Synthesis of 1,5,6,7-Tetrahydroindol-4-ones from Amino-sugars and Cyclohexane-1,3-diones

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Reactions of 2-amino-2-deoxy-D-glucose with cyclohexane-1,3-diones produced 2-deoxy-2-(3-oxocyclohex-1-enylamino)-D-glucoses (1), which were cyclized to give 1,5,6,7-tetrahydro-2-(D-*arabino*-1,2,3,4-tetrahydroxybutyl)indol-4-ones (2). Other products of the cyclization reactions were the 1,5,6,7-tetrahydroindol-4-ones (5), the 2-(β-D-erythrofuranosyl)-1,5,6,7-tetrahydroindol-4-ones (6), and D-erythrose. Similar reactions with 1-amino-1-deoxy-D-fructose yielded the enamines (3), which were further transformed into 1,5,6,7-tetrahydro-3-(D-*arabino*-1,2,3,4-tetrahydroxybutyl)indol-4-ones (4). A series of formyl-1,5,6,7-tetrahydroindol-4-ones [(11) and (12)] were obtained by oxidation of compounds (2) and (4) with periodate.

THE reaction of amino-sugars with acyclic β-dicarbonyl compounds [1] has been used to prepare a variety of pyrrole derivatives, in some cases in high yields. We considered that the extension of this reaction to cyclohexane-1,3-diones could provide a convenient synthesis of 1,5,6,7-tetrahydroindol-4-ones. These substances have aroused interest recently [2] because of the possibility of their conversion into indoles, and their methods of synthesis and chemistry have been reviewed.[3] We have reported briefly [4] the reaction of 2-amino-2-deoxy-D-glucose with 5,5-dimethylcyclohexane-1,3-dione (dimedone) to yield 1,5,6,7-tetrahydro-2-(D-*arabino*-1,2,3,4-tetrahydroxybutyl)-6,6-dimethylindol-4-one (2c), and

[1] (*a*) F. Garcia González and A. Gómez Sánchez, *Adv. Carbohyd. Chem.*, 1965, **20**, 303; (*b*) F. García González, A. Gómez Sánchez, and M. I. Goñi de Rey, *Carbohydrate Res.*, 1965, **1**, 261; (*c*) A. Gómez Sánchez, M. Gómez Guillén, and U. Scheidegger, *ibid.*, 1967, **3**, 468; (*d*) A. Gómez Sánchez, A. Cert Ventulá, and U. Scheidegger, *ibid.*, 1971, **7**, 275.

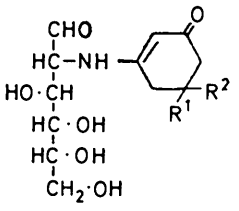
[2] W. A. Remers and M. J. Weiss, *J. Amer. Chem. Soc.*, 1965, **87**, 5262; W. A. Remers, R. H. Roth, G. J. Gibs, and M. J. Weiss, *J. Org. Chem.*, 1971, **36**, 1232; W. A. Remers and M. J. Weiss, *ibid.*, p. 1241.

[3] M. J. Weiss, G. R. Allen, jun., G. J. Gibs, J. F. Poletto, and W. A. Remers, *Topics Heterocyclic Chem.*, 1969, 178.

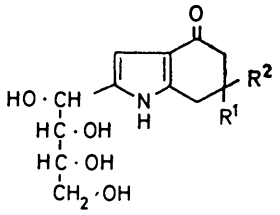
[4] F. García González, A. Gómez Sánchez, and M. Gómez Guillén, *Anales real Soc. espaň. Fis. Quím.*, 1968, **62B**, 471.

the transformation of this substance into simple 1,5,6,7-tetrahydroindol-4-one derivatives. We now report the results of a more general study of the reaction of amino-sugars with cyclohexane-1,3-diones.

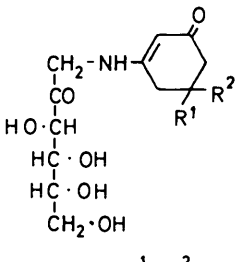
The primary products of the reaction of 2-amino-2-deoxy-β-D-glucopyranose with cyclohexane-1,3-diones in aqueous solution at room temperature were enamines (1), which cyclized spontaneously in the reaction medium to give 1,5,6,7-tetrahydro-2-(D-*arabino*-1,2,3,4-tetrahydroxybutyl)indol-4-ones (2). Both products were obtained as mixtures that were separated by fractional crystallization or by chromatography on a cellulose column; yields of pure products were consequently low (25—30%), although those of the tetrahydroindoles (2) could be improved by allowing long reaction times or raising the temperature.



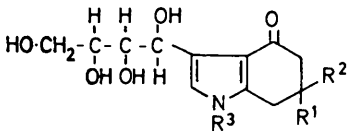
(1) a ; $R^1=R^2=H$
b ; $R^1=H$, $R^2=Me$



(2) a ; $R^1=R^2=H$
b , $R^1=H$, $R^2=Me$
c ; $R^1=R^2=Me$



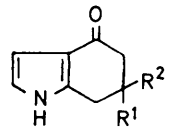
(3) a ; $R^1=R^2=H$
b ; $R^1=H$, $R^2=Me$



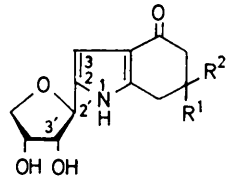
(4) a ; $R^1=R^2=R^3=H$
b ; $R^1=R^3=H$, $R^2=Me$
c ; $R^1=R^2=Me$, $R^3=H$
d ; $R^1=R^2=H$, $R^3=CH_2Ph$

Similar reactions with 1-amino-1-deoxy-D-fructose afforded enamines (3) in admixture with tetrahydroindole derivatives (4). Ketose enamines (3) were more stable than the isomeric aldose derivatives (1) and could be more comfortably handled and purified; yields of these enamines were then higher (*ca.* 70%). On the other hand, derivatives from cyclohexane-1,3-dione [(1a) and (3a)] were more stable than their homologous compounds [(1b) and (3b)]. Apparently, the introduction of a methyl group into the enamine system increases the facility for cyclization, and we attribute our failure to obtain enamines similar to (1) and (3) derived from dimedone to this fact; the products of the reactions of this β-diketone were indole derivatives [(2c) and (4c)] only. Also, the reaction of 1-benzylamino-1-deoxy-D-fructose with cyclohexane-1,3-dione gave compound (4d), and no intermediate was isolated or detected chromatographically.

