

## Synthesis and Body Distribution of Several Iodine-131 Labeled Centrally Acting Drugs

Ulrich Braun, Alexander T. Shulgin, Gisela Braun, and Thornton Sargent III\*

Donner Laboratory, Lawrence Berkeley Laboratory, University of California, Berkeley, California 94720.  
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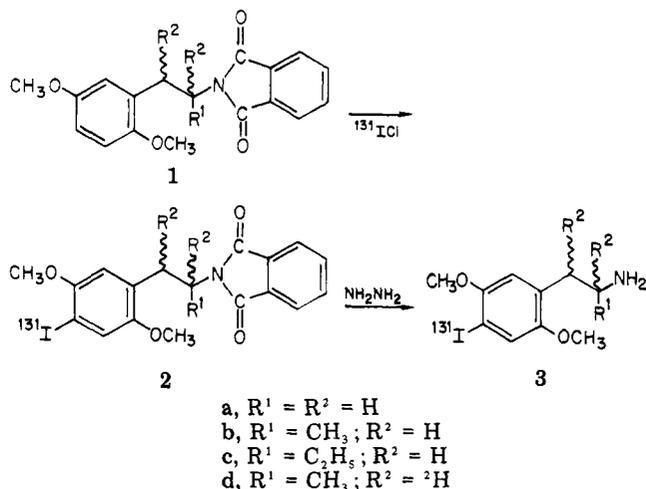
1-(4-Iodo-2,5-dimethoxyphenyl)-2-aminopropane (**3b**), 4-iodo-2,5-dimethoxyphenylethylamine (**3a**), and 1-(4-iodo-2,5-dimethoxyphenyl)-2-aminobutane (**3c**) have been synthesized with  $^{131}\text{I}$ . Labeled iodine monochloride reacts with the appropriately substituted phthalimide at the aromatic 4 position, and the phthalic acid group is removed with hydrazine. Body distribution was measured in rats; the most prominent difference between the three compounds was a much greater concentration in the lung with **3b** than with **3a** or **3c**.  $\gamma$ -Ray scintigraphs of **3a-c** in rats and of **3b** in a dog indicate an uptake by the brain similar to that of the bromine analogue of **3b** (DOB) in humans. [ $^{82}\text{Br}$ ]-DOB has been suggested as a potential brain scanning agent for nuclear medicine; **3b** would have the advantage over DOB of providing the superior  $\gamma$ -ray imaging properties of  $^{131}\text{I}$  or  $^{123}\text{I}$ .

When a radiopharmaceutical is administered to a patient for purposes of therapy or diagnosis, its localization and kinetics can be determined by means of external detection and imaging devices. All previous agents that have been used for brain scintigraphy owe their effectiveness to the fact that they are normally excluded from the brain, and their appearance in the brain is then an indication of a disease process. Recently 4-bromo-2,5-dimethoxyphenylisopropylamine (DOB, a psychodysleptic agent<sup>1</sup>) has been reported as a potential brain-scanning radiopharmaceutical.<sup>2</sup> In kinetic studies employing  $^{82}\text{Br}$ - or  $^{77}\text{Br}$ -labeled DOB, the radioactivity was found to be quickly removed from the circulating plasma of normal human subjects, with 2% deposition in the brain and about 12-18% in the lung.<sup>3</sup> Although this compound was the first radiopharmaceutical of practical half-life which concentrated in normal brain tissue, the high-energy  $\gamma$  rays of bromine isotopes limit resolution by  $\gamma$ -imaging devices.

The iodine isotopes  $^{131}\text{I}$  and, especially,  $^{123}\text{I}$  emit lower energy  $\gamma$  rays which are superior for imaging purposes. The iodine counterpart of DOB (DOI, **3b**) has been described chemically<sup>4</sup> but not studied pharmacologically. This compound has the three-carbon side chain normally associated with maximum central potency.<sup>5</sup> The two-carbon or four-carbon homologues had not been previously reported, and it was considered that they might also be CNS-seeking compounds with different and possibly useful quantitative and qualitative properties. In studies with 4-methyl-2,5-dimethoxyphenylisopropylamine (DOM), the corresponding phenethylamine is nearly an order of magnitude less potent in man<sup>6</sup> and the phenyl-*sec*-butylamine has no psychotomimetic action.<sup>7</sup> The synthesis and initial animal studies of **3b** and its two homologues are described in the present report.

