Table I. Nuclear Magnetic Resonance Spectra of Both Isomers of I

Chemical Shifts			
Higher melting I	Lower melting I	Proton Ratio	Assignment
8.34τ	8.36τ	6	Methylene hydrogens
5.95τ	5.93τ	2	Methine 2,6-hydrogens
5.70τ	5.74τ	1	Amino hydrogen

N-Acetyl derivatives were made of both isomers. For the higher melting isomer, this derivative was recrystallized from water, yielding white leaflets melting at 131.2–32.1° C. The lower melting derivative was recrystallized from a toluene-hexane mixture, giving white crystals melting at 62.5–64.1° C.

Anal. Calcd. for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.72. Found: (higher melting derivative) C, 61.02; H, 6.48; N, 23.64; (lower melting derivative) C, 60.78; H, 6.18; N, 23.55.

The spectra in Table I were obtained in pyridine solutions using tetramethylsilane as internal standard.

Preparation of 1-Nitroso-2,6-dicyanopiperidine (from Higher Melting Isomer). A solution of 7.2 grams (0.10 mole) of sodium nitrite in 25 ml. of water was added in one-half hour to a solution of 13.5 grams (0.10 mole) of 2,6-dicyanopiperidine (m.p. 113–14° C.) in 300 ml. of 1.25% hydrochloric acid at 25.30° C. After 2 hours, the slurry was cooled in an ice bath, filtered, washed, and dried to yield 14.8 grams (90%) of a pale yellow, fluffy solid melting at 140–41° C. Recrystallization from a chloroform–carbon tetrachloride mixture gave pale yellow needles melting at 142–43° C. The infrared spectrum in chloroform showed strong nitrosoamine absorptions at 6.65, 7.90, 9.15, 10.40, and 10.80 microns. The nuclear magnetic spectrum taken in deuterochloroform solution showed a broad unresolved peak at 7.87τ, corresponding to 6 protons, and two doublets at 4.09τ with $J_{2\text{-}3a}$ = 21.5 c.p.s. and $J_{2\text{-}3e}$ = 12.6 c.p.s. (*a* = axial, *e* = equitorial). This pattern is indicative of an ABX system and to this apparently rigid (noninterconverting) compound can be assigned the cis configuration.

Anal. Calcd. for $C_7H_8N_4O$: C, 51.22; H, 4.91; N, 34.15. Found: C, 51.20; H, 5.05; N, 33.94.

Preparation of *cis*-2,6-Dicarbomethoxypiperidine. 2,6-Dicarbomethoxypyridine (*1*) was reduced by catalytic hydrogenation by the procedure of Rubtsov, Nikitskaya, and Usovskaya (*7*) at 30 to 40 pounds of hydrogen pressure with platinum oxide catalyst, but with one necessary modification. The reported solvent was methanol containing 2% hydrogen chloride. No hydrogen uptake was observed under these conditions. However, in the absence of hydrogen chloride the reaction proceeded readily in 2 hours to form *cis*-2,6-dicarbomethoxypiperidine in 76.5% yield, melting at 90.5–91.2° C. [lit. (*1*) m.p. 92° C.].

Preparation of 1-Nitroso-*cis*-2,6-dicarbomethoxypiperidine. A solution of 5 grams (0.07 mole) of sodium nitrite in 10 ml. of water was added in 10 minutes to a solution of 13.3 grams (0.066 mole) of *cis*-2,6-dicarbomethoxypiperidine in 75 ml. of water containing 5.5 ml. of concentrated hydrochloric acid, while the temperature was kept at 0° to 5° C. A pale yellow, fluffy solid was formed, weighing 13.8 grams and melting at 55.5–57.0° C. An analytical sample, recrystallized from hexane, melted at 56.5–57.7° C.

Anal. Calcd. for $C_9H_{14}N_2O$: C, 46.95; H, 6.13; N, 12.17. Found: C, 47.24; H, 6.37; N, 11.94.

