white solid obtained was dried at 100° *in vacuo* over $P_2O_5$.

*Anal.*—Calcd. as for above. Found: C, 42.08; H, 5.59; N, 7.00.

**1 - (Penta-O-benzoyl - D - glycero - D - gulo-heptopyranosyl)uracil**—To 19 ml. of dry pyridine was added 88.6 mg. of 1-D-*glycero*-D-*gulo*-heptopyranosyluracil and the mixture was stirred in an ice bath. Benzoyl chloride (2 ml.) was added dropwise and after 0.5 hr. at 0° the mixture was stored at room temperature for 21 hr. It was then heated on a steam bath for 20 min., cooled, 50 ml. of benzene was added, followed shortly thereafter by 50 ml. of water. The mixture was stirred for several minutes and the layers were separated. The benzene solution was washed three times with 50-ml. portions of 2 *N* sulfuric acid solution, once with 50 ml. of water, 4 times with 50-ml. portions of saturated sodium bicarbonate solution, and finally with 50 ml. of water. The dried ($MgSO_4$) solution was evaporated to a thin, orange oil. This was triturated with hot petroleum ether and cooled in an ice bath for 1 hr. The petroleum ether was decanted and the procedure was repeated. A hard syrup remained which was dissolved in warm methanol and placed in a freezer. A solid was filtered off in two crops (203 mg.). Recrystallization from chloroform–ethanol in an open flask at room temperature yielded beautiful, clear, star-like clusters of large rods, 117 mg. in two crops; m.p. 123–124.5° (to a very viscous liquid) with prior softening at 119°. $[\alpha]_D^{28}$° −55.9° (c 2.81, $CHCl_3$). $\lambda_{max}^{film}$ (cm.$^{-1}$) 1730 (benzoate ester), 1680 (—NHCO— of pyrimidinone), 1600 (C=C of phenyl and pyrimidine ring), 1260 (benzoate C—O—C), 1100, 1090, 1065 (sugar C—O—), 706 (monosubstituted phenyl). The product was homogeneous on TLC. The $R_f$ was 0.84 using chloroform–methanol (9:1) as the irrigating solvent.

*Anal.*—Calcd. for $C_{46}H_{36}N_2O_8$: C, 66.99; H, 4.40; N, 3.40. Found: C, 67.02; H, 4.48; N, 3.37.


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*Keyphrases*

D-*Glycero*-D-*gulo*-heptose derivatives—synthesis
Nucleosides—D-*glycero*-D-*gulo* heptose derivatives
TLC—separation
Column chromatography—separation
UV spectrophotometry—identity
Optical rotation—identity


# New Compounds: Synthesis of Heterocyclic Estrogens

By LARRY GORUM* and W. LEWIS NOBLES

**Several nitrogen analogs of diethylstilbestrol have been prepared by a convenient route from pyridyl lithium and the appropriate ketone. These compounds are expected to have estrogenic activity with possible greater selectivity of action than previous known synthetic estrogens.**

THE INVESTIGATIONS of Dodds and co-workers (1) on synthetic compounds possessing the physiological action of the female sex hormone estrone reached a climax with the discovery of diethylstilbestrol (1). Since that time much work with molecular modification has been done in an effort to improve the selectivity of pharmacological action in the therapeutic uses of diethylstilbestrol. Endocrine therapy in metastatic prostatic cancer consists initially of estrogen therapy as first demonstrated by the pioneering investigation of Huggins (2). Oral estrogen preparations such as diethylstilbestrol are effective to a limited extent but elicit side effects such as nausea, gynecomastea, and edema. Because of these undesirable side effects it is necessary to find new compounds which possess a more selective estrogenic action.