**Chemistry.** It was desirable to design a synthetic scheme which would not only be practical on a small scale (for economy of isotope and high specific activity) but

Scheme I



which would also be sufficiently rapid to allow eventual use of  $^{123}\text{I}$  ( $t_{1/2} = 13$  h). This isotope is considered to be the best of the iodine isotopes for human use because of its high production of useful  $\gamma$  rays per unit of radiation dose to the patient.<sup>8</sup> In these initial studies, the isotope  $^{131}\text{I}$  was employed because the radiation dose is not of concern in animal studies, the  $\gamma$  energy is excellent for  $\gamma$  scintigraphy, and the half-life ( $t_{1/2} = 8.0$  days) allows sufficient time for study of chemical reactions and body kinetics.

All attempts to introduce the iodine directly into the aromatic nucleus of the 2,5-dimethoxyphenylalkylamine by direct halogenation, as was successful with  $\text{Br}_2$  and bromine water in the synthesis of DOB,<sup>3</sup> resulted in a preferential oxidative attack on the amine group. Protection of this function as the phthalimide proved adequate to allow direct insertion of iodine by the use of  $\text{ICl}$  in acetic

Table I. Organ Distribution of  $^{131}\text{I}$ -Labeled Compounds **3a-c** in the Rat<sup>a</sup>

Organ	<b>3a</b>				<b>3b</b>				<b>3c</b>			
	%/organ		%/g		%/organ		%/g		%/organ		%/g	
	40 min	4 h	40 min	4 h	40 min	4 h	40 min	4 h	40 min	4 h	40 min	4 h
Lung	2.9	0.7	1.95	0.47	8.5	3.6	5.71	2.42	2.6	1.6	1.75	1.07
Liver	9.0	4.2	0.71	0.33	15.5	8.4	1.22	0.66	14.4	6.6	1.13	0.52
Kidneys	3.4	1.2	1.51	0.53	4.5	1.1	2.00	0.49	2.1	0.9	0.93	0.38
Spleen	0.40	0.07	0.49	0.09	0.39	0.27	0.47	0.33	0.50	0.17	0.61	0.21
Brain	0.57	0.30	0.31	0.16	0.58	0.20	0.31	0.11	0.92	0.30	0.49	0.16
Heart	0.28	0.04	0.28	0.04	0.26	0.10	0.26	0.10	0.21	0.14	0.21	0.14
Testes	0.30	0.50	0.12	0.20	0.37	0.92	0.15	0.37	0.60	0.92	0.24	0.37
Gut	13.9	63.4			13.3	16.1			14.8	35.3		
Stomach	15.8	4.8			1.8	3.3			3.2	8.1		
Blood		1.5			1.3	2.1			3.2	12.8		
Bladder	2.4	0.7			0.66	12.2				7.3		
Thyroid	0.06	0.04			0.07	0.09			0.04	0.03		
Trachea	0.02	0.00			0.01	0.07			0.01	0.00		
Carcass	50.8	22.6			52.8	51.5			57.3	25.8		

<sup>a</sup> Animals were sacrificed at 40 min and 4 h after iv injection. %/organ is the percent of the total observed radioactivity in each organ divided by the weight of the organ to yield relative concentrations. Animals were anesthetized with pentobarbital (50 mg/kg) and supported with ether as necessary.

acid. The final products were formed by the removal of phthalic acid with hydrazine in ethanol (see Scheme I). The generation of radioactive ICl was achieved in the reaction medium from inorganic iodide ion, according to the equation  $^{131}\text{I}^- + \text{ICl} \rightleftharpoons \text{I}^- + ^{131}\text{ICl}$ . The equilibration of the radioisotope into ICl was extremely rapid. The two-carbon and the four-carbon homologues **3a** and **3c** were prepared at specific activities of 3.2 and 1.7 mCi/mM and the three-carbon counterpart **3b**, to permit a smaller total pharmacologic dose in the animal studies, was prepared at a specific activity of 9.4 mCi/mM.