Cyclizations of pure enamines (1) and (3) to 1,5,6,7-tetrahydroindol-4-ones were carried out by heating in water or in a buffer of pH 9—10. In the case of D-glucose derivatives (1), the products of the reaction at

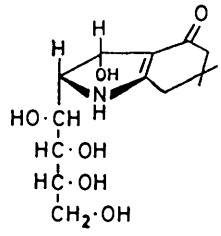


(5) a ; $R^1=R^2=H$
b ; $R^1=H$, $R^2=Me$

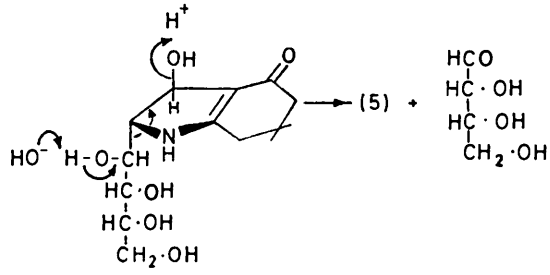


(6) a ; $R^1=R^2=H$
b ; $R^1=H$, $R^2=Me$

neutral pH were 1,5,6,7-tetrahydro-2-(D-*arabino*-1,2,3,4-tetrahydroxybutyl)indol-4-ones (2), isolated in yields up to 85%, smaller amounts (*ca.* 9%) of 1,5,6,7-tetrahydroindol-4-ones (5), and D-erythrose (chromatographically detected). When the reactions were performed at pH 9—10, yields of compounds (5) were 30%, and 2-(β-D-erythrofuranosyl)-1,5,6,7-tetrahydroindol-4-ones (6) were also formed. The cyclizations under similar conditions of D-fructose enamines (3) yielded 1,5,6,7-tetrahydro-3-(D-*arabino*-1,2,3,4-tetrahydroxybutyl)indol-4-ones (4) (*ca.* 80%); the formation of compounds lacking the



(7a)



(7b)

SCHEME

tetrahydroxylbutyl chain was not observed in these cases.

The foregoing results can be rationalized by assuming [1] that cyclization of the enamines (1) and (3) takes place

through an internal aldehyde–enamine condensation that would yield the intermediates (7) and (8), respectively, as a pair of diastereoisomers. The introduction of a methyl group, or other electron-releasing groups, into the cyclohexene ring would increase the availability of electrons at the enamine system and would facilitate the electrophilic attack by the sugar carbonyl group. On the other hand, the ketone group of compound (3) can be expected to be less reactive than the aldehyde group of (1). *trans*-Elimination of the elements of water in the diastereoisomer (7a) would yield the derivatives (2). The fission of the sugar chain, which produces compounds (5) and D-erythrose, can occur in the diastereoisomer (7b) and might be envisaged as a concerted *trans*-elimination catalysed by both hydroxide and hydrogen ions, as shown in the Scheme. *trans*-Elimination of the elements of water is possible in both diastereoisomers of (8), yielding (tetrahydroxybutyl)indole derivatives (4); compounds lacking the tetrahydroxybutyl chain cannot be formed in this case.

Acetylation of the enamines (1) with acetic anhydride in pyridine afforded the tetra-acetates (9). Similar treatment of the isomeric compounds (3) gave syrupy mixtures.

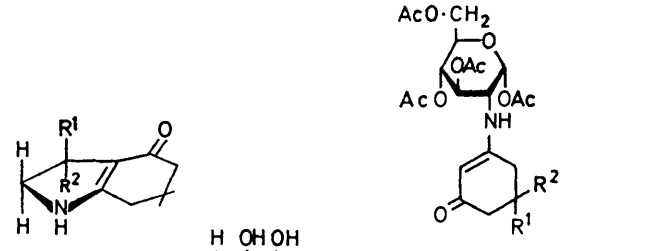
Compounds (1) and (3) and the tetra-acetates (9) had u.v. absorptions [$\lambda_{max.}$ *ca.* 290 nm (log ε 4·5)] similar to those [5,6] of simple 3-alkylaminocyclohex-2-enones. Their i.r. spectra showed the ν(C=O) band displaced to low frequencies (*ca.* 1615 cm^{-1}; enamine band I), and also showed bands at *ca.* 1585 (enamine band II) and 1520—1550 cm^{-1} (enamine band III) attributable [6,7] to mixed vibrations of the C=C–NH grouping; this pattern of absorption is typical of *N*-monosubstituted 3-aminocyclohex-2-enones.[6,7] The n.m.r. spectra of the acetates (9) were also consistent with the keto-enamine structure and showed the sugar proton signals at δ values and with coupling constants similar to those observed [1c,d] in other enamines derived from 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranose and β-dicarbonyl compounds.

In the formation of the enamines (1b) and (3b) derived from 5-methyl-1,3-cyclohexanedione, a new chiral centre arises at position 5 of the cyclohexene ring and two diastereoisomers could result. In each case we have only been able to isolate, or to detect chromatographically, a single product; however, the n.m.r. spectrum of chromatographically homogeneous acetylated enamine (9b) showed a pair of doublets, of different intensities, at δ 4·58 and 4·60, and a pair of singlets, also of different intensities, at δ 5·20 and 5·23, that we attribute to the NH and =CH groups, respectively, of the two possible diastereoisomers. On deuteriation, both NH doublets disappeared, and, on irradiation of the H-2 sextuplet at δ 3·85, they both collapsed into singlets. This duplicity of signals was observed neither in the cyclohexane-1,3-dione derivative (9a) nor in simple 3-alkylaminocyclohex-2-enones.[6]

[5] C. Kashima, M. Yamamoto, and N. Sugiyama, *J. Chem. Soc.* (*C*), 1970, 111.

[6] A. Gómez Sanchez, E. Toledano, and J. Bellanato, unpublished results.

Hydrolysis of the enamines (1b) and (3a) to the parent amino-sugar and diketone took place on heating with dilute hydrochloric acid; that of ketose derivative required a longer reaction time.

