subject.) Spindle stage examination of crystals followed that described previously (8, 11).

RESULTS AND DISCUSSION

Preliminary orthoscopic examination revealed that the lath-shaped crystals (Fig. 1) exhibited a single plane of optical symmetry from which a single β refractive index value could be obtained. The crystals were quite thin, and most grains lay on the 100 orthopinacoid.

To obtain β and γ refractive index values, the crystals were mounted (Fig. 2) onto a spindle stage. The crystals were rotated on their b-axis to orientations that presented the principal vibration directions, and refractive index values were determined by immersion in various fluids.

Crystals could not be oriented to provide a 010 end view, and therefore, a β-angle could not be observed or measured microscopically. Subsequent data reported from X-ray diffraction methods gave a value of 96°. An orthographic projection of a typical crystal of I is shown in Fig. 3, and Table I presents the optical properties.

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Synthesis of Dehydroepiandrosterone Sulfatide and 16α-Halogenated Steroids

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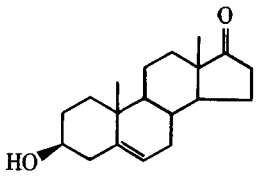
Received December 8, 1980, from the *Fels Research Institute and Department of Chemistry, Temple University, Philadelphia, PA 19122.* Accepted for publication March 5, 1981.

Abstract □ Dehydroepiandrosterone sulfatide was prepared in a 68% yield by the reaction of 5-androstene-3β-ol-17-one 3-sulfate (silver salt) with dipalmitoyl α-iodopropylene glycol. The sulfatide was found to be a more potent inhibitor of human glucose-6-phosphate dehydrogenase than dehydroepiandrosterone. 16α-Halogenated steroids also were prepared by direct halogenation of the steroid or indirect halogenation of an appropriate steroidal intermediate. Among various halogenated steroids, 16α-bromoepiandrosterone was ~50 times as potent as dehydroepiandrosterone as an inhibitor of glucose-6-phosphate dehydrogenase.

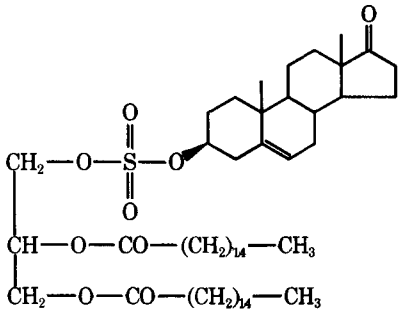
Keyphrases □ Dehydroepiandrosterone sulfatide—synthesis, tested as glucose-6-phosphate dehydrogenase inhibitor □ 16α-Halogenated derivatives of epiandrosterone—synthesis, tested as glucose-6-phosphate dehydrogenase inhibitors □ Glucose-6-phosphate dehydrogenase—synthesis of dehydroepiandrosterone sulfatide and 16α-halogenated steroids

Of the naturally occurring steroids that had been tested, dehydroepiandrosterone (I) proved to be an outstanding noncompetitive inhibitor of glucose-6-phosphate dehydrogenase (1, 2). The sulfated form of I (Ia) is a major adrenal secretory product in humans. Approximately 99% of the plasma form of this steroid is sulfated, while the remainder is unconjugated steroid. The plasma concentration of the sulfated form of I exceeds that of any other steroidal hormone, yet its biological role is unknown. (Most investigators refer to the conjugated form as the sulfate.)

According to Oertel and coworkers (3, 4), the sulfated form of the hormone found in human plasma is I-sulfatide (II), the ester of sulfatidic acid, which must be isolated under extremely mild conditions because of its lability. In



I



II

the search for analogs of considerably higher potency than I or II in inhibiting glucose-6-phosphate dehydrogenase to diminish or eliminate undesirable side effects of high dosage dehydroepiandrosterone therapy, the sulfatide (II) and 16α-halogenated derivatives of epiandrosterone were synthesized.