Many compounds of this type have been prepared and tested and are described in a review by Grundy (3). However, thus far none of the compounds tested offered sufficient selective antineoplastic activity to replace diethylstilbestrol in the clinic. In the hundreds of compounds reported, several contain

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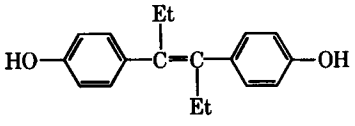
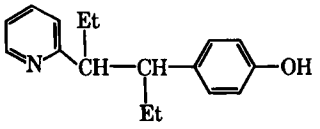
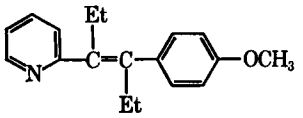
heterocyclic atoms but none in an aromatic arrangement such as pyridine which might incorporate greater antineoplastic specificity in an analog of diethylstilbestrol such as 3-(2-pyridyl)-4-(*p*-hydroxyphenyl)-hexane (II), and 3-(2-pyridyl)-4-(*p*-methoxyphenyl)-3-hexene (III). This report describes the synthesis of II and III by a convenient route.



I



II



III

## DISCUSSION

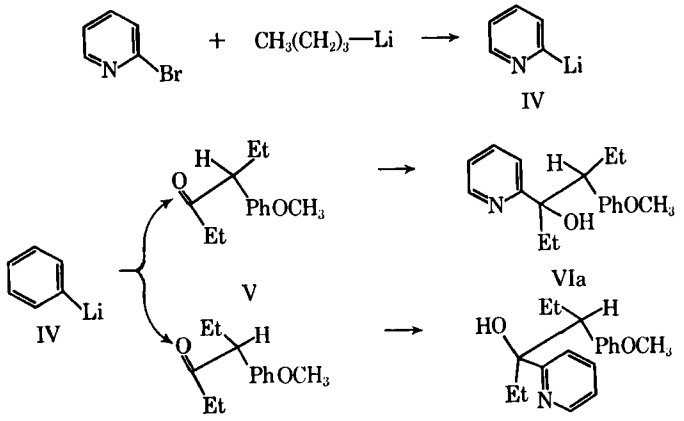
This preparation involved a synthetic route employing 2-pyridyl lithium (IV) and 3-(*p*-anisyl)-4-hexanone (V) in a Grignard-type reaction. A racemic mixture of the resultant alcohol VI*a* and VI*b* was predicted by invoking Cram's rule of asymmetric synthesis (4). This rule states that the asymmetric carbon in the starting ketone is so oriented that the carbonyl function is flanked by the two smaller groups and subsequent attack by the Grignard reagent on the carbonyl carbon occurs over the smallest group.

Unexpected difficulty with the dehydration of the resultant alcohol (VI), necessitated a dehydrohalogenation approach to the olefin (VII). This was accomplished by chlorination with thionyl chloride with subsequent elimination of hydrogen chloride with potassium hydroxide to afford 3-(2-pyridyl)-4-(*p*-methoxyphenyl)-3-hexene (III). Assurance that the reaction afforded the *trans* olefin has strong support from studies by Cram and Greene (5). Reduction of the olefin using 15% palladium on carbon resulted in a good yield of the desired 3-(2-pyridyl)-4-(*p*-methoxyphenyl)-hexane (VIII). Extensive work on similar systems by Wessely (6) demonstrated that a *d, l* pair of *threo* form enantiomers represented by structure VIII resulted from *cis* addition of hydrogen to the olefin (III).

Demethylation of VIII with a mixture of hypophosphoric acid and hydrobromic acid resulted in 3-(2-pyridyl)-4-(*p*-hydroxyphenyl)-hexane(IX). The phenol (IX) was a very hygroscopic solid foam and was converted to $\alpha$, $\beta$-diethyl-4'-benzoyloxydihydro-2-stilbazole hydrochloride (X), which was a white powder suitable for instrumentation studies for structure analysis.