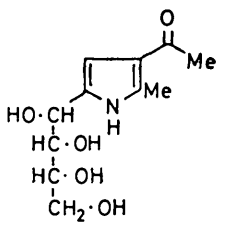


(8) a ; R^1=OH, R^2= H OH OH / OH H H –C–C–C–CH_2·OH

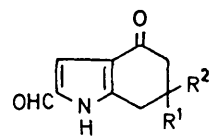
(9) a ; R^1=R^2=H

b ; R^1=H, R^2=Me

b ; R^1 = H OH OH / OH H H –C–C–C–CH_2·OH , R^2=OH

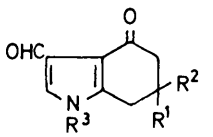


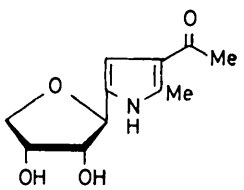
(10)



(11) a ; R^1= R^2=H

b ; R^1= H , R^2= Me





(12) a ; R^1 = R^2= R^3= H

b ; R^1 = R^3= H , R^2= Me

c ; R^1 = R^2= Me , R^3 = H

d ; R^1 = R^2= H , R^3= CH_2Ph

(13)

1,5,6,7-Tetrahydro-2-(D-*arabino*-1,2,3,4-tetrahydroxybutyl)indol-4-ones (2) and their isomers (4) had u.v. and i.r. spectra very similar to those [1b] of 3-acetyl-5-(D-*arabino*-1,2,3,4-tetrahydroxybutyl)-2-methylpyrrole (10). Their acetylations afforded the corresponding tetra-*O*-acetyl derivatives, and, in their oxidations with sodium periodate, 4,5,6,7-tetrahydro-4-oxo-1*H*-indolecarbaldehydes [(11) and (12)] were obtained in high yields. All these substances had spectroscopic properties consistent with the assigned structures.

Treatment of 1,5,6,7-tetrahydro-2-(D-*arabino*-1,2,3,4-tetrahydroxybutyl)indol-4-ones (2) with a buffer of pH 9—10 caused dehydration of the tetrahydroxybutyl chain and formation of derivatives formulated as (6) on the

[7] J. Dabrowski and U. Dabrowska, *Chem. Ber.*, 1968, **101**, 2365.

basis of their u.v., i.r., and n.m.r. spectra, which were similar to those of the parent substances (2), and by analogy with the similar reaction of compound (10) which yields [1b] (3,4-dihydroxytetrahydro-2-furyl)pyrrole (13). The β-D anomeric configuration assigned to these substances is based on the $J_{1',2'}$ values (>6 Hz) and the values of the optical rotations ($[\alpha]_{5461}$ *ca.* −100°), which are similar to those [1,8] of other *C*-β-D-erythrofuranosides; the α-D anomers would be expected to have [8] $J_{1',2'}$ *ca.* 4·5 Hz and $[\alpha]_{5461}$ *ca.* −20°.

EXPERIMENTAL

Specific rotations were recorded at 5461 Å with a 143C Bendix-NPL polarimeter. U.v. spectra were taken with a Unicam SP 800 spectrophotometer and i.r. spectra with a Perkin-Elmer 577 or 621 spectrophotometer. N.m.r. spectra (solvent $CDCl_3$ unless otherwise specified) were measured with a Varian XL-100 spectrometer or with a Perkin-Elmer–Hitachi R-20B instrument. Paper chromatography was performed on Whatman No. 1 paper by the horizontal technique, with n-butyl alcohol–ethanol–water–ammonia (40 : 10 : 49 : 1; organic phase) as the developer and with the following reagents for detection: (*a*) alkaline silver nitrate; (*b*) Ehrlich's reagent.[1b] T.l.c. was performed on silica gel (Merck HF_{254}). Column chromatography on cellulose (Merck) was effected with the same solvent as in paper chromatography. Light petroleum refers to the fraction of b.p. 50—70°. Solutions were dried with magnesium sulphate and were evaporated *in vacuo* below 40° unless otherwise specified. Identification of compounds was based on mixed m.p., i.r. spectral, and chromatographic comparisons.

2-Deoxy-2-(3-oxocyclohex-1-enylamino)-D-glucose (1a) *and 1,5,6,7-Tetrahydro-2-(D-arabino-1,2,3,4-tetrahydroxybutyl)-indol-4-one* (2a).—Cyclohexane-1,3-dione (2·24 g, 20 mmol) in water (10 ml) was added to a solution of 2-amino-2-deoxy-β-D-glucopyranose (3·58 g, 20 mmol) in water (30 ml), and the mixture was left at room temperature. Paper chromatography showed the formation of the enamine (1a) [R_F 0·41; reagents (*a*) and (*b*)], and then of compounds (2a) [R_F 0·50; reagents (*a*) and (*b*)] and (5a) [R_F 0·87; reagent (*b*)]. After 3 days the relative intensity of the spot of R_F 0·41 reached a maximum. The mixture was then evaporated and the syrupy residue was chromatographed on a cellulose column (3 × 58 cm). Fractions containing pure compound of R_F 0·41 were combined and evaporated (temperature below 10°) to *ca.* 5 ml. Refrigeration of this solution caused crystallization of the *enamine* (1a) (1·32 g, 27%), m.p. 114—115° (from methanol), $[\alpha]_{5461}^{28}$ +55° (*c* 1 in H_2O), $\lambda_{max.}$ (H_2O) 291 nm (log ε 4·47), $\nu_{max.}$ (KBr) 3300 (NH, OH) and 811 cm^{-1} (=CH), $\nu_{max.}$ (Me_2SO) 1608 (CO), and 1580 and 1560 cm^{-1} (C=C–NH) (Found: C, 52·7; H, 7·25; N, 5·3. $C_{12}H_{19}NO_6$ requires C, 52·75; H, 7·0; N, 5·15%).

Fractions containing pure compound of R_F 0·50 were evaporated yielding the *indole* (2a) (1·19 g, 37%), m.p. 151—153° (from water), $[\alpha]_{5461}^{18}$ −38° (*c* 0·5 in H_2O), $\lambda_{max.}$ (H_2O) 214, 246, and 285 nm (log ε 4·17, 3·96, and 3·87), $\nu_{max.}$ (KBr) 3260 (NH, OH), 1640 (CO), and 1612 and 1490 cm^{-1} (ring) (Found: C, 56·55; H, 6·95; N, 5·6. $C_{12}H_{17}NO_5$ requires C, 56·45; H, 6·7; N, 5·5%). It consumed 3·09 mol. equiv. of periodate.

Compound (2a) was obtained without column chromatography by leaving the reaction mixture, prepared as indicated, at room temperature for 5 days. The solution was then evaporated to one-third volume and extracted with chloroform (4 × 5 ml). Evaporation of the aqueous fraction and refrigeration afforded compound (2a) (1·41 g, 28%), m.p. 151—153° (from water).