RESULTS AND DISCUSSION

Dipalmitoyl-L-α-iodopropylene glycol (III) was prepared in an 80% yield by facile acylation of L-α-iodopropylene glycol with two equivalents

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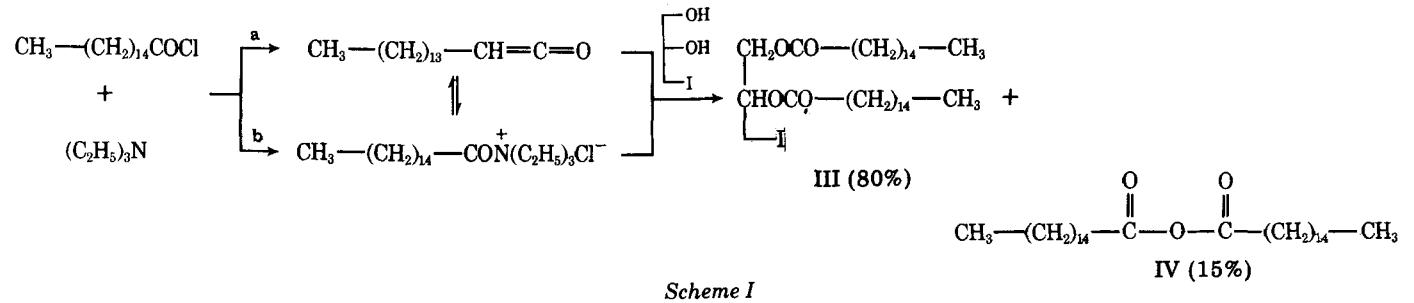


Scheme I

of palmitoyl chloride in the presence of triethylamine (Scheme I). Reaction of carboxylic acid halides in the presence of triethylamine has been found (5, 6) to involve two pathways, an elimination pathway (a) involving a ketene intermediate and a substitution route (b) involving an acyl ammonium salt intermediate. The product palmitic anhydride (IV) also was isolated in a 15% yield. When quinoline was used instead of triethylamine, as suggested in the literature (7), only 67% of the diglyceride, in addition to 25% of palmitic acid, was formed after a reaction time of 7 days.

Dehydroepiandrosterone sulfatide (II) was then prepared in a 68% yield by alkylation of the sulfate (silver salt) (I*b*) with the iododiglyceride (III) in dry benzene (Scheme II). The sulfatide (II) was found to be a more potent inhibitor of human glucose-6-phosphate dehydrogenase than I*a* itself. It is a labile material and decomposes readily within a few days, even at −5°, to the sulfate with loss of biological activity.

The fact that α-substitution at the C-16-position enhances biological activity of certain steroids, coupled with the intention to find more potent and stable compounds, led to the preparation of 16α-halo derivatives of epiandrosterone (8–10). 16α-Chloro, bromo, and fluoro derivatives were prepared from epiandrosterone according to reaction sequence shown in Scheme III.

Treatment of epiandrosterone with isoamyl nitrite in basic medium afforded 16-oximino-17-ketone (V). The observed melting point, 218–219°, does not agree with the value of 245–247° reported by Mateos *et al.* (11) but is in agreement with that reported earlier by Huffman and Lott (12). IR spectra and elemental analyses of V were consistent with the structure shown.

Treatment of V with sodium hydroxide, ammonia, and sodium hypochlorite (11, 13–15) yielded the yellow 16-diazo compound (VI), which, upon treatment with the appropriate hydrogen halide (hydrochloric, hydrobromic, and hydrofluoric acids) afforded the corresponding colorless 16α-halo derivative. Hydriodic acid, however, reduced the diazo compound to epiandrosterone. The 16α-configuration was established by comparing the melting points of the products with those reported in the literature (16–20) and by independent synthesis.

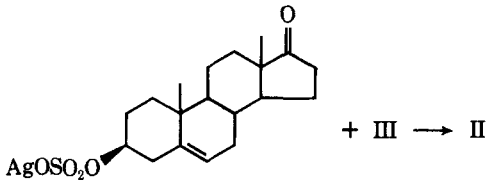
The 16α-fluoro derivative was also prepared (but in only a 28% yield) by a halogen-exchange technique by refluxing the corresponding bromo derivative (VII*a*) with five equivalents of anhydrous silver fluoride in toluene–isopropanol for 48 hr. The 16α-bromo derivative (VII*a*) was independently prepared in a 60% yield by refluxing epiandrosterone with cupric bromide in methanol for 24 hr (17).

The 16α-iodo derivative (VII*d*) was prepared by direct iodination of the enol diacetate (VIII) with iodine in the presence of mercuric acetate or with *N*-iodosuccinimide, followed by hydrolysis of the 3β-acetoxy derivative (IX) with concentrated hydrochloric acid (Scheme IV). Overall yields of VIII to VII*d* were 89%.