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Methyl-1-(β-D-glucopyranosyl)-3-indoleacetate

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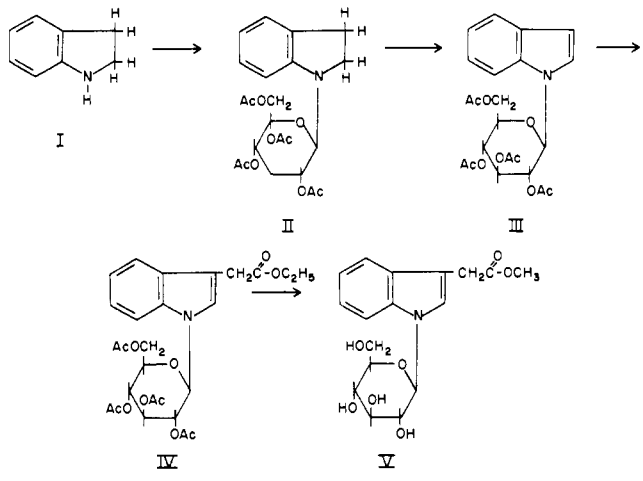
The synthesis of methyl-1-(β-D-glucopyranosyl)-3-indoleacetate, a hydrophilic compound related to the naturally occurring plant hormone, 3-indoleacetic acid, is described.

A NATURALLY occurring plant growth regulator, 3-indoleacetic acid, has been extensively investigated both as the parent acid and in the form of its derivatives in order to learn more about the relationship of structure to biological activity (*8*). Such investigations are important to other areas of research as well, in particular to the area of animal hormone investigations. This synthesis is part of an attempt to relate the effects of solubility, steric requirement, and electronic density to the physiological activity of 3-indoleacetic acid derivatives. These may also serve as models for investigation of animal hormones. The extreme hydrophilic nature of the glucosyl moiety led to its choice as a group for imparting water solubility to 3-indoleacetic acid.

Indoline (I) was converted efficiently (66% yield) to 1-(β-D-tetra-*O*-acetylglucopyranosyl)indoline (II) by treatment with tetra-*O*-acetyl-α-D-glucopyranosyl bromide in ether solution, using Na_2CO_3 to neutralize the HBr evolved (*4*). Pyridine used as an acid in ethanol solution gave only low yields of approximately 20% of product II. Suvorov

and Preobrazhenskaya reported 57% yield, using hot benzene as a solvent (*7*), and 60 to 90% yields using glucose pentaacetate in an unspecified solvent (*6*). A bathochromic shift of 3 to 4 mμ was noted in the ultraviolet spectrum of II relative to indoline.



Dehydrogenation of II to 1-(β-D-tetra-*O*-acetylglucopyranosyl)indole (III) was much more effective if 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was used rather than chloranil (*7*). No chromatographic purification of the reaction mixture was necessary with DDQ and the yield was materially increased from 32 to 79%. It was necessary to prevent premature precipitation of III in the separation of the substituted hydroquinone by-product. The hydroquinone was removed by filtering while the solution was still warm. Product III crystallized spontaneously upon cooling the filtrate slightly. It could then be filtered and recrystallized or the solvent could be removed in vacuo by water aspiration and the product crystallized from methanol.

The ultraviolet spectrum of product III showed the reported absorbence peaks at 222 and 264 mμ (*6*) as well as a smaller peak at 277 mμ and the typical indolic peak at approximately 289 mμ. This latter peak corresponds to an almost insignificant bathochromic shift from that of indole, which is usually shifted 5 to 10 mμ on *N*-substitution (*2, 3*).

Attempts were made to use benzene as a solvent to attach the ethyl acetate side chain to III; however, some material with the same R_f value was detected by thin-layer chromatography (TLC) during the formation of ethyl-1-(β-D-tetra-*O*-acetylglucopyranosyl-3-indoleacetate (IV). [Eastman sheet 6060 with fluorescent indicator was used for thin-layer chromatography of compounds II, III, and IV. Compounds V and VI were chromatographed on sodium acetate–buffered kieselguhr (*5*)]. The low intensity of the spot and proximity of the by-products discouraged the use of benzene. Xylene was then tested and found to afford a reasonable yield of IV in 8 to 12 hours when a 6- to 12-fold excess of ethyl diazoacetate was used. Considerable nonindolic by-product(s) in the form of a heterogeneous clear oil appeared under these conditions. It was readily separated by elution in the early chromatographic fractions. The fractions containing IV were yellow, but afforded a white product on recrystallization from methanol.

An infrared spectrum of IV showed that the carbonyl absorbence peak broadened toward the long-wavelength side, as would be expected of the substituted acetate of the side chain (*9*). Significant peaks attributable to the R—O—C(=O)— group were seen at 1190 and 1150 $cm.^{-1}$. The remainder of the spectrum was very similar to III.