In one synthesis of **3b**, the starting phthalide **1b** was admixed exactly with an equal weight of the dideuterio analogue **1d**, prepared by the action of lithium aluminum deuteride on 1-(2,5-dimethoxyphenyl)-2-nitropropene, followed by reaction with phthalic anhydride to provide **1d**. The final product was thus a 50:50 mixture of **3b** and **3d**, suitable for chemical ionization mass spectral determination of metabolites in tissue analysis.

## Results and Discussion

The  $\gamma$ -ray scintigraphs of the rats are shown in Figure 1 (top). The general sequence with time appears to be similar in all three compounds; the earliest and highest concentration of radioactivity is in the liver. At 40 min, and especially at 200 min, it appears to move into the gut. The bladder accumulates radioactivity following **3b** and **3c** but not **3a**. The study was then extended to a dog because the larger brain should be more readily visualized. Figure 1 (bottom) shows a scintigraph of the dog's head 2.5 h after injection of **3b**, and the brain area clearly contains a larger amount of radioactivity than surrounding tissue. One rat was injected intraventricularly with **3b** via a cannula permanently implanted in a lateral ventricle, and the biological removal rate, observed with a pinhole collimator, was found to have a half-time of approximately 1 h.

The distribution of radioactivity in dissected organs of the rats is shown in Table I for each of the three compounds, as percent of the total observed activity. Table I also shows this percent divided by the average organ weight, yielding specific organ concentrations. From these results it appears that these compounds are excreted primarily via the gut, much more rapidly with **3a** and **3c** than **3b**. As observed in the scintigraphs, **3a** does not appear in the bladder and, combined with the appearance of activity in the dissected gut, suggests that this compound is primarily excreted by the liver via bile into the

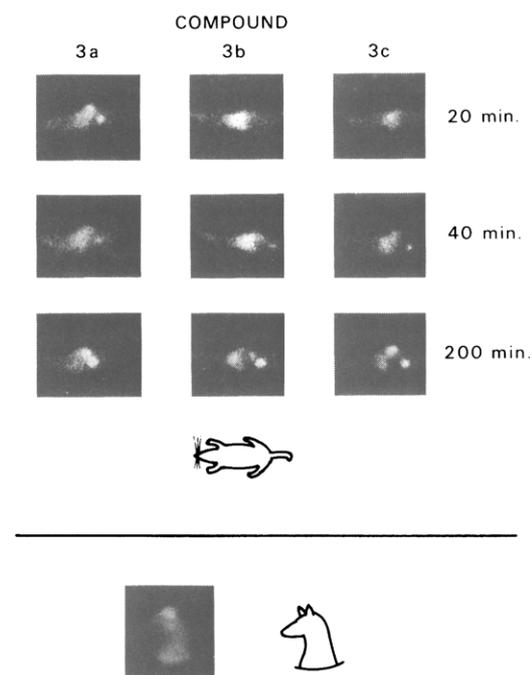


Figure 1. Top: Anger camera scintigraphs of anesthetized rats at intervals following administration of **3a-c** (dorsal views, diverging collimator, 5-min exposures). Bottom: scintigraph of head and neck of female beagle dog 2.5 h following administration of **3b** (lateral view, medium energy collimator, 1.5-min exposure).

gut. The appearance of **3a** in the stomach is unusual; possibly it could have resulted from pyloric regurgitation from the gut or from salivary or direct secretion. The dissected rat brain contained less than 1%, although an elevated concentration of **3b** relative to the surrounding tissue is evident in the dog brain (Figure 1, bottom). The thyroids, dissected with an attached section of trachea, were compared to a control section of trachea, and the  $^{131}\text{I}$  in this gland was at most 0.07% of the injected dose. This explains the lack of concentration of radioiodine in this organ in the scintigraphs and suggests in vivo stability of the agents.