16α-Iodo steroids were first synthesized in 1973 *via* the 17-bromo-16,17-epoxy derivative or by a halogen-exchange procedure (16). The current procedure is more convenient since the starting materials are commercially available and yields are higher.

Contrary to expectation, VII*a* was the most active halogenated derivative of the four; it is ~50 times as active as dehydroepiandrosterone in inhibiting glucose-6-phosphate dehydrogenase in mouse and human red blood cells. Compound VII*a* is also ~50 times as active in antagonizing the *O*-tetradecanoylphorbol acetate-induced stimulation in the rate of DNA synthesis in mouse skin. A dose of 0.4 mg/kg ip of VII*a* is about as active as 20 mg of dehydroepiandrosterone/kg.

Compounds VII*b* and VII*d* were less active than VII*a*; VII*c* was inactive.



Ib

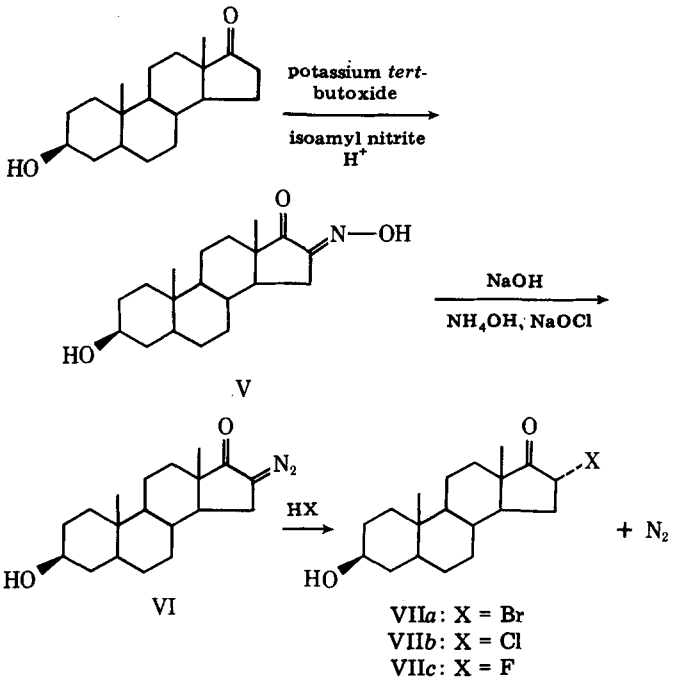
Scheme II

EXPERIMENTAL[1]

Dipalmitoyl-L-α-iodopropylene Glycol (III)—All apparatus was flame dried; strictly dry conditions were used throughout the study. To a stirred solution of dry, redistilled triethylamine (3.64 ml, 26 mmoles) and L-α-iodopropylene glycol (2.7 g, 13.5 mmoles) in dry chloroform (15 ml) at 0°, a solution of palmitoyl chloride (7.42 g, 26 mmoles) in *n*-pentane (50 ml) was added dropwise. The reaction mixture was then stirred for 3 hr at 0°, and the precipitated triethylamine hydrochloride was removed by filtration. The solvent was evaporated from the filtrate under reduced pressure, and the residual solid was digested with hot absolute methanol. The insoluble material was filtered and recrystallized from acetone to afford 1.92 g (15% yield) of the by-product palmitic anhydride (IV), mp 61–63°; IR (KBr): ν_{max} 1745 and 1800 cm^{-1} [–C(=O)–O–(C=O)–].

