (a) D. H. R. Barton and S. W. McCombie, *J. Chem., Soc., Perkin Trans. 1*, 1574 (1975); (b) D. H. R. Barton and R. Subramanian, *ibid.*, 1718 (1977).
(6) T. H. Haskell, P. W. K. Woo, and D. R. Watson, *J. Org. Chem.*, **42**, 1302 (1977).
(7) R. H. Bell, D. Horton, D. M. Williams, and E. Winter-Mihaly, *Carbohydr. Res.*, **58**, 109 (1977).
(8) R. O. Hutchins, C. A. Milewski, and B. E. Maryanoff, *J. Am. Chem. Soc.*, **95**, 3662 (1973), and references therein.
(9) (a) R. F. Borch and H. D. Durst, *J. Am. Chem. Soc.*, **91**, 3996 (1969); (b) R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, **93**, 2897 (1971).
(10) M. M. Kreevoy and J. E. C. Hutchins, *J. Am. Chem. Soc.*, **91**, 4329 (1969).

(11) R. J. Ferrier, *Adv. Carbohydr. Chem. Biochem.*, **24**, 199 (1969); **20**, 67 (1965).
(12) V. Nair and D. J. Emanuel, *J. Am. Chem. Soc.*, **99**, 1571 (1977).
(13) (a) *Synth. Proced. Nucleic Acid Chem.*, **2**, (1973); (b) *ibid.*, **1**, 193 (1968).
(14) T. Mori, Y. Kyotani, I. Watanabe, and T. Oda, *J. Antibiot.*, **25**, 149 (1972).
(15) K. F. Koch and J. A. Rhoades, *Antimicrob. Agents Chemother. (1970)*, 309 (1971).
(16) A. Rosenthal and P. Catsoulacos, *Can. J. Chem.*, **47**, 2747 (1969).
(17) K. Kitahara, S. Takahashi, H. Shibata, N. Kurihara, and M. Nakajima, *Agric. Biol. Chem.*, **33**, 748 (1969).
(18) C. L. Brewer and R. D. Guthrie, *J. Chem. Soc., Perkin Trans. 1*, 657 (1974).
(19) K. Onodera, S. Hirano, and N. Kashimura, *Carbohydr. Res.*, **6**, 276 (1968).
(20) B. R. Baker and D. H. Buss, *J. Org. Chem.*, **30**, 2304 (1965).
(21) R. H. Shapiro, *Org. React.*, **23**, 405 (1976).
(22) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952).
(23) J. R. Berschied, Jr., and K. F. Purcell, *Inorg. Chem.*, **9**, 624 (1970).
(24) See Experimental Section; also cf. W. B. Gleason and R. Barker, *Carbohydr. Res.*, **21**, 447 (1972).
(25) R.R. Ernst, *Adv. Magn. Reson.*, **2**, 1 (1966).
(26) G. H. Jones and J. G. Moffatt, *Methods Carbohydr. Chem.*, **6**, 315 (1972).
(27) D. M. Brown and G. H. Jones, *J. Chem. Soc. C*, 252 (1967).
(28) J. S. Brimacombe, M. E. Evans, E. J. Forbes, A. B. Foster, and J. M. Webber, *Carbohydr. Res.*, **4**, 239 (1967).

Synthesis of Vinca Alkaloids and Related Compounds. 8.[1] Unusual Alkylation of an Enamine

György Kalaus, Péter György, Lajos Szabó, and Csaba Szántay*

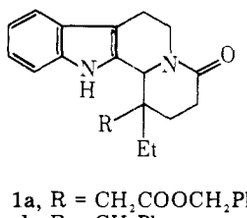
Institute for Organic Chemistry, Technical University, H-1521, Budapest, and Central Research Institute for Chemistry, H-1525, Budapest, Hungary

Received March 28, 1978

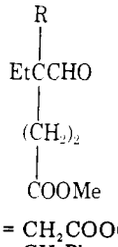
As a promising intermediate for the synthesis of indoloquinolizidine derivative **1a**, we intended to prepare the aldehyde's diester **2a** through the alkylation of enamine **3**[2] with benzyl α-bromoacetate **4**. The alkylation of enamines by α-halocarbonyl compounds is known to proceed smoothly.[2,3]

Enamine **3** was prepared from aldehyde **2c**[4] and reacted with benzyl α-bromoacetate. The aldehyde obtained from the hydrolysis was treated with tryptamine and surprisingly the indole lactam (**1b**) was obtained instead of the expected **1a.**

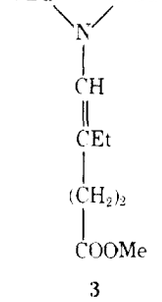
To fully substantiate the structural assignment for **1b**, enamine **3** was alkylated with benzyl chloride. Aldehyde **2b** obtained after hydrolysis was treated with tryptamine to generate a crystalline material identical with **1b.**



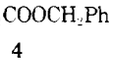
1a, R = CH_2COOCH_2Ph
b, R = CH_2Ph



2a, R = CH_2COOCH_2Ph
b, R = CH_2Ph
c, R = H



3



4

Although it is well known that esters of strong acids, e.g., those of *p*-toluenesulfonic acid, have strong alkylating power,[5] the fact that **4** alkylates with its benzyl group instead of the very reactive carbon atom α to the carbonyl function seems to be rather surprising and represents a small contribution to the scope and limitations of enamine chemistry.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded using a SPEKTROMOM 2000 instrument; NMR spectra were obtained with Perkin-Elmer R-12 spectrometer. Mass spectra were taken with a AEI-MS-902 spectrometer system.

