

hydrazide (VI) was obtained as plates in 79% yield, m.p. 166–167° (lit.<sup>15</sup> m.p. 165–167°).

**B.**—To 10.4 g. of benzyloxycarbonylglycine (0.05 mole) and 12.7 g. of N-ethyl-5-phenylisoxazolium-3'-sulfonate<sup>10</sup> (0.05 mole) suspended in 200 ml. acetonitrile was added 7.0 ml. of triethylamine (0.05 mole). After being stirred at room temperature for 30 min. the solution became homogeneous, and 4.6 g. of glycyldiazide<sup>18</sup> (prepared by treatment of ethyl glycinate hydrochloride with hydrazine or by hydrogenation of benzyloxycarbonylglycylhydrazide) was added in one portion. Precipitation of the product occurred after 15 min., and the suspension was stirred at room temperature overnight. On filtration and crystallization from methanol, benzyloxycarbonylglycylglycylhydrazide (VI) was obtained as plates (8.6 g., 62%), m.p. 166–167°, identical (mixture melting point and infrared spectra) with an authentic sample (see above). The mother liquors on working up did not yield any more VI.

*Anal.* Calcd. for C<sub>12</sub>H<sub>16</sub>N<sub>4</sub>O<sub>4</sub>: C, 51.4; H, 5.75; N, 20.0. Found: C, 51.3; H, 5.8; N, 20.2.

**Oxidation of Benzyloxycarbonylglycylglycylhydrazide (VI).**—The hydrazide (97 mg.) was added during 10 min. to a solution of 123 mg. of N-bromosuccinimide (2 molar equiv.) in water. Benzyloxycarbonylglycylglycine (VII) (68 mg., 74%) was obtained on cooling and filtration. Recrystallized from methanol, it had m.p. 181–181.5 (lit.<sup>17</sup> m.p. 178–179°).

**Oxidation of Benzyloxycarbonylglycylhydrazide.**—This reaction was carried out under two conditions.

**A.**—When carried out as in the previously described reaction, benzyloxycarbonylglycine was obtained as the sole product.

**B.**—To 890 mg. of benzyloxycarbonylglycylhydrazide in 150 ml. of water was added, in small portions with vigorous stirring, N-bromosuccinimide during 15 min. until a yellow color was generated. The weight of N-bromosuccinimide required was 1.11 g. (1.56 molar equiv.). The solid precipitated during the reaction was filtered and crystallized from ethanol to give small needles of 1,2-bis(benzyloxycarbonylglycyl)hydrazine (180 mg.), m.p. 217–219° (lit.<sup>4</sup> m.p. 211–212°).

*Anal.* Calcd. for C<sub>20</sub>H<sub>22</sub>N<sub>4</sub>O<sub>6</sub>: C, 57.95; H, 5.35. Found: C, 57.85; H, 5.6.

Concentration of the filtrate gave needles of benzyloxycarbonylglycine (180 mg.).

**Benzyloxycarbonyl-L-alanylglycylglycylhydrazide (XII).**—To 2 g. of benzyloxycarbonyl-L-alanine and 12.7 g. N-ethyl-5-phenylisoxazolium-3'-sulfonate<sup>10</sup> suspended in 100 ml. of acetonitrile was added with cooling 7.0 ml. of triethylamine. When the solution became homogeneous a solution of glycyldiazide (XI) (prepared by hydrogenation of 14.5 g. of benzyloxycarbonylglycylglycylhydrazide in methanol over palladium-charcoal) in 20 ml. of absolute ethanol was added with cooling and stirring. Precipitation of the product occurred at once. Acetonitrile (70 ml.) was added, and the solution was stirred at room temperature overnight. On filtration and crystallization of the solid from ethanol there was obtained 11.0 g. (63%) of small prisms of benzyloxycarbonyl-L-alanylglycylglycylhydrazide (XII) m.p. 200–202°, [ $\alpha$ ]<sub>D</sub><sup>25</sup> –8° (c 0.24, methanol).

*Anal.* Calcd. for C<sub>15</sub>H<sub>21</sub>N<sub>3</sub>O<sub>5</sub>: C, 51.3; H, 6.0; N, 19.9. Found: C, 51.0; H, 6.1; N, 20.1.

(15) K. D. Kopple and R. J. Renick, *J. Org. Chem.*, **23**, 1565 (1958).

(16) T. Curtius and L. Levy, *J. prakt. Chem.*, **70**, 89 (1904).

(17) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. II, John Wiley and Sons, New York, N. Y., 1961, p. 1170.

## Equilenin 3-Benzyl Ether

W. M. HOEHN,<sup>1</sup> CLIFFORD R. DORN,  
AND BERNARD A. NELSON

Division of Chemical Research, G. D. Searle and Company,  
Chicago, Illinois 60680

Received August 14, 1964

Several methods for the preparation of equilenin and some of its derivatives have been described.<sup>2</sup> The

(1) To whom communications concerning this paper should be addressed.

selenium dioxide dehydrogenation of 6-dehydroestrone derivatives described by Djerassi and his co-workers,<sup>2a,b</sup> when used by us, has not given the anticipated yield of equilenin derivatives relatively free of selenium. A modification of their procedures has overcome these objections. 6-Dehydroestrone 3-benzyl ether was dehydrogenated with selenium dioxide in acetic acid, zinc dust was added, and the mixture was heated at 90–100° for 1 hr. Equilenin 3-benzyl ether was isolated from this mixture and was readily purified. Hydrogenolysis removed the benzyl group to yield equilenin.