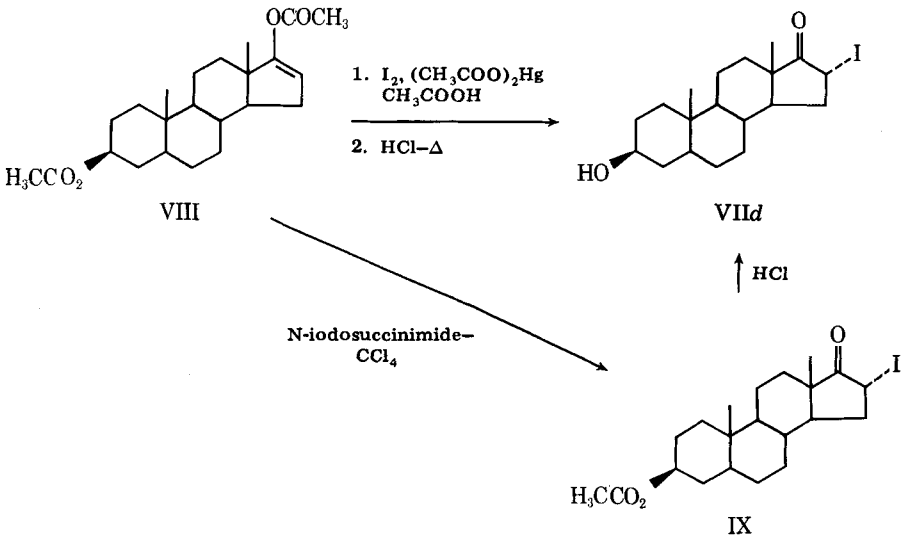
The hot methanol filtrate was cooled, and the solid that precipitated was separated by filtration and recrystallized from petroleum ether (bp 30–60°)–methanol (1:1) to afford 7.4 g (80% yield) of the diglyceride (III), mp 46–48°; IR (KBr): ν_{max} 1730 and 1745 cm^{-1} [–O–C(=O)–]; ^{1}H-NMR ($CDCl_3$): δ 0.65–1.10 (t, 6H), 1.1–2.00 (m, 52H), 2.20–2.45 (m, 4H), 3.30 (d, 2H), 4.2–4.35 (d, 2H), and 4.9–5.2 (q, 1H).

Anal.—Calc. for $C_{35}H_{67}IO_4$: C, 61.92; H, 9.94; I, 18.69. Found: C, 61.96; H, 10.04; I, 18.58.



Scheme III

[1] Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. IR spectra were recorded on a Unicam SP-1000 spectrophotometer. The ^{1}H-NMR spectra were determined using an XL-100 instrument and tetramethylsilane as the internal standard. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.



Scheme IV

Replacement of triethylamine by quinoline was unsatisfactory; the yield of III was only 67% after 7 days of reaction time. Palmitic acid was obtained in a 25% yield; it was separated as its sodium salt by neutralization with sodium carbonate solution. The acid was regenerated by acidification with 6 *N* HCl, mp 58–60°; IR (KBr): ν_{max} 1700 cm^{-1} [–C(=O)–OH].

Dehydroepiandrosterone Sulfatide (II)—A mixture of the diglyceride III (0.37 g, 0.54 mole) and dehydroepiandrosterone sulfate silver salt (0.28 g, 0.860 mmole) (*Ib*) was refluxed in dry benzene (15 ml) for 2 hr. Silver iodide was separated by filtration while hot and washed with dry benzene (10 ml), and the combined benzene filtrates were evaporated to dryness under reduced pressure. The residual yellow solid was washed with cold petroleum ether and dried, mp 66–68°, yield 68%; IR (KBr): ν_{max} 1730 and 1745 cm^{-1} {[–O–C(=O)–] and cyclic O=C–}; ^{1}H-NMR ($CDCl_3$): absence of signal at δ 3.3 for III and appearance of signal at δ 4.45 (m, 1H, vinylic).

Anal.—Calc. for $C_{54}H_{90}O_9S$: C, 70.85; H, 9.90. Found: C, 70.81; H, 9.43.

Androstan-3β-ol-16-oximino-17-one (V)—To a fresh solution of potassium *tert*-butoxide, prepared from potassium (3.8 g, 100 mmoles) and anhydrous *tert*-butyl alcohol (120 ml), epiandrosterone (3.6 g, 12.4 mmoles) was added with vigorous stirring. The mixture was refluxed under nitrogen until a clear yellow solution was obtained and then cooled, and isoamyl nitrite (6.3 ml) was added over 2 hr. The reaction mixture was poured into water (1 liter), acidified with 6 *N* HCl, and then stored at 5° overnight. The separated crude ketooxime (V) was filtered, washed with water, and recrystallized from methanol to afford 3.0 g (68% yield) of V, mp 218–219° [lit. (11) mp 245–247° and (12) mp 218–219°]; IR (KBr): ν_{max} 1630 (C=N), 1740 (C=O), 3200 (N–OH), and 3400 (OH) cm^{-1}.

Anal.—Calc. for $C_{19}H_{29}NO_3$: C, 71.43; H, 9.15; N, 4.38. Found: C, 71.18; H, 9.32; N, 4.30.

5α-Androstan-3β-hydroxy-16α-bromo-17-one (VII*a*)—Compound VII*a* was prepared in a 60% yield by bromination of epiandrosterone with cupric bromide and in a 72% yield from the diazoketone (VII) following reported procedures (11), mp 158–160° [lit. (11) mp 164–165°]; IR (KBr): ν_{max} 1740 (C=O) and 3400 (OH) cm^{-1}.