When considered on the basis of concentration rather than total percent in the organ, the lung is the predominant organ followed by liver and kidneys, with other organs all considerably lower. The uptake in the lung is comparable to that seen with the bromine analogue in humans.<sup>2,3</sup>

The total body retention curves obtained by measuring individual living animals successively over a period of 5 days, with a whole-body counter, consisted of two exponential components. The first slope had a biological  $t_{1/2}$  of 5–7 h and the second, of 3–7 days. The latter curve had a zero-time intercept of 1.5–3.5%. These retention curves represent unanesthetized animals which lost radioactivity by excretion and should not be compared to the anesthetized animals used for scintigraphy and dissection.

These studies suggest that **3b** and possibly **3c** might be worthy of further investigation as potential scanning agents in nuclear medicine. The iodine atom does not appear to be removed from the parent molecule, and the appearance of radioactivity in the brain of the dog and in the lung and liver of the rat suggests a possible use of these compounds for imaging of these organs. Iodine-123 is the isotope of choice for reasons mentioned earlier. The pharmacologic properties and structural similarities to catecholamine neurotransmitters suggest application of such labeled compounds in fundamental research on the etiology of psychotic illness. More detailed studies with **3b** are in progress and will be reported elsewhere.

### Experimental Section

The infrared spectra were determined on a Beckman IR-18. Melting points were taken in open capillaries in a Mel-Temp apparatus and are uncorrected. Where analyses are indicated only by the symbols of the elements, analytical results obtained for the elements were within 0.4% of the theoretical values. NMR data were recorded with a Perkin-Elmer R-32-B in CDCl<sub>3</sub> or D<sub>2</sub>O. Chemical ionization mass spectra were obtained on an AEI MS-902. Thin-layer chromatographic analyses were performed on Brinkmann plates, 0.25-mm silica gel UV-254. The solvents used for the phthalide separation were dichloromethane or dichloromethane-acetonitrile (100:3). The solvent mixture for the radiochemical purity verification of the final amine was ethyl acetate-methanol-concentrated ammonium hydroxide (170:20:3).

A whole-body counter (designed and built at this laboratory) was used to measure the <sup>131</sup>I in intact living animals and in dissected organs and also to determine radiochemical yields. This counter uses a 235 × 10 cm NaI(Tl) crystal inside a 15-cm thick iron shield. Organs, animals, and samples were counted 1 m from the crystal, a distance which minimizes the effect of geometrical variables on counting efficiency. The Anger scintillation camera used for in vivo visualization of body distribution of the <sup>131</sup>I was invented and built by Hal Anger of this laboratory. Radioisotope doses were determined by a Squibb CRC 6a radioisotope calibrator.

**Compound Administration.** The three <sup>131</sup>I-labeled compounds **3a**, **3b** (including **3b** + **3d**), and **3c** were administered intravenously in a tail vein to male WAG/Rij rats (a special strain originally developed in the Netherlands) weighing approximately 200 g each. Organ distributions were obtained by injecting four rats (tail vein) with each labeled compound. One animal was kept alive for 7 days for determination of whole-body retention, one was utilized for consecutive scintigraphs, one was sacrificed at 40 min, and one was sacrificed at 4 h for organ counting. Animals were anesthetized with pentobarbital (50 mg/kg) with additional light ether anesthesia as necessary to maintain immobility for the scintillation camera and dissection studies. The dose levels of the compounds were 28 mg/kg of **3a**, 4.5 mg/kg of **3b**, and 12.5 mg/kg of **3c**. A female beagle dog (12 kg) was given **3b** at a dose iv of 7.5 mg/kg containing 1.45 mCi of [<sup>131</sup>I]-**3b**.