## EXPERIMENTAL[1]

**3-(2-Pyridyl)-4-(p-methoxyphenyl)-3-hexanol (VI)**—A modification of the procedure of Woodward (7) was followed. To a solution of 30 ml. (0.1 mole) of *n*-butyl lithium in 100 ml. of dry ether in a nitrogen atmosphere and dry ice acetone bath was added dropwise a dry ethereal solution of 20 Gm. (0.12 mole) of 2-bromopyridine. After the addition was complete, the mixture was allowed to stir 30 min. at −40° and 10 Gm. (0.1 mole) of 3-(*p*-anisyl)-4-hexanone was added dropwise over a 15-min. period. The reaction mixture developed a dark rust color and was stirred for an additional hr. at −40°. Stirring was continued until the reaction mixture attained room temperature. The dark mixture was then allowed to sit overnight followed by filtration and washing with three 100-ml. portions of water. The early filtration facilitated work-up of the reaction by removing much of the dark reaction



IV

V

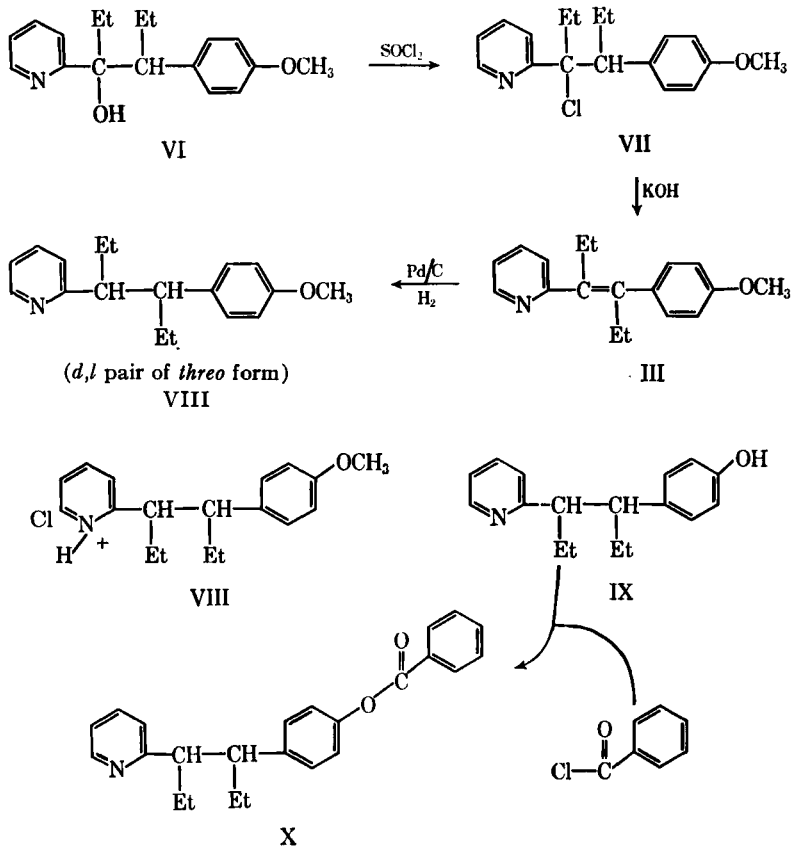
Racemic mixture of starting ketone

VIa

VIb

Racemic mixture of resultant alcohol $PhOCH_3$-*p*-methoxyphenyl

[1] All melting points were taken on a Thomas-Hoover Uni-melt apparatus and are corrected. The NMR spectra were taken using a Varian model A60-A instrument. The elemental analyses were determined by Dr. Alfred Bernhardt, 433 Mulheim (Ruhr), West Germany and Dr. Paul N. Craig, Smith Kline & French Laboratories, Philadelphia, Pennsylvania. The NMR spectra were measured at 60 Mc., and the chemical shifts are reported as $\tau$-values (p.p.m.) from tetramethylsilane (internal standard). The multiplicity is shown by *s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, and *m* = incompletely resolved multiplet.




by-products. The ether phase was then evaporated *in vacuo* to leave a dark residue which was refluxed in water until crystallization occurred. The water was then decanted off and the solid recrystallized three times from ethanol to yield 7.1 Gm. (40%) of the desired alcohol m.p. 94–95°. The hydrochloride of this compound was prepared by dissolving the free base in anhydrous ether and bubbling dry HCl gas through the solution until precipitation was complete. The precipitate, collected by filtration, had a m.p. of 204–205°.