Cyclizations of the Enamine (1a).—(*a*) A solution of the enamine (1a) (0·27 g) in water (10 ml) was heated at 100° for 1·5 h. Paper chromatography showed the formation of compound (2a) (major product), compound (6a) [R_F 0·67; reagent (*b*)], and 2-amino-2-deoxy-D-glucose. The mixture was extracted with chloroform (3 × 5 ml), and the aqueous layer was evaporated to give crystalline, almost chromatographically pure, compound (2a) (0·23 g), m.p. 142—145°, which was recrystallized from water; yield 0·12 g (47%), m.p. 151—153°.

(*b*) A solution of the enamine (1a) (1·36 g) in sodium carbonate–sodium hydrogen carbonate buffer (20 ml; pH 9—10) was heated at 100° for 0·5 h, and, after being cooled, was neutralized with Amberlite IR-120 (H^+) resin. Paper chromatography indicated the presence of compounds (6a) (main product), (2a), and (5a) [R_F 0·87; reagent (*b*)]. The solution was extracted with chloroform (10 × 5 ml). Evaporation of the extract afforded 1,5,6,7-tetrahydroindol-4-one (5a) (0·19 g, 24%), m.p. 185—187° (from ethanol–light petroleum) (lit.,[9] 188—190°), $\lambda_{max.}$ (EtOH) 242 and 275 nm (log ε 3·78 and 3·73), $\nu_{max.}$ (KBr) 3180 (NH), 1620 (CO), and 1540 cm^{-1} (ring) (Found: C, 71·3; H, 6·8; N, 10·4. Calc. for C_8H_9NO: C, 71·1; H, 6·7; N, 10·35%).

The aqueous layer was concentrated to a small volume and refrigerated, yielding *1,5,6,7-tetrahydro-2-(2,3-dihydroxytetrahydro-2-furyl)indol-4-one* (6a) (0·39 g, 33%), m.p. 233—235° (from ethanol–water), $[\alpha]_{5461}^{30}$ −125° (*c* 0·2 in H_2O), $\lambda_{max.}$ (H_2O) 212, 243, and 281 nm (log ε 4·33, 3·98, and 3·96), $\nu_{max.}$ (KBr) 3470 and 3200 (NH, OH), 1620 (CO), 1580 and 1490 cm^{-1} (ring), δ (Me_2SO; 60 MHz) 2·15 (4H, m), 2·72 (2H, t, *J* 6·0 Hz), 4·43 (1H, d, $J_{2',3'}$ 7·2 Hz, H-2'), and 6·13 (1H, d, $J_{1,3}$ 2·25 Hz, H-3) (Found: C, 60·55; H, 6·1; N, 5·8. $C_{12}H_{15}NO_4$ requires C, 60·75; H, 6·35; N, 5·9%).

1,3,4,6-Tetra-O-acetyl-2-(3-oxocyclohex-1-enylamino)-α-D-glucopyranose (9a).—A solution of the enamine (1a) (0·2 g) in pyridine (1 ml) was treated with acetic anhydride (3 ml). After being stored in the refrigerator for 24 h, the mixture was poured onto ice, yielding the chromatographically (t.l.c. in ether; R_F 0·60) homogeneous *product* (0·25 g, 78%), m.p. 259—261° (from ethanol), $[\alpha]_{5461}^{27}$ −50° (*c* 0·5 in $CHCl_3$), $\lambda_{max.}$ (EtOH) 282 nm (log ε 4·49), $\nu_{max.}$ ($CDCl_3$) 3420 (NH), 1755 (OAc), 1620 (CO), 1594 and 1520 (C=C–NH), and 815 cm^{-1} (=CH), δ (100 MHz) 2·01, 2·02, and 2·08 (each 3H, s, OAc), 2·19 (3H, s, 1-AcO), 2·24 (2H, t, *J* 4·0 Hz, CH_2·CO), 3·78 (1H, sext, $J_{1,2}$ 3·5, $J_{2,3}$ 9·0, $J_{2,NH}$ 9·5 Hz, H-2), 4·1 (1H, m, H-5), 4·26 (2H, m, 2 H-6), 4·52 (1H, d, NH), 5·14 (1H, t, $J_{3,4} \simeq J_{4,5}$ 9 Hz, H-4), 5·22 (1H, s, =CH), 5·26 (1H, t, H-3), 6·20 (1H, d, H-1) (Found: C, 54·65; H, 6·15; N, 3·25. $C_{20}H_{27}NO_{10}$ requires C, 54·45; H, 6·15; N, 3·15%).

2-(D-arabino-1,2,3,4-Tetra-acetoxybutyl)-1,5,6,7-tetrahydroindol-4-one.—Acetylation of compound (2a), as indicated for the enamine (1a), gave the *tetra-acetate* (74%), m.p. 157—158° (from ethanol), $[\alpha]_{5461}^{25}$ −66° (*c* 1 in $CHCl_3$), ν_{max} ($CHCl_3$) 3440 (NH), 1750, (AcO), 1655 (CO), and 1600 and 1480 cm^{-1} (ring) (Found: C, 56·95; H, 5·95; N, 3·5. $C_{20}H_{25}NO_9$ requires C, 56·75; H, 5·95; N, 3·3%).

4,5,6,7-Tetrahydro-4-oxo-1H-indole-2-carbaldehyde (11a).—A solution of compound (2a) (0·51 g, 2 mmol) in water (15

[8] A. Gómez Sánchez and A. Rodríguez Roldán, *Carbohydrate Res.*, 1972, **22**, 53.

[9] H. Stetter and R. Lauterbach, *Annalen*, 1962, **655**. 20.

ml) was treated with sodium periodate (1·28 g, 6 mmol) in water (20 ml). The mixture was kept at 5° for 0·5 h, and was then extracted with chloroform (8 × 10 ml). Evaporation of the combined extracts gave *aldehyde* (11a) (0·24 g, 71%), m.p. 202—205° (from ethanol–water), $\lambda_{max.}$ (EtOH) 228, 260, and 299 nm (log ε 4·38, 4·05, and 4·43), $\nu_{max.}$ (KBr) 3230 (NH), 2760 and 2820 (CHO), 1680 (CHO), 1645 (CO), and 1560 and 1508 cm^{-1} (ring), δ (Me_2SO; 60 MHz) 2·30 (2H, m, H-6), 2·60 (2H, t, *J* 6·0 Hz), 3·00 (2H, t, *J* 6·0 Hz), 7·30 (1H, s, =CH), and 9·50 (1H, s, CHO) (Found: C, 66·6; H, 5·7; N, 8·85. $C_9H_9NO_2$ requires C, 66·25; H, 5·55; N, 8·6%).