**N-[2-(2,5-Dimethoxyphenyl)-1-methylethyl]phthalimide (1b).** The free base, 2,5-dimethoxyphenylisopropylamine (1.95 g, 10 mM), is mixed with phthalic anhydride (1.5 g, 10 mM) and the suspension fused with a soft flame (maximum temperature, 150 °C) until no more water is evolved, and the resulting mixture is a clear pale amber melt. After return to room temperature, the residue is dissolved in methylene chloride (100 mL) and washed with 1% HCl, with 1% NH<sub>4</sub>OH, and finally with water. Removal of the solvent yielded 2.6 g of an amber oil which was dissolved in 20 mL of methanol. There was a spontaneous crystallization of the product as a white solid, which after filtration

and washing with cold methanol yielded 2.0 g of **1b** as white crystals, mp 105.5–106 °C. A second crop of product was recrystallized from boiling methanol (25 mL/g) to provide an additional 0.3 g for a total yield of 62% of theory: NMR (CDCl<sub>3</sub>) δ 1.49, 1.61 (d, 3 H, CCH<sub>3</sub>), 3.08–3.32 (2 d, 2 H, CH<sub>2</sub>), 3.58, 3.73 (2 s, 6 H, OCH<sub>3</sub>), 4.73 (m, centered, CH), 6.69 (s, 3 H, ArH), 7.71, 7.74 (d, 4 H). Anal. (C<sub>19</sub>H<sub>19</sub>NO<sub>4</sub>) C, H, N.

**N-[2-(2,5-Dimethoxyphenyl)-1-methyl-1,2-dideuterioethyl]phthalimide (1d).** A solution of 1-(2,5-dimethoxyphenyl)-2-nitropropene (1.0 g, 4.5 mM) in THF (15 mL) was added dropwise to a refluxing suspension of 1.25 g of lithium aluminum deuteride (Stohler Isotope Chemicals Lot No. 5116) in THF (60 mL). The mixture was held at reflux for 20 h and cooled with external ice water, and there was added in sequence, with good stirring, 1.25 mL of water in 10 mL of THF, 1.25 mL of 15% NaOH, and 3.75 mL of water. The resulting solids were removed by filtration and washed with THF, and the combined solutions were evaporated in vacuo to give 1.1 g of a pale amber oil. This was transferred to a long-stemmed test tube and 0.90 g of phthalic anhydride was added. The mixture was fused with an open flame and heated to 150 °C until the evolution of water ceased. The amber melt was allowed to cool and then dissolved in methanol (2 mL), allowing spontaneous crystallization of the product as a white crystalline mass. This was removed by filtration, washed sparingly with cold methanol, and air-dried to yield the title compound as white crystals: yield 0.85 g (58%); mp 103–104 °C. In the NMR (CDCl<sub>3</sub>), the α-methyl group appeared as a three-proton singlet at δ 1.55 and the benzylic hydrogen appeared as two singlets at δ 3.08 and 3.26, with a combined integration of one proton, representing the threo and the erythro isomers. The remaining spectrum was identical with that of the completely protonated isomer **1b**.

**N-[2-(2,5-Dimethoxyphenyl)ethyl]phthalimide (1a).** A suspension of phthalic anhydride (3.3 g, 22 mM) in 100 mL of toluene was held at reflux in a Dean-Stark apparatus until there was a clear solution and no additional water was removed. To this solution there was added 2,5-dimethoxyphenethylamine (3.6 g, 20 mM) and refluxing continued until the water evolution was complete (20 h). Removal of the solvent in vacuo gives the crude product which is recrystallized from methanol to provide 5.5 g (86%) of white crystals, mp 110–111 °C. Anal. (C<sub>18</sub>H<sub>17</sub>NO<sub>4</sub>) C, H, N.

**N-[2-(2,5-Dimethoxyphenyl)-1-ethylethyl]phthalimide (1c).** Employing the same procedure used in the preparation of **1b**, **1c** was prepared from 2,5-dimethoxyphenyl-sec-butylamine and phthalic anhydride. The product was recrystallized from methanol to yield 48% of off-white crystals, mp 76.5–77.5 °C. Anal. (C<sub>20</sub>H<sub>21</sub>NO<sub>4</sub>) C, H, N.