The infrared spectrum of the free base had hydroxyl group absorption at 3500 cm.$^{-1}$.

*Anal.*—Calcd. for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.92; H, 8.32; N, 5.08.

The NMR spectrum in carbon tetrachloride was $\delta$ = 4.79 (*s*, indicated to be OH, the peak disappeared on $D_2O$ exchange), 0.5 (*q*, C—$CH_3$, 6H), 1.4 (*t*, C—$CH_2$, 3H), 7.00 (*q*, 2,3,5, and 6H of phenyl ring, 4H), 8.66 (*d*, 3, 4, 5, and 6H of pyridyl ring, 4H).

**3 - (2 - Pyridyl) - 4 - (p - methoxyphenyl) - 3-hexene Hydrochloride (III)**—Modifications of procedures by Hall (8) and Smith (9) were followed. To 1.0 Gm. (3.5 mmoles) of 3-(2-pyridyl)-4-(*p*-methoxyphenyl)-3-hexanol in a three-necked flask equipped with a stirrer, reflux condenser with calcium chloride tube, and dropping funnel in an ice bath was added dropwise 10 ml. of thionyl chloride. After the addition was complete, the solution was allowed to reach room temperature gradually and then heated to a gentle reflux for an additional hr. The cooled solution was then added slowly, under the hood, to 100 ml. of ethanol cooled in an ice bath in order to decompose the unreacted thionyl chloride. This solution was then evaporated to dryness *in vacuo* to leave a light red oil that was then dissolved in 25 ml. of ethanol. This solution was added dropwise to a cooled 25-ml. solution of 15% KOH in ethanol while the temperature was maintained at less than 50°. After addition was complete, stirring was continued for 4 hr. and the solution was allowed to stand overnight. Addition of water and evaporation *in vacuo* resulted in a light yellow oil which was extracted with three 50-ml. portions of ether. The ether extracts were dried over anhydrous magnesium sulfate and dry HCl gas bubbled through the solution to result in precipitation of a light oil. The oil was dissolved in hot ethyl acetate and refluxed until the oil crystallized into a light yellow solid. After recrystallization twice with ethyl acetate, 0.5 Gm. (42%) of the hydrochloride of the desired olefin resulted as a white powder, m.p. 146–147°. The product gave a positive $Br_2/CHCl_3$ test for an olefin.

*Anal.*—Calcd. for $C_{18}H_{23}ClNO$: C, 70.93; H, 7.60; Cl, 11.63; N,4.59. Found: C, 70.77; H, 7.40; Cl, 11.77; N, 4.34.

The NMR spectrum in deuterated chloroform was $\delta$ = 0.83 (*m*, C—$CH_3$, 6H), 1.65 (*q*,—$CH_2$—, 4H), 3.65 (*s*, O—$CH_3$, 3H), 6.00 (*s*, H of hydrochloride, 1H), 6.75 (*m*, 2,3,5, and 6H of phenyl ring, 4H), 8.81 (*m*, 3,4,5, and 6H of pyridyl ring, 4H).