Formation of the Dihydroxytetrahydrofuryl Compound (6a) *from the Indole* (2a).—A solution of compound (2a) (0·25 g) in sodium carbonate–sodium hydrogen carbonate buffer (20 ml; pH 9—10) was heated at 100° for 2·5 h, neutralized with Amberlite IR-120 (H^+) resin, and concentrated to a small volume, yielding compound (6a) (0·21 g, 90%), m.p. 233—235° (from methanol), identical with the sample already described.

2-*Deoxy*-2-(5-*methyl*-3-*oxocyclohex*-1-*enylamino*)-D-*glucose* (1b).—2-Amino-2-deoxy-β-D-glucopyranose (3·58 g, 20 mmol) in water (10 ml) was treated with a solution of 5-methylcyclohexane-1,3-dione (2·52 g, 20 mmol) in acetone–water (1 : 1; 30 ml), and the mixture was stored at room temperature for 6 days. Paper chromatography showed the rapid formation of the enamine (1a) [R_F 0·50; reagents (*a*) and (*b*)], and then of compounds (2b) [R_F 0·61; reagents (*a*) and (*b*)] and (5b) [R_F 0·90; reagent (*b*)], and D-erythrose. The mixture was extracted with chloroform (4 × 5 ml), and the aqueous layer was evaporated (below 10°) yielding the *enamine* (1b) (1·57 g, 27%), m.p. 161—163° (from methanol), $[\alpha]_{5461}^{23}$ −36° (*c* 1 in H_2O), $\lambda_{max.}$ (H_2O) 294 nm (log ε 4·48), $\nu_{max.}$ (KBr) 3305 (NH, OH), 815sh (=CH), $\nu_{max.}$ (Me_2SO) 1609 (CO), 1578 and 1552 cm^{-1} (C=C–NH) (Found: C, 54·3; H, 7·65; N, 4·65. $C_{13}H_{21}NO_6$ requires C, 54·35; H, 7·35; N, 4·85%).

Cyclizations of the Enamine (1b).—(*a*) The enamine (1b) (2·87 g) in water (50 ml) was heated at 100°. Paper chromatography showed the formation of compounds (2b) (major product), (5b), and (6b) [R_F 0·70; reagent (*b*)], and D-erythrose. After 2 h all the starting substance had reacted. The mixture was extracted with chloroform (6 × 10 ml), and the combined extracts were evaporated yielding 1,5,6,7-*tetrahydro*-6-*methylindol*-4-*one* (5b) (0·14 g, 9%), m.p. 140—141° (from ethanol–light petroleum), $\lambda_{max.}$ (EtOH) 243 and 275 nm (log ε 3·88 and 3·79), $\nu_{max.}$ (KBr) 3230 (NH), 1645 (CO), and 1600sh and 1510 cm^{-1} (ring) (Found: C, 72·4; H, 7·4; H, 9·25. $C_9H_{11}NO$ requires C, 72·55; H, 7·45; N, 9·35%).

The aqueous layer was evaporated, and the syrupy residue was treated with methanol and refrigerated yielding 1,5,6,7-*tetrahydro*-2-(D-arabino-1,2,3,4-*tetrahydroxybutyl*)-6-*methylindol*-4-*one* (2b) (1·28 g, 48%), m.p. 142—144° (from water), $[\alpha]_{5461}^{20}$ −43° (*c* 1 in H_2O), $\lambda_{max.}$ (H_2O) 216, 246, and 285 nm (log ε 3·98, 3·88, and 3·79), $\nu_{max.}$ (KBr) 3300 (NH, OH), 1640 (CO), and 1585 and 1480 cm^{-1} (ring) (Found: C, 59·1; H, 7·3; N, 5·35. $C_{13}H_{19}NO_5$ requires C, 59·35; H, 7·25; N, 5·35%). It consumed 3·03 mol. equiv. of periodate.

(*b*) The enamine (1b) (1·43 g) was treated with sodium carbonate–sodium hydrogen carbonate buffer (pH 9—10) as indicated for compound (1a). Paper chromatography of the neutralized reaction mixture showed the formation of compounds (2b), (5b), and (6b) [major product, R_F 0·70; reagent (*b*)]. Extraction with chloroform and work-up of the extract as before yielded compound (5b) (0·21 g, 27%), m.p. 140—141° (from ethanol–light petroleum), identical with that obtained in (*a*).

The aqueous layer was evaporated to a small volume and refrigerated, yielding 1,5,6,7-*tetrahydro*-2-(2,3-*dihydroxytetrahydro*-2-*furyl*)-6-*methylindol*-4-*one* (6b) (0·35 g, 28%), m.p. 195—197° (from ethanol), $[\alpha]_{5461}^{25}$ −96° (*c* 0·5 in H_2O), $\lambda_{max.}$ (H_2O) 221, 246, and 284 nm (log ε 4·03, 3·83, and 3·84), $\nu_{max.}$ (KBr) 3205 (NH, OH), 1610 (CO), and 1560 and 1490 cm^{-1} (ring), δ (Me_2SO; 60 MHz) 1·05 (3H, d, *J* 6·0 Hz, Me), 4·43 (1H, d, $J_{2',3'}$ 7·2 Hz, H-2'), and 6·12 (1H, d, $J_{1,3}$ 2·25 Hz, H-3) (Found: C, 61·85; H, 6·85; N, 5·5. $C_{13}H_{17}NO_4$ requires C, 62·15; H, 6·8; N, 5·55%).

Hydrolysis of the Enamine (1b).—A solution of the enamine (2·87 g, 10 mmol) in 0·1N-hydrochloric acid (120 ml) was heated at 100° for 1·5 h. The mixture was extracted with chloroform (12 × 10 ml), and the aqueous phase was passed down a column of Amberlite IR-120 (H^+) resin. The column was washed thoroughly with water, and then with N-hydrochloric acid till the eluate gave a negative Fehling's test. The acidic eluate was evaporated to *ca.* 5 ml and refrigerated yielding 2-amino-2-deoxy-D-glucose hydrochloride (1·27 g, 59%), m.p. 192—194° (decomp.), identical with an authentic specimen.