Methanolic barium methoxide solution (*1*) was effective in deacetylating the glucose moiety of IV, but also catalyzed transesterification of the side chain ester. The methyl ester hydrolyzed in aqueous $Ba(OH)_2$ solution. One-step removal of both the acetate blocking groups and side chain ester could not be carried out in aqueous $Ba(OH)_2$, probably because of the insolubility of IV. (All melting points are uncorrected and were taken on a Fisher-Johns melting point block.)

EXPERIMENTAL

1-(β-D-Tetra-O-acetylglucopyranosyl)indoline (II). Three grams (0.025*M*) of indoline was made to react with 10.3 grams (0.025*M*) of tetra-*O*-acetyl-α-D-glucopyranosyl bromide in the presence of 2.6 grams (0.025*M*) of Na_2CO_3 at 0° C. Anhydrous ether was added to make a slurry and the mixture was stirred while it warmed to room temperature. The solution was then refluxed for 3 days. Water was added to the mixture and the product extracted twice with ether. The organic phase was washed twice with H_2O, dried with anhydrous $MgSO_4$, and evaporated to dryness in vacuo, and the product was crystallized from 95% ethanol. Thin-layer chromatography showed a single spot when treated with DMACA spray reagent which was red in color and moved at R_f 0.39 in 25% butanone-hexane. (The DMACA reagent was a 1% solution of 4-dimethylaminocinnamaldehyde in a 1 to 1 solution of 6*N* HCl and ethanol.) The yield was 7.38 grams (66%) [m.p. 117.8–18° C., lit. (*8*) m.p. 117.8–18.5° C.]

1-(β-D-Tetra-O-acetylglucopyranosyl)indole (III). 1-(β-D-Tetra-*O*-acetylglucopyranosyl)indoline (II) (7.35 grams) (0.0164*M*) was dehydrogenated with 3.72 grams (0.0164*M*) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in a solution of 150 ml. of xylene by refluxing for 6 hours. This solution soon lost the dark red-violet color and the substituted hydroquinone by-product precipitated. After the warm solution had been filtered the solvent was removed in vacuo and the residue crystallized from methanol as compound III. It migrated as one spot to an R_f value of 0.26 to 0.28 in 25% butanonehexane. The DMACA reagent slowly gave a blue color. Yield was 5.85 grams (79%) [m.p. 148–49.5° C., lit. (*6*) m.p. 148.5–49.5° C.].

Ethyl - 1 - (β-D-tetra-O-acetylglucopyranosyl) - 3 - indoleacetate (IV). A solution of 0.85 grams (0.00189*M*) of 1-(β-D-tetra-*O*-acetylglucopyranosyl)indole in 10 ml. of xylene was brought to reflux on a wax bath (Fisher Scientific Co.) and a catalytic amount of anhydrous cuprous chloride was added. To the refluxing solution was added dropwise a solution of 1.2 to 2.5 grams (0.0073 to 0.222*M*) of ethyl diazoacetate in 10 ml. of xylene. Addition was continued at a rate to allow slow evolution of the nitrogen gas which formed. When addition of ethyl diazoacetate was complete, the reaction mixture was allowed to reflux for 8 to 12 hours. The dark yellow solution was cooled and the solvent evaporated leaving an oil.

The product was purified by chromatography on a 3 (i.d.) × 4.5 inch column of silicic acid powder (Mallinckrodt 2844). Silicic acid was added to the crude oil along with acetone to make a slurry and the solvent was evaporated to yield a powder containing the product. This was placed on top of the adsorbent in the column and eluted with 30% butanone-hexane. Approximately 13 ml. of effluent per fraction was collected and the product was found in tubes 95 to 116. The eluates from tubes 96 to 106 were pooled because they gave the strongest indolic color spot on TLC plates with the DMACA reagent and evaporated in vacuo, and methanol was added. After distillation and readdition of methanol, the product crystallized when left for 3 hours at −15° C. Yield of crystalline material from tubes 96 to 106 was approximately 280 mg. An additional crop (115 mg.) could be obtained from the filtrate of the first crop and from the fractions following tube 106 by

addition of water. The R_f value was 0.20 to 0.23 in 25% butanone-hexane. The material slowly gave a magenta spot when sprayed with DMACA reagent.