**3 - (2 - Pyridyl) - 4 - (p-methoxyphenyl) - hexane Hydrochloride (VIII)**—A modification of the procedure by Horning (10) was followed. To 4.0 Gm. (0.014 mole) of 3-(2-pyridyl)-4-(*p*-methoxyphenyl)-3-hexene hydrochloride in 50 ml. of ethanol was

added 0.2 Gm. of 10% palladium on carbon. This mixture was then allowed to shake on a Parr hydrogenation apparatus under 45 p.s.i. of hydrogen for 48 hr. and then gravity filtered. The solution was then evaporated to dryness *in vacuo* and the residue was taken up in anhydrous ether. The ether solution was dried over anhydrous magnesium sulfate and then saturated with dry HCl gas which yielded a light yellow oil. After prolonged refluxing with ethyl acetate, the yellow oil crystallized into a light yellow solid which was collected by filtration and recrystallized twice from ethyl acetate to result in 2.59 Gm. (57%) of the desired compound, m.p. 154–155°. This product gave a negative $Br_2/CHCl_3$ test for an olefin.

*Anal.*—Calcd. for $C_{18}H_{24}ClNO$: C, 70.69; H, 7.91; Cl, 11.59; N, 4.59. Found: C, 71.69; H, 7.33; Cl, 11.63; N, 4.34.

The NMR spectrum in deuterated chloroform was $\delta$ = 0.85 (*m*, —C—$CH_3$, 6H), 1.71 (*d*, —$CH_2$—, 4H), 3.71 (*s*, O—$CH_3$, 3H), 6.00 (*m*, —CH—, 2H), 6.25 (*s*, H of hydrochloride, 1H), 7.00 (*m*, 2,3,5, and 6H of phenyl ring, 4H), 8.81 (*m*, 3,4,5, and 6H of pyridyl ring, 4H).

**$\alpha,\beta$ - Diethyl - 4′ - benzoyloxydihydro - 2 - stilbazole Hydrochloride (X)**—A modification of the demethylation procedure reported by Franck and Schlinghoff (11) was followed. While maintaining an atmosphere of nitrogen, 20 ml. of a mixture of hydrobromic acid and hypophosphorous acid (prepared from 0.5 Gm. of 50% hypophosphorous acid and 50 Gm. of 48.5% hydrobromic acid) was added to 1.0 Gm. of the 3-(2-pyridyl)-4-(*p*-methoxyphenyl)-hexane hydrochloride. The mixture was heated on an oil bath at 125–130° for 8 hr. and then gradually cooled to 0°. To the cold solution was added 15 ml. of ammonium hydroxide which resulted in separation of a light green oil. The oil was extracted with two 25-ml. portions of ether and the ether extracts dried over magnesium sulfate and evaporated to dryness *in vacuo* to yield a clear solid form unsuitable for purification for analysis. Preparation of the hydrochloride resulted in a similar problem. The free base was then dissolved in 15 ml. of benzoyl chloride and allowed to reflux for 2 hr. The solution was then poured into water and made basic with 10% sodium carbonate and stirred for 2 hr. before extracting the solution with three 50-ml. portions of ether. The ether extracts were dried over magnesium sulfate and dry hydrogen chloride gas bubbled through the solution until saturation was complete. The light yellow oil that separated was allowed to reflux in ethyl acetate for several minutes causing the solid hydrochloride product to precipitate as a white powder. The powder was collected by filtration and recrystallized twice from ethyl acetate and ethanol solution to yield 0.5 Gm. (36%) m.p. 187–188°.

The infrared spectrum showed carbonyl absorption at 1740 $cm.^{-1}$.

*Anal.*—Calcd. for $C_{24}H_{26}ClNO_2$: C, 72.81; H, 6.62; Cl, 8.96; N, 3.53. Found: C, 72.29; H, 6.00; Cl, 8.88; N, 3.54.

The NMR spectrum in deuterated chloroform was $\delta$ = 1.0 (*m*, C—$CH_3$, 6H), 1.8 (*m*, —$CH_2$—, 4H), 7.2 (*m*, phenyl protons, 9H), 8.5 (protons of pyridine ring, 4H). The spectrum did not show absorption at $\delta$ = 3.65 due to methoxy group.

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**Keyphrases**

Estrogens, heterocyclic—synthetic
Diethylstilbestrol analogs—synthesis
IR spectrophotometry—structure
NMR spectrometry—structure