Evaporation of the combined chloroform extracts gave 5-methylcyclohexane-1,3-dione (0·7 g), m.p. 127—129°, identical with an authentic sample. The aqueous eluate from the column was extracted with chloroform, and the extract was evaporated yielding an additional fraction of the diketone (0·33 g, total yield 81%), m.p. 126—128°.

1,3,4,6-*Tetra*-O-*acetyl*-2-*deoxy*-2-(5-*methyl*-3-*oxocyclohex*-1-*enylamino*)-α-D-*glucopyranose* (9b). Acetic anhydride (3 ml) was added to a suspension of the enamine (1b) (0·57 g) in pyridine (4 ml), and the mixture was shaken until dissolution was complete. After 20 h at 20°, the solution was diluted with ice-cooled water (60 ml) and extracted with chloroform (12 × 5 ml). The combined extracts were washed with N-sulphuric acid, saturated aqueous potassium hydrogen carbonate, and water. Evaporation gave the chromatographically (t.l.c. in ether; R_F 0·55) homogeneous *product* (0·82 g, 90%), m.p. 209—210° (from ethanol–ether), $[\alpha]_{5461}^{19}$ −47° (*c* 0·5 in $CHCl_3$), $\lambda_{max.}$ (EtOH) 282 nm (log ε 4·51), $\nu_{max.}$ ($CDCl_3$) 3418 (NH), 1755 and 1745 (AcO), 1622 (CO), 1593, 1545sh, and 1521 (C=C–NH), and 811 cm^{-1} (=CH), δ (100 MHz) 2·01, 2·03, and 2·09 (each 3H, s, AcO), 2·18 (3H, s, 1-AcO), 2·23 (2H, d, *J* 4·0 Hz, CH_2·CO), 3·85 (1H, sext, $J_{1,2}$ 3·5, $J_{2,3} \simeq J_{2,NH}$ 9·0 Hz, H-2), 4·1 (1H, m, H-5), 4·24 (2H, m, 2 H-2), 4·58 (d, NH), 4·60 (d, NH), 5·13 (1H, t, $J_{3,4} \simeq J_{4,5}$ 9·0 Hz, H-4), 5·20 (s, =CH), 5·23 (s, =CH), 5·29 (1H, t, H-3), and 6·19 (1H, d, H-1) (Found: C, 55·35; H, 6·4; N, 3·05. $C_{21}H_{29}NO_{10}$ requires C, 55·4; H, 6·4; N, 3·05%).

2-(D-arabino-1,2,3,4-*Tetra-acetoxybutyl*)-1,5,6,7-*tetrahydro*-6-*methylindol*-4-*one*.—Acetylation of the indole (2b), as indicated for the enamine (1a), gave the *tetra-acetate* (65%), m.p. 146—148° (from ethanol–water), $[\alpha]_{5461}^{23}$ −80° (*c* 1 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3430 (NH), 1745 (AcO), 1655 (CO), and 1580 and 1480 cm^{-1} (ring) (Found: C, 57·4; H, 6·3; N, 3·2. $C_{21}H_{27}NO_9$ requires C, 57·65; H, 6·2; N, 3·2%).

4,5,6,7-*Tetrahydro*-6-*methyl*-4-*oxoindole*-2-*carbaldehyde* (11b).—Compound (2b) (0·53 g, 2 mmol) in water (30 ml) was treated with sodium periodate (1·26 g, 6 mmol) in water (10 ml). The solid that separated was recrystallized from ethanol, yielding the *aldehyde* (0·28 g, 80%), m.p. 227—228°, $\lambda_{max.}$ (EtOH) 227, 259, and 299 nm (log ε 4·28, 3·92,

and 4·38), $\nu_{max.}$ (KBr) 3220 (NH), 2790 and 2870 (CHO), 1670 (CHO), 1645 (CO), and 1560 and 1510 cm^{-1} (ring), δ (Me_2SO; 60 MHz) 1·05 (3H, d, J 3·6 Hz, Me), 2·30 (2H, s), 3·30 (2H, s), 7·15 (1H, s, =CH), 9·44 (1H, s, CHO), and 12·47 (1H, s, NH) (Found: C, 67·95; H, 6·35; N, 8·1. $C_{10}H_{11}NO_2$ requires C, 67·8; H, 6·25; N, 7·9%).

Formation of Compound (6b) *from the Indole* (2b).—Treatment of compound (2b) with sodium carbonate–sodium hydrogen carbonate buffer (pH 9—10) as indicated for compound (2a) gave the furan (6b) (80%), m.p. 195—197° (from methanol), identical with the sample already described.

Reaction of 2-Amino-2-deoxy-β-D-glucopyranose with Dimedone.—2-Amino-2-deoxy-β-D-glucopyranose (1·79 g, 10 mmol) in water (5 ml) was treated with dimedone (1·39 g, 10 mmol) in acetone–water (1 : 1; 15 ml) for 5 days at room temperature. Paper chromatography showed the formation of the indole (2c) [R_F 0·68; reagents (*a*) and (*b*)] and traces of 1,5,6,7-tetrahydro-6,6-dimethylindol-4-one [R_F 0·92; reagent (*b*)]. The mixture was evaporated to a small volume yielding 1,5,6,7-tetrahydro-2-(D-*arabino*-1,2,3,4-tetrahydroxybutyl)-6,6-dimethylindol-4-one (2c) (1·98 g, 70%), m.p. 155—157° (decomp.) (from water), identical with the substance previously described.[4]

1-*Deoxy*-1-(3-*oxocyclohex*-1-*enylamino*)-D-*fructose* (3a) *and* 1,5,6,7-*Tetrahydro*-3-(D-arabino-1,2,3,4-*tetrahydroxybutyl*)-*indol*-4-*one* (4a).—A solution of 1-amino-1-deoxy-D-fructose acetate (2·39 g, 10 mmol) and sodium carbonate (0·53 g, 5 mmoles) in water (65 ml) was treated with cyclohexane-1,3-dione (1·12 g, 10 ml) in water (35 ml), and the mixture was kept at 40° for 5 days. Paper chromatography showed the formation of the enamine (3a) [R_F 0·55; reagent (*a*)] (major product) and the indole (4a) [R_F 0·63; reagents (*a*) and (*b*)]. The mixture was evaporated to one-third volume and extracted with chloroform (3 × 5 ml). Evaporation of the aqueous fraction left a syrup that was chromatographed (cellulose; 3 × 60 cm). Fractions containing pure compound of R_F 0·55 were evaporated, yielding the *enamine* (3a) (1·75 g, 63%), m.p. 161—162° (decomp.) (from methanol), $[\alpha]_{5461}^{24}$ −85° (*c* 1 in H_2O), $\lambda_{max.}$ (H_2O) (log ε 4·48), $\nu_{max.}$ (Me_2SO) 3300 (NH, OH), 1608 (CO), 1579, 1560sh, and 1540 (C=C–NH), and 808 cm^{-1} (=CH) (Found: C, 52·7; H, 7·0; N, 5·0. $C_{12}H_{16}NO_6$ requires C, 52·75; H, 7·0; N, 5·15%).