Methyl (5-Dibutylamino)-4-ethyl-4-pentenoate (3). A solution of methyl 4-formylhexanoate[4] (**2c**, 50.0 g, 316 mmol) and dibutylamine (46.0 g, 365 mmol) in dry benzene (100 mL) was refluxed for 2 h under a water separator meanwhile 5.5 mL (96.6%) of water was distilled off from the system. After evaporating the solvent under reduced pressure the residue was distilled to give **3** as a yellow oil (61.8 g, 72.6 %): bp 108–110 °C (0.2 mm); $n^{25}D$ 1.4532; IR (film) 1747 (>C=O), 1660 cm^{-1} (>C=C<); NMR (CCl_4) δ 3.49 (s, 3, CH_3O), 5.12 (s, 1, -CH=C<).

Methyl (4-Benzyl-4-formyl)hexanoate (2b). (a) A solution of dibutylamine (12.9 g, 100 mmol) and methyl 4-formylhexanoate (**2c**, 15.8 g, 100 mmol) in dry benzene (60 mL) was refluxed for 8 h under a water separator meanwhile 0.9 mL (50.0%) of water was distilled off from the mixture. Bromacetic acid benzyl ester (**4**, 22.9 g, 100 mmol) and dry acetonitrile (20 mL) were added and the mixture was refluxed for 5 days (~120 h). Glacial acetic acid (6 mL) and water (18 mL) were added and the heating was continued for 1 h. The solution was cooled to room temperature and diluted with water (300 mL) and the product was extracted with ether. After washing with water, 5% sodium hydrogen carbonate solution, and water, the ether was dried and evaporated under reduced pressure. Distillation of the residue afforded **2b** as a yellow oil (6.4 g, 25.7%): bp 126–128 °C (0.2 mm); $n^{26}D$ 1.5070; IR (film) 1740 cm^{-1} (>C=O); NMR ($CDCl_3$) δ 0.86 (t, 3, CH_3CH_2), 2.82 (s, 2, benzyl CH_2), 3.63 (s, 3, CH_3O), 7.56–6.86 (m, 5, ArH), 9.60 (s, 1, aldehyde H); MS 248 (12.5), 220 (29.9), 234 (10.5), 188 (72.1), 142 (57.4), 129 (55.4), 117 (30.5), 105 (27.7), 91 (*100*).

(b) A solution of methyl 4-formylhexanoate (**2c**, 38.0 g, 240 mmol) and dibutylamine (31.0 g, 240 mmol) in dry benzene (130 mL) was refluxed for 8 h under a water separator meanwhile 2.2 mL (50.9%) of water was distilled off from the system. The benzene was removed in reduced pressure and the residue was dissolved in dry dioxane (120 mL). Benzyl chloride (45.7 g, 360 mmol) was added and the mixture was refluxed for 5 days (~120 h). After adding glacial acetic acid (14.4 mL) and water (43.2 mL) the heating was continued for 2 h. The solution was cooled to room temperature, diluted with water (600 mL), and extracted with ether. After washing with water, 5% sodium hydrogen carbonate solution, and water the ether was dried and removed under reduced pressure. The residue was distilled in vacuo to give **2b** as a yellow oil (7.0 g, 11.7%): bp 123–125 °C (0.15 mm); $n^{27}D$ 1.4990.

The product is identical in every respect with that obtained by the method "a".

1-Benzyl-1-ethyl-1,2,3,4,5,6,7,12-octahydro-12b*H*-indolo[2,3-*a*]quinolizin-4-one (1b). (a) A solution of tryptamine (0.5 g, 3.13 mmol) and methyl (4-benzyl-4-formyl)hexanoate (**2b**, prepared by method "a") (1.5 g, 6.04 mmol) in glacial acetic acid (5 mL) was refluxed for 72 h. After 27 h of heating a further amount (0.5 g, 2.01 mmol) of **2b** was added. The solution was diluted with water (50 mL), stirred, cooled (ice bath), and alkalized with 40% aqueous sodium hydroxide. The product was extracted with methylene chloride, the extract was dried, and the solvent was removed under reduced pressure. The residue was triturated with petroleum ether. Crystallization of the crude product from ethyl acetate afforded white, crystalline **1b** (0.35 g, 31.2%), mp 210–212 °C. Recrystallization from ethyl acetate raised the mp to 212–213 °C. Anal. Calcd for $C_{24}H_{26}N_2O$: C, 80.40; H, 7.31; N, 7.81. Found: C, 80.35; H, 7.18; N, 8.02. IR (KBr) 3335 (indole NH), 1605 cm^{-1} (>C=O); NMR ($CDCl_3$) δ 4.86 (s, 2, benzyl CH_2), 7.68–6.80 (m, 9, ArH), 7.96 (s, 1, indole H); MS 358 (70), 329 (0.4), 267 (7.3), 266 (9.9), 251 (4.4), 211 (30), 170 (*100*), 169 (61).

(b) A solution of tryptamine (1.0 g, 6.24 mmol) and methyl (4-benzyl-4-formyl)hexanoate (**2b**, prepared by method "b") (1.85 g, 7.45 mmol) in glacial acetic acid (10 mL) was reacted and worked up as in "a", to give white, crystalline **1b** (0.6 g, 26.8%), mp 212–213 °C.

The product was identical in every respect with that obtained by method "a".

0022-3263/78/1943-5017$01.00/0