Anal.—Calc. for $C_{19}H_{29}BrO_2$: C, 61.78; H, 7.79; Br, 21.69. Found: C, 61.60; H, 8.01; Br, 21.87.

5α-Androstan-3β-hydroxy-16α-chloro-17-one (VII*b*)—Compound VII*b* was prepared in a 70% yield from the diazoketone (VI) following a reported procedure, mp 178–180° [lit. (11) mp 170–171°]; IR (KBr): ν_{max} 1750 (C=O) and 3450 (OH) cm^{-1}.

5α-Androstan-3β-hydroxy-16α-fluoro-17-one (VII*c*)—Compound VII*c* was prepared in a 20% yield from the diazoketone (VI) and pyridine–hydrofluoric acid and in a 28% yield by refluxing VII*d* with five equivalents of anhydrous silver fluoride in toluene–isopropanol (3:1) for 48 hr, mp 177–179°; IR (KBr): ν_{max} 1760 (C=O) and 3400 (OH) cm^{-1}; mass spectra: *m/z* 308 (M^+, *m/z* calc. 308).

Anal.—Calc. for $C_{19}H_{29}FO_2$: F, 6.15. Found: F, 5.87.

5α-Androstan-3β-hydroxy-16α-iodo-17-one (VII*d*)—*Method A* (21)—To a stirred solution of the enol diacetate (VIII) (20) (496 mg, 1.3 mmoles) in acetic acid (18 ml) containing mercuric acetate (10 mg), iodine (580 mg) dissolved in acetic acid (20 ml) was added over 2 hr. Stirring was continued for an additional hour, and the mixture was then poured into cold water (50 ml) and extracted with chloroform. The extract was washed successively with aqueous potassium iodide, sodium bicarbonate, and water. Evaporation of the chloroform afforded 481 mg (89% yield) of VII*d*, mp 170–172° [lit. (16) mp 173–175°]; IR (KBr): ν_{max} 1730 (C=O) and 3450 (OH) cm^{-1}.

Anal.—Calc. for $C_{19}H_{29}IO_2$: C, 54.80; H, 7.02; I, 30.48. Found: C, 55.17; H, 7.00; I, 30.77.

Method B—*N*-Iodosuccinimide (0.2 g, 0.88 mmole) was added to a solution of the enol diacetate (VIII) (200 mg, 0.53 mmole) in dioxane (15 ml); after slight warming to ensure complete dissolution, the reaction mixture was left in the dark for 24 hr. Potassium iodide solution was added to the reaction mixture, followed by excess 10% aqueous sodium thiosulfate solution. The reaction mixture was extracted with chloroform, dried, and evaporated. The white solid residue was recrystallized from methanol–ether to afford 208 mg (86% yield) of the 3β-acetoxy-16α-iodo derivative (IX), mp 147–148° [lit. (16) mp 144–147°]; IR (KBr): ν_{max} 1735 [O–C(=O)–CH_3] and 1740 (C=O) cm^{-1}. To a solution of 250 mg of IX in methanol (10 ml) at room temperature, 37% HCl (1 ml) was added. After the mixture stood at room temperature overnight, VII*d* was separated by filtration, mp 170–172° (mixed melting point with sample prepared by Method A showed no depression).

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Dosage Form Design for Improvement of Bioavailability of Levodopa V: Absorption and Metabolism of Levodopa in Intestinal Segments of Dogs

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Received November 10, 1980, from the *Product Development Laboratories, Sankyo Company, Ltd., 1-2-58, Hiromachi, Shinagawa, Tokyo, Japan.* Accepted for publication March 10, 1981.

Abstract □ Plasma levels of levodopa, total dopamine, and residual amounts of levodopa and its metabolites at the administered site were analyzed following administration of single 100-mg doses of levodopa in solution into isolated segments of the duodenum, jejunum, and ileum of the dog. The largest area under the plasma concentration–time curve (*AUC*) of levodopa during the 1.0-hr study was obtained following administration in the duodenum, followed by the jejunum and ileum. In addition, the residual amounts of levodopa and its metabolites detected at the administration sites were: ileum, 23%; jejunum, 7%; and duodenum, <1%. The largest *AUC* of total dopamine was obtained following administration in the jejunum, followed by the ileum and duodenum. This order was consistent with the order of levodopa decarboxylase enzyme activity reported previously. Therefore, it can be concluded that the major absorption site of levodopa in the intestine resides in the upper small intestine. Levodopa in 10-, 50-, and 100-mg doses was administered into isolated duodenal segments. The *AUC* of levodopa increased nonlinearly with increasing dose. Negligible amounts of both levodopa and its metabolites were observed in the segment at 1.0 hr after administration, indicating that the duodenal absorption of levodopa was not saturable within the dose range tested.