Fractions containing pure compound of R_F 0·63 were combined and evaporated affording the *indole* (4a) (0·19 g, 3%), m.p. 174—176° (from water), $[\alpha]_{5461}^{23}$ −32° (*c* 0·5 in H_2O), $\lambda_{max.}$ (H_2O) 215, 253, and 283 nm (log ε 3·94, 3·94, and 3·72), $\nu_{max.}$ (KBr) 3210 (NH, OH), 1625 (CO), and 1575 and 1475 cm^{-1} (ring) (Found: C, 56·45; H, 6·85; N, 5·7. $C_{12}H_{17}NO_5$ requires C, 56·45; H, 6·7; N, 5·5%). It consumed 3·09 mol. equiv. of periodate.

Hydrolysis of the Enamine (3a).—Hydrolysis of compound (3a), as described for (1b), gave cyclohexane-1,3-dione (73%), m.p. 104—105°, and 1-amino-1-deoxy-D-fructose hydrochloride (65%), m.p. 130° (decomp.), identical with authentic samples.

Cyclizations of the Enamine (3a).—(*a*) The enamine (3a) (0·27 g) in water (10 ml) was heated at 100° for 2·5 h. Paper chromatography showed the formation of compound (4a) and traces of an unidentified substance of R_F 0·68 [reagent (*b*)]. The mixture was extracted with chloroform, and the aqueous layer was evaporated, yielding the indole (4a) (0·21 g, 82%), m.p. 172—174° (from water), identical with the sample previously described.

(*b*) The enamine (3a) was treated with a buffer of pH 9—10, as indicated for compound (1a). Paper chromatography of the neutralized mixture indicated the formation of the indole (4a) (major product) and the compound of R_F 0·68; the indole (5a) was not detected. Evaporation left a syrup that was crystallized from water yielding compound (4a) (31%), m.p. 172—174°, identical with the samples already described.

3-(D-arabino-1,2,3,4-*Tetra-acetoxybutyl*)-1,5,6,7-*tetrahydro-indol*-4-*one.*—Acetylation of the indole (4a), as indicated for the enamine (1b), gave the *tetra-acetate* (77%), m.p. 128—130° (from carbon tetrachloride–ethanol), $[\alpha]_{5461}^{23}$ −20° (*c* 1 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3450 (NH), 1740 (AcO), 1655 (CO), and 1570 and 1470 cm^{-1} (ring) (Found: C, 56·7; H, 6·0; N, 3·5. $C_{20}H_{25}NO_9$ requires C, 56·8; H, 5·85; N, 3·3%).

4,5,6,7-*Tetrahydro*-4-*oxoindole*-3-*carbaldehyde* (12a).—Periodate oxidation of the indole (4a), as indicated for compound (2b), gave the *aldehyde* (78%), m.p. 249—251° (decomp.) (from ethanol–water), $\lambda_{max.}$ (EtOH) 227, 263, and 293 nm (log ε 4·45, 4·01, and 3·96), $\nu_{max.}$ (KBr) 3190 (NH), 2760 and 2820 (CHO), 1660 (CHO), 1635 (CO), and 1570 and 1520 cm^{-1} (ring), δ (Me_2SO; 60 MHz) 2·12 (2H, t, J 6·0 Hz), 2·77 (2H, t, J 6·0 Hz), 7·50 (1H, s, =CH), and 9·25 (1H, s, CHO) (Found: C, 66·0; H, 5·75; N, 8·75. $C_9H_9NO_2$ requires C, 66·25; H, 5·65; N, 8·6%).

1-*Deoxy*-1-(5-*methyl*-3-*oxocyclohex*-1-*enylamino*)-D-*fructose* (3b).—1-Amino-1-deoxy-D-fructose acetate was treated with sodium carbonate and 5-methylcyclohexane-1,3-dione in similar manner to that for the preparation of the enamine (3a). Paper chromatography showed the formation of compounds (3b) [R_F 0·50; reagent (*a*)] and (4b) [R_F 0·60; reagents (*a*) and (*b*); trace amounts]. Work-up and chromatography as indicated for (3a) gave the *enamine* (24%), m.p. 167—169° (from methanol–water), $[\alpha]_{5461}^{26}$ −155° (*c* 0·5 in H_2O), $\lambda_{max.}$ (H_2O) 293 nm (log ε 4·50), $\nu_{max.}$ (Me_2SO) 3300 (NH, OH), 1610 (CO), 1580, 1560sh, and 1540sh (C=C–NH), and 802 cm^{-1} (=CH) (Found: C, 54·2; H, 7·2; N, 4·65. $C_{13}H_{21}NO_6$ requires C, 54·35; H, 7·35; N, 4·85%).

1,5,6,7-*Tetrahydro*-3-(D-arabino-1,2,3,4-*tetrahydroxybutyl*)-6-*methylindol*-4-*one* (4b).—The enamine (3b) was cyclized as indicated under (*a*) for the enamine (3a). Paper chromatography showed the formation of the indole (4b) and minor amounts of an unidentified substance of R_F 0·70 [reagent (*b*)]. Work-up as indicated before gave the *indole* (4b) (86%), m.p. 168—170° (from water), $[\alpha]_{5461}^{25}$ −28° (*c* 0·5 in H_2O), $\lambda_{max.}$ (EtOH) 218, 252, and 285 nm (log ε 3·66, 3·55, and 3·62), $\nu_{max.}$ (KBr) 3220 (NH, OH), 1622 (CO), and 1575 and 1472 cm^{-1} (ring) (Found: C, 59·6; H, 7·25; N, 5·6. $C_{13}H_{19}NO_5$ requires C, 59·35; H, 7·25; N, 5·35%). It consumed 3·03 mol. equiv. of periodate.