**N-[2-(2,5-Dimethoxy-4-iodophenyl)-2-deuterio-1-methyl-1-deuterioethyl]phthalimide (2d).** Na<sup>131</sup>I (50 mCi) in 0.1 N NaOH (New England Nuclear NEZ-035A) was transferred with 2.5 mL of acetic acid containing 50 mg of NaI (in three portions) to a 25-mL Erlenmeyer flask equipped with a magnetic stirring bar. To this was added 2.5 mL of acetic acid containing 0.115 mL of warm iodine monochloride. After a few moments of stirring, there was added a solution of 250 mg of **1b** and 250 mg of **1d** in 5 mL of acetic acid. Stirring was continued for 2 h at ambient temperature, followed by 0.5 h at 60 °C (external water bath). The reaction mixture was quenched in 200 mL of water, sufficient solid sodium dithionite was added to discharge the iodine color, and it was extracted with 3 × 50 mL of methylene chloride. The pooled extracts were washed twice with a solution of KI and dithionite in water (1%) and taken to dryness in a rotary evaporator in vacuo. The product appeared as a pale yellow crystalline mass, which was employed without further purification in the dephthalidization step. In unlabeled runs, the product was further purified and characterized. After recrystallization from boiling methanol, **2b** was obtained as fine white crystals [1.5 g from 2.0 g of **1b**, for a yield of 54%; mp 103–103.5 °C; mmp (with **1b**) 85–98 °C with softening at 81 °C]. Anal. (C<sub>19</sub>H<sub>18</sub>NO<sub>4</sub>I) C, H, N.

**N-[2-(2,5-Dimethoxy-4-iodophenyl)ethyl]phthalimide (2a).** Employing the procedure described for **2d**, **1a** was iodinated with 5 mCi of Na<sup>131</sup>I. In unlabeled runs, the product was further purified and characterized. The crude iodophthalide was recrystallized from boiling isopropyl alcohol to yield 46% of the

theoretical amount of cream-colored crystals, mp 155.5–157 °C. Anal. (C<sub>18</sub>H<sub>16</sub>NO<sub>4</sub>I) C, H, N.

**N-[2-(2,5-Dimethoxy-4-iodophenyl)-1-ethylethyl]-phthalimide (2c).** Employing the procedure described for **2d**, **1c** was iodinated with 5 mCi of Na<sup>131</sup>I. In the labeled run, as in the unlabeled runs, the product **3c** was obtained only as an oil and was processed directly on to the final amine without characterization or further purification.

**2,5-Dimethoxy-4-iodophenyl- $\alpha,\beta$ -dideuterioisopropylamine Hydrochloride (3d).** The crude product **2d** (from the iodination of **1d**) was transferred to a 25-mL round-bottomed flask equipped for refluxing. The transfer was accomplished with 12 mL of 95% ethanol, 0.2 mL of hydrazine hydrate was added, and the mixture was held at reflux for 18 h, during which time solid phthalimide appeared. The reaction mixture was quenched in 200 mL of water, made basic with NaOH to a pH of about 10, and extracted with 3  $\times$  50 mL of methylene chloride. The pooled extracts were washed with a 1% solution of KI and Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> in water, and the solvent was removed in vacuo. The residual pale amber oil was dissolved in 8 mL of isopropyl alcohol, acidified with concentrated HCl (8 drops), and flooded with anhydrous ether (200 mL). After several minutes, fine crystals began to form. After about 1 h of standing at room temperature, these were removed by filtration and washed with anhydrous ether. The product weighed 0.232 g and assayed at 9.44 mCi/mM, representing an overall chemical yield of 43% and a radioisotope incorporation efficiency of 12%. The physical properties of the product **3b** were determined from unlabeled runs: mp (after recrystallization from ethanol-ether) 200.5–201.5 °C. The melting point was undepressed when admixed with an authentic sample prepared by a different synthesis (lit.<sup>4</sup> mp 199.5–201.0 °C; mmp 199.5–201.0 °C). The possible incorporation of chlorine into the product was assayed by chemical ionization mass spectroscopy (reactant isobutane, at 0.6 Torr and 210 °C), mH<sup>+</sup> = 322 principle peak, with a companion pair (peak height of 4%) at mH<sup>+</sup> = 230 and 232 indicating minor chlorination. Anal. (C<sub>11</sub>H<sub>17</sub>ClINO<sub>2</sub>) C, H, N.