Keyphrases □ Levodopa—absorption and metabolism, intestinal segments, dogs, bioavailability, dosage form design □ Dosage form design—bioavailability of levodopa, absorption and metabolism in dog intestinal segments □ Bioavailability—levodopa, dosage form design, absorption and metabolism in dog intestinal segments

It was previously reported (1) that the reduced bioavailability of levodopa following oral administration was primarily due to levodopa metabolism by levodopa decarboxylase in the intestinal tissue, with the most enzyme activity in the jejunum and the least in the duodenum. The present investigation attempted to validate these findings by a study of levodopa absorption from intestinal segments.

EXPERIMENTAL

Major Absorption Site of Levodopa in Intestine of Dogs—Nine healthy male mongrel dogs, 11.1–13.9 kg, were fasted for ~16 hr and anesthetized with 25-mg/kg iv doses of pentobarbital sodium. They were divided into three equal groups according to the segment to be ligated. After the dog was fixed on its back, a laparotomy was performed on each dog, and a 20-cm segment of the duodenum, the jejunum, or the ileum was ligated. A single 100-mg dose of levodopa was injected as a 1% solution[1] into the ligated segment of each dog. Blood samples were withdrawn with a heparinized syringe from the brachial or femoral vein.

At 0, 2, 5, 15, 30, and 60 min after dosing, blood samples were withdrawn and processed as described previously (2). The animals were killed by exsanguination at 1 hr after levodopa administration, and the ligated loop was washed with saline and then three times with 0.04 *N* $HClO_4$ solution. The irrigating solution was assayed for residual amounts of levodopa and its metabolites.

Influence of Levodopa Dose on Absorption and Metabolism of Levodopa in Duodenum of Dogs—Nine healthy male mongrel dogs, 10.2–13.5 kg, were fasted for ~16 hr and anesthetized as described previously. After the dog was fixed on its back, a laparotomy was performed and a 20-cm segment of the duodenum was ligated. Ten-milligram doses of levodopa in a 0.2% solution[1] were injected into the duodenal loops of the first three dogs, 50-mg doses in a 0.5% solution[1] were injected into the duodenal loops of the second three dogs, and 100-mg doses in a 1.0% solution[1] were injected into the duodenal loops of the third group.

Blood samples were withdrawn with a heparinized syringe from the hepatoportal vein at 0, 2, 5, 15, 30, and 60 min after administration. Blood samples and the irrigating solution obtained from the final wash of the ligated loops were processed as already described.

Assay of Levodopa and Its Metabolites in Plasma and in Administered Site—Levodopa and its metabolite in plasma were determined according to a reported method (3). Residual amounts of levodopa and its metabolites in the dosing site of the intestine were determined according to the method reported previously (1).

RESULTS

Major Absorption Site of Intestine of Levodopa in Dogs—The average plasma levels of levodopa and total dopamine[2] are shown in Fig. 1 following administration of single 100-mg doses of levodopa to the duodenum, jejunum, and ileum. The highest plasma levodopa levels were obtained after duodenal administration; peak concentrations of 9.5 ± 1.9 mg/liter were observed at 5 min. Plasma levodopa levels following administration to the jejunum reached the peak levels of 5.0 ± 0.8 mg/liter at 15 min. Plasma levodopa levels following administration to the ileum were not only lowest but also increased so slowly that they reached peak levels of only 3.2 ± 0.3 mg/liter at 30 min after administration.

The average *AUC* of levodopa up to 1.0 hr after administration is shown in Fig. 2. The *AUC* of levodopa after administration to the ileum was approximately one-half that observed after duodenal administration.

[1] The 0.2, 0.5, and 1% levodopa solutions were prepared by dissolving levodopa in the buffer solution containing 0.2% sodium bicarbonate and 0.5% polyvinyl acetate (~pH 8.0).

[2] Total dopamine = unconjugated dopamine + conjugated dopamine.

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