## Experimental

The authors are indebted to Dr. R. T. Dillon and his staff of the analytical division for the analytical data in this paper. Rotations were taken in chloroform at about 1% concentrations at 25 ± 2° unless otherwise stated, and the ultraviolet spectra were observed in methyl alcohol. The n.m.r. spectrum was determined at 60 Mc, in deuteriodimethyl sulfoxide as the solvent and the value reported was in cycles per second as shifts downfield from tetramethylsilane as an internal standard.

**6-Dehydroestrone 3-Benzyl Ether.**—A mixture of 10 g. (0.037 mole) of 6-dehydroestrone,<sup>2a</sup> 27.5 g. (0.219 mole) of benzyl chloride, 25 g. (0.252 mole) of anhydrous potassium carbonate, and 550 ml. of ethyl alcohol (2B anhydrous) was stirred at reflux for 1.5 hr. The mixture was cooled, diluted with 1 l. of water, and extracted with 1.5 l. of methylene chloride. The extract was washed with 400 ml. of 10% aqueous sodium hydroxide solution, dried over anhydrous sodium sulfate, and filtered; the solvent was removed. Trituration with methyl alcohol (500 ml.) followed by filtration and washing of the solid with methyl alcohol yielded 9.8 g. of crude product, m.p. 135–145°, and 9.3 g. of 6-dehydroestrone 3-benzyl ether (crystallized from methylene chloride–methyl alcohol): m.p. 124–145°, [ $\alpha$ ]<sub>D</sub><sup>25</sup> –104°,  $\lambda_{\max}$  262 m $\mu$  ( $\epsilon$  8600) and 272 m $\mu$  ( $\epsilon$  7900),  $\lambda_{\max}^{\text{CHCl}_3}$  5.75  $\mu$  (C=O).

*Anal.* Calcd. for C<sub>25</sub>H<sub>26</sub>O<sub>2</sub>: C, 83.76; H, 7.31. Found: C, 83.77; H, 7.40.

**Equilenin 3-Benzyl Ether.**—To a stirred solution of 49 g. (0.136 mole) of 6-dehydroestrone 3-benzyl ether in 950 ml. of hot (90°) acetic acid was added 8.8 g. (0.067 mole) of selenic acid. The mixture was stirred rapidly and heated to 100–110° for 70 min., and cooled to 80°; 65 g. (1.0 mole) of zinc dust was added. The mixture was stirred and heated to 90–100° for 1 hr., and filtered hot; the filter cake was washed with 200 ml. of hot acetic acid. The filtrate was cooled overnight at room temperature and filtered, the orange leaf crystals were washed with methyl alcohol, and the product was air dried to yield 29 g. of crude equilenin 3-benzyl ether, m.p. 168–177°. Crystallization from methylene chloride–methyl alcohol gave 19 g.: m.p. 178–180°; [ $\alpha$ ]<sub>D</sub><sup>25</sup> +53°;  $\lambda_{\max}$  233 m $\mu$  ( $\epsilon$  61,200), 267 (5700), 278 (5300), 289 (3300), 321 (1600), and 336 (2050);  $\lambda_{\max}^{\text{KBr}}$  5.72  $\mu$  (C=O), 6.15  $\mu$  (C=C), and 6.23  $\mu$  (C=C).

*Anal.* Calcd. for C<sub>25</sub>H<sub>24</sub>O<sub>2</sub>: C, 84.24; H, 6.79. Found: C, 84.06; H, 6.74.

A second crop 6.5 g., m.p. 165–178° (85% purity from ultraviolet absorption data), was isolated from the mother liquor.

**Equilenin.**—Equilenin 3-benzyl ether (10 g., 0.028 mole) in 500 ml. of tetrahydrofuran was hydrogenated<sup>3</sup> at room temperature and 1-atm. pressure for 6.5 hr. in the presence of 1.0 g. of Pd-C (5%). The catalyst was removed by filtration, the filtrate was evaporated to dryness *in vacuo*, and the residue was crystallized from 400 ml. of methyl alcohol to yield 6.0 g. (in 2 crops): m.p. 254–256°; [ $\alpha$ ]<sub>D</sub><sup>25</sup> +90.5° (c 1.009, dioxane);  $\lambda_{\max}$  229 m $\mu$  ( $\epsilon$  62,400), 269 (4550), 280 (5250), 291 (3700), 326 (2000), and 340 (2400); n.m.r. 4.0 c.p.s. (CH<sub>2</sub>);  $\lambda_{\max}^{\text{KBr}}$  3.05  $\mu$  (OH), 5.82  $\mu$  (C=O), and 6.17 and 6.25  $\mu$  (C=C).

*Anal.* Calcd. for C<sub>18</sub>H<sub>18</sub>O<sub>2</sub>: C, 81.17; H, 6.81. Found: C, 81.22; H, 6.91.

The compound was identical with a sample prepared according to the method of Djerassi and co-workers.

(2) (a) St. Kaufmann, J. Pataki, G. Rosenkranz, J. Romo, and C. Djerassi, *J. Am. Chem. Soc.*, **72**, 4531 (1950); (b) C. Djerassi, G. Rosenkranz, J. Romo, St. Kaufmann, and J. Pataki, *ibid.*, **72**, 4534 (1950); (c) for other references, see M. Heller, R. H. Lenhard, and S. Bernstein, *ibid.*, **86**, 2309 (1964).

(3) The hydrogenation was carried out by Mr. J. D. Choi of G. D. Searle and Co.