This compound was obtained without isolation of the enamine by keeping the solution of 1-amino-1-deoxy-D-fructose acetate, sodium carbonate, and 5-methylcyclohexane-1,3-dione at room temperature for 5 days. The mixture was extracted with chloroform (3 × 5 ml), and the aqueous fraction was heated at 100° for 2·5 h and extracted again with chloroform (3 × 5 ml). Refrigeration of the aqueous layer caused crystallization of pure compound (4b) (1·56 g, 57%), m.p. 171—173°, identical with the sample described before.

3-(D-arabino-1,2,3,4-*Tetra-acetoxybutyl*)-1,5,6,7-*tetrahydro*-6-*methylindol*-4-*one.*—A suspension of the indole (4b) (0·34 g) in pyridine (3 ml) and acetic anhydride (3 ml) was shaken until dissolution was complete, and the solution was stored at 0° for 36 h. The mixture was poured onto ice, yielding

the *product* (0·38 g, 78%), m.p. 144—145° (from ethanol), $[\alpha]_{5461}^{24}$ −16° (*c* 0·5 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3450 (NH), 1740 (AcO), 1660 (CO), and 1570 and 1470 cm^{-1} (ring) (Found: C, 57·55; H, 6·35; N, 3·5. $C_{21}H_{27}NO_9$ requires C, 57·65; H, 6·2; N, 3·2%).

4,5,6,7-*Tetrahydro*-6-*methyl*-4-*oxoindole*-3-*carbaldehyde* (12b).—Periodate oxidation of compound (4b), as indicated for (2b), afforded the *aldehyde* (93%), m.p. 229—230° (from ethanol–water), $\lambda_{max.}$ (EtOH) 237, 269, and 294 nm (log ε 3·88, 4·00, and 3·94), $\nu_{max.}$ (KBr) 3200 (NH), 2760 and 2810 (CHO), 1670 (CHO), 1635 (CO), and 1570 and 1520 cm^{-1} (ring), δ (Me_2SO; 60 MHz) 1·09 (3H, d, *J* 3·75 Hz, Me), 2·35 (2H, s), 7·50 (1H, s, =CH), and 10·22 (1H, s, CHO) (Found: C, 67·85; H, 6·1; N, 7·8. $C_{10}H_{11}NO_2$ requires C, 67·8; H, 6·25; N, 7·9%).

1,5,6,7-*Tetrahydro*-3-(D-arabino-1,2,3,4-*tetrahydroxybutyl*)-6,6-*dimethylindol*-4-*one* (4c).—A solution of 1-amino-1-deoxy-D-fructose acetate (11·9 g, 50 mmol) and sodium carbonate (2·65 g, 25 mmol) in water (65 ml) was treated with dimedone (7·0 g, 50 mmol) in acetone–water (1 : 1; 130 ml). The mixture was stored at room temperature for 7 days, and the acetone was evaporated off. The residual aqueous solution was extracted with benzene (15 × 15 ml) and with chloroform (10 × 15 ml). The *indole* (4c) (1·3 g, 13%) crystallized from the aqueous fraction and was recrystallized from methanol; m.p. 158—160°, $[\alpha]_{5461}^{25}$ −34° (*c* 1 in H_2O), $\lambda_{max.}$ (H_2O) 253 and 283 nm (log ε 3·99 and 3·82), $\nu_{max.}$ (Nujol) 3356 and 3185 (NH, OH), 1629 (CO), and 1570 and 1510 cm^{-1} (ring) (Found: C, 59·25; H, 7·7; N, 5·2. $C_{14}H_{21}NO_5$ requires C, 59·35; H, 7·45; N, 4·95%). It consumed 3·09 mol. equiv. of periodate.

4,5,6,7-*Tetrahydro*-6,6-*dimethyl*-4-*oxoindole*-3-*carbaldehyde* (12c).—To a stirred suspension of the indole (4c) (0·28 g, 1 mmol) in water (30 ml) were added sodium periodate (1·0 g, 3·7 mmol) and ether (30 ml). After 1·5 h, the ether layer was separated, and the aqueous layer was extracted with ether (30 ml). The combined ethereal extracts were evaporated, yielding the *product* (0·1 g, 52%), m.p. 204—205° (from benzene), $\lambda_{max.}$ (EtOH) 235, 269, and 295 nm (log ε 3·99, 4·07, and 3·99), $\nu_{max.}$ (Nujol) 3145 (NH), 2725sh and 2667 (CHO), 1675 (CHO), 1635 (CO), and 1575 and 1527 cm^{-1} (ring) (Found: C, 69·35; H, 6·7; N, 7·4. $C_{11}H_{13}NO_2$ requires C, 69·1; H, 6·85; N, 7·35%).

1-*Benzyl*-1,5,6,7-*tetrahydro*-3-(D-arabino-1,2,3,4-*tetrahydroxybutyl*)*indol*-4-*one* (4d).—A solution of 1-benzylamino-1-deoxy-D-fructose oxalate (3·48 g, 10 mmol) and sodium carbonate (1·06 g, 10 mmol) in water (80 ml) was treated with cyclohexane-1,3-dione (1·12 g, 10 mmol) in water (30 ml), and the mixture was kept at 50° for 7 days. The solution was evaporated, and the solid that separated was extracted with ethanol (3 × 5 ml). Evaporation of the extract afforded the *product* (0·12 g, 8%), m.p. 152—153° (from ethanol–water), $[\alpha]_{5461}^{26}$ −16° (*c* 0·5 in H_2O), $\lambda_{max.}$ (EtOH) 217, 257, and 288 nm (log ε 4·04, 4·02, and 3·75), $\nu_{max.}$ (KBr) 3300 (NH, OH), 1658 (CO), and 1570 and 1472 cm^{-1} (ring) (Found: C, 66·15; H, 6·9; N, 4·2. $C_{19}H_{23}NO_5$ requires C, 66·1; H, 6·7; N, 4·05%). This compound consumed 3·03 mol. equiv. of periodate.

1-*Benzyl*-4,5,6,7-*tetrahydro*-4-*oxoindole*-3-*carbaldehyde* (12d).—Periodate oxidation of compound (4d), as indicated for (4b), gave the *aldehyde*, m.p. 148—150° (from ethanol–water), $\lambda_{max.}$ (EtOH) 225, 275, and 296 nm (log ε 4·39, 3·96, and 3·92), $\nu_{max.}$ (KBr) 2740 and 2820 (CHO), 1668 (CHO), 1650 (CO), and 1575 and 1460 cm^{-1} (ring) (Found: C, 75·75; H, 5·65; N, 5·25. $C_{16}H_{15}NO_2$ requires C, 75·85; H, 5·65; N, 5·25%).

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