**2,5-Dimethoxy-4-iodophenylethylamine Hydrochloride (3a).** Employing the procedure described for **3d**, **2a** was converted

to **3a**. The product was obtained with a specific activity of 3.16 mCi/mM, in an overall chemical yield of 52% and an overall radioisotope incorporation efficiency of 22%. The physical properties and characterization were achieved on an unlabeled sample. An analytical sample from 2-propanol gave mp 246–247 °C; NMR (D<sub>2</sub>O)  $\delta$  3.37 (m, 4 H, CH<sub>2</sub>), 4.06, 4.08 (2 s, 6 H, OCH<sub>3</sub>), 7.17, 7.67 (2 s, 2 H, ArH) (DOH at 4.95). Anal. (C<sub>10</sub>H<sub>15</sub>ClINO<sub>2</sub>) C, H, N.

**1-(2,5-Dimethoxy-4-iodophenyl)-2-aminobutane (3c).** Employing the procedure described for **3d**, **2c** was converted to **3c**. The product was obtained in a specific activity of 1.7 mCi/mM. The physical properties were determined on a non-radioactive sample: white crystalline solids; mp 214–215 °C. Anal. (C<sub>12</sub>H<sub>19</sub>ClINO<sub>2</sub>) C, H, N.

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## Contraceptational Agents. 1. Steroidal O-Aryloximes

Allen F. Hirsch,\* George O. Allen, Benny Wong, Sandra Reynolds, Chris Exarhos, William Brown, and Do Won Hahn

*Divisions of Chemical Research and Pharmacology, Ortho Pharmaceutical Corporation, Raritan, New Jersey 08869. Received December 28, 1976*

The preparation of a series of *O*-aryloximes of various steroids by two different routes is described. These compounds were prepared by reacting a keto steroid with a substituted *O*-arylhydroxylamine in the presence of an acid catalyst or, alternatively, by the reaction of a steroidal oxime with a substituted aryl halide in the presence of a suitable base. These compounds were examined for their ability to interrupt postimplantive gestation in female rats. The most significant contraceptive activity was seen with compounds in which the basic steroid structure was a 5 $\alpha$ -androstane and the 3-oxime was of the *p*-nitrophenyl series. One of the most active compounds in the series (**16**) was shown to have the ability to terminate pregnancy, when orally administered to rats at 2.5 mg/kg on days 9–12 of gestation. This compound was found to be devoid of androgenic activity at this dose level.

Efforts in our laboratory have been directed toward the synthesis of a new generation of antifertility agents having contraceptive effects, i.e., the ability to interrupt pregnancy. Reports on the first preparation of *O*-phenylhydroxylamine<sup>1</sup> and the synthesis and reactions of *O*-arylhydroxylamines and *O*-aryloximes<sup>2</sup> led us to prepare a series of steroidal *O*-aryloximes. This paper describes the synthesis and some of the biological properties of this series of compounds, several members of which have contraceptive activity while being devoid of androgenic activity at the active dose levels.

Naqvi and Warren<sup>3</sup> reported that oxymetholone (17 $\beta$ -hydroxy-2-hydroxymethylene-17 $\alpha$ -methyl-5 $\alpha$ -androstane-3-one) and nandrolone phenpropionate (17 $\beta$ -hydroxy-

estr-4-en-3-one 17-phenylpropionate) had the ability to interrupt pregnancy in the rat when administered daily subcutaneously for 6 days, starting on the seventh day of pregnancy at doses of 5.0 and 2.0 mg per animal, respectively. Marois<sup>4</sup> reported that a single subcutaneous dose of 3 mg of testosterone propionate to rats on either days 7, 8, 9, 10, or 11 postcoitally is effective in interrupting pregnancy. Likewise, Dreisbach<sup>5</sup> found that a single 4 mg/kg dose of testosterone given to rats produced fetal loss when subcutaneously injected on days 9–11.

The steroidal *O*-aryloximes reported herein also exert their effects postimplantively but unlike oxymetholone, nandrolone phenpropionate, testosterone, or testosterone propionate they are effective orally and have no androgenic