The total yield was 395 mg. (40%) (m.p. 138–39° C.) Anal. Calcd. for $C_{26}H_{31}NO_{11}$: C, 58.53; H, 5.86; N, 2.63. Found: C, 58.19; H, 5.83; N, 2.87.

Methyl-1-(β-D-glucopyranosyl-3-indoleacetate (V). To an ice-cold solution of 250 mg. of ethyl-1-(β-tetra-*O*-acetylglucopyranosyl)-3-indoleacetate in 25 ml. of methanol was added 3.2 ml. of 0.04*N* $Ba(OCH_3)_2$ solution. The solution was allowed to stand for 24 hours at 5° C. Approximately 100 mg. of damp IR Amberlite resin was added and the mixture stirred for 1 hour and filtered. After evaporation and readdition of methanol, the product crystallized on standing at −5° C. for 1 to 2 days. The R_f was 0.15 in $HCCl_3$–ETOAc–HCO_2H(5:4:1 v./v.). A slowly developing magenta spot appeared when the material was treated with DMACA reagent. The yield was 110 mg. (67%) {m.p. 163–64°, $[\alpha]_D^{25} = -8.3°$ C. (c = 1.0, CH_3OH)}. Absorption spectra indicated $\lambda_{max(\mu)}^{KBr}$ 2.75 to 3.20 (OH), 5.83 (ester C=O), 8.10 to 8.55 (R—O—C(=O)—); $\lambda_{max(m\mu)}^{ethanol}$ (95%) 272, 279, and 290. Anal. Calcd. for $C_{17}H_{21}NO_7$: C, 58.11; H, 6.03; N, 3.99. Found: C, 57.73; H, 6.17; N, 3.96.

Saponification of the methyl ester with barium hydroxide gave an amorphous precipitate which could be separated from the starting material with preparative thin-layer chromatography, but resisted crystallization.

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Hydrogenation of Acetophenone Oxime and Its *O*-Acylated Derivatives

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The *O*-acetyl and *O*-benzoyl derivatives of acetophenone oxime give faster rates of hydrogenation and higher primary amine yields than the oxime itself in the presence of palladium and rhodium catalyst. Secondary amine formation was also examined and a technique for determining the possible intermediacy of Schiff bases in the hydrogenation of the oximes is proposed.

IN CONNECTION with the investigation of factors involved in the formation of primary and secondary amines in the hydrogenation of oximes, the reduction of acetophenone oxime and its *O*-acetyl and *O*-benzoyl derivatives was studied using palladium and rhodium catalysts.

EXPERIMENTAL

Acetophenone oxime was recrystallized from ethanol before use. The *O*-acetyl (*1*) and *O*-benzoyl (*3*) derivatives of acetophenone oxime and the Schiff base II, *N*-methylbenzylidene-α-methylbenzylamine (*4*), were prepared by known procedures. The solvents were analytical reagent grade.

The palladium and rhodium catalysts were commercial preparations manufactured by Engelhard Industries, Newark, N.J., of 5% reduced metal on carbon of high surface area (Norit).

The hydrogenations were carried out in a Parr low pressure hydrogenation apparatus at room temperature at an initial pressure of 50 p.s.i. In a typical run, 0.1 mole of the oxime or its derivative in 75 ml. of solvent was charged together with 5 grams of catalyst. After an essentially quantitative uptake of 0.2 mole of hydrogen, the catalyst was filtered off. Concentrated hydrochloric acid (16 ml.) was added to the filtrate and the solution evaporated to dryness. The amine hydrochlorides that formed were washed with ether, dried, and weighed. The salts were then treated with a 10% sodium hydroxide solution and the free amines extracted with ether. The ether layer was washed once with water and subjected to gas chromatographic analysis. The chromatography was carried out with an Aerograph Autoprep, Model A-700, using a 10-foot 30% Carbowax 20M on 60/80 Chromosorb W column at 220°. To this ether layer was again added concentrated hydrochloric acid (16 ml.) and the mixture evaporated to dryness to yield approximately the same weight of amine hydrochlorides as originally isolated. These hydrochlorides when converted again to the free amines with base gave the same ratios of primary to secondary amine and of *d,l*- to *meso*-secondary amine, indicating that no losses were encountered in our original workup procedure.