some black material. The $CHCl_3$ layer was washed with 2 *N* HCl and H_2O before evaporating to a brown solid (9.9 g). Chromatography on silica gel using EtOAc as eluent afforded a solid: 7.2 g; mp 182–195°. Recrystallization from a small volume of EtOAc gave a yellow solid: yield 6.2 g; mp 198–201°. *Anal.* ($C_{20}H_{18}N_4O_{10}$) C, H, N.

The following compounds were prepared in a similar manner but were used without purification in further reactions: *N*-acetyl-4-(1,3-benzodioxol-5-yloxy)-3,5-dinitro-L-phenylalanine methyl ester (**16**); *N*-acetyl-4-(2,3-dihydro-1,4-benzodioxin-6-yloxy)-3,5-dinitro-L-phenylalanine methyl ester (**17**); *N*-acetyl-4-(2-methyl-2,3-dihydrobenzofuran-5-yloxy)-3,5-dinitro-L-phenylalanine ethyl ester (**4**, R′ = H); *N*-acetyl-4-(2,2-dimethyl-2,3-dihydrobenzofuran-5-yloxy)-3,5-dinitro-L-phenylalanine ethyl ester (**4**, R′ = Me).

***N*-Acetyl-4-(3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-yloxy)-3,5-diiodo-L-phenylalanine (14).** The dinitrobenzoxazine derivative **15** (5 g, 0.011 mol) was hydrogenated at atmospheric pressure in glacial AcOH (100 ml) in the presence of 10% Pd/C (1 g) until H_2 uptake had ceased (70 min). The solution was cooled in an ice bath and concentrated H_2SO_4 (20 ml) added, and the catalyst was removed by filtration. The diamine solution was placed in a pressure equalizing dropping funnel under N_2 and added during 1 hr to a stirred solution of $NaNO_2$ (3.4 g, 0.05 mol) in concentrated H_2SO_4 (37.5 ml, prepared at 50°) to which glacial AcOH (37.5 ml) had been added. The mixture was maintained at −5° during addition of the diamine; concentrated H_2SO_4 (37 ml) was added concomitantly to prevent freezing. When the addition was complete the orange-red solution was stirred at −5° for 1 hr and then added rapidly with vigorous stirring to a solution of I_2 (13.4 g), NaI (18.6 g), and urea (1.92 g) in H_2O (190 ml) and $CHCl_3$ (190 ml) at 0°. The resultant mixture was stirred 1 hr at <10°, 1 hr at room temperature, and 1 hr at 40° and then filtered. The $CHCl_3$ layer was separated, washed with H_2O, 10% $NaHSO_3$ solution, H_2O and brine, and dried (Na_2SO_4). Evaporation gave a solid foam which crystallized from EtOAc as a buff powder: yield 2.0 g; mp 225–227°.

The powder (1.0 g) was dissolved in dioxane (30 ml). To this stirred solution, a solution of KOH (0.88 g) in water (4 ml) was added. An oil formed and after 10 min the whole mixture was evaporated. H_2O was added to the residue and the solution adjusted to pH 5 (dilute HCl). The resultant solid was recrystallized from Me_2CO-H_2O as an off-white solid: yield 0.5 g; mp 210–212° dec. *Anal.* ($C_{19}H_{16}I_2N_2O_6$) C, H, N.

4-(1,4-Benzodioxan-6-yloxy)-3,5-diiodo-L-phenylalanine (13). The crude dinitrobenzodioxane derivative **17** (11.2 g) was hydrogenated, tetrazotized, and iodinated as described above and furnished *N*-acetyl-4-(1,4-benzodioxan-6-yloxy)-3,5-diiodo-L-phenylalanine methyl ester (**12**) as a solid foam, 8 g.

The ester **12** (2.5 g) was dissolved in EtOH (75 ml) and a solution of KOH (2.15 g) in H_2O (10 ml) added with stirring. After 10 min the solution was evaporated to dryness and the residue acidified to pH 5 (dilute HCl). The solid was filtered and recrystallized from Me_2CO-H_2O furnishing the acetamido acid **18** as an off-white solid: yield 1.3 g; mp 222–223° dec. *Anal.* ($C_{19}H_{17}I_2NO_6$) C, H, N.

The protected amino acid **12** (3 g) was dissolved in concentrated HCl-AcOH (60 ml of 1:1) and heated under reflux for 2 hr. The mixture was cooled and filtered and the solid recrystallized from MeOH-H_2O giving the title compound **13** as an off-white powder: yield 0.75 g; mp 258–260°. *Anal.* ($C_{17}H_{15}I_2NO_5$) C, H, N.

***N*-Acetyl-4-(2*H*-1,3-benzodioxol-5-yloxy)-3,5-diiodo-L-phenylalanine Methyl Ester (11).** The crude dinitrobenzodioxole **16** (7.8 g) was hydrogenated, tetrazotized, and iodinated as described for the foregoing compounds, furnishing the title compound as a pale brown solid: yield 6.9 g; mp 134–137°. Recrystallization from EtOH raised the melting point to 153–155°. *Anal.* ($C_{19}H_{17}I_2NO_6$) C, H, N.

4-(2,2-Dimethyl-2,3-dihydrobenzofur-5-yloxy)-3,5-diiodo-L-phenylalanine (5, R″ = Me). Hydrogenation, subsequent tetrazotization, and iodination of the crude dinitrodihydrobenzofuran derivative **4** (R′ = Me, 4 g) afforded the protected amino acid as a solid foam. This was hydrolyzed in 1:1 HCl-AcOH at reflux. Decolorization (charcoal-MeOH) and crystallization (MeOH-H_2O) afforded the somewhat light-sensitive product: yield 570 mg; mp 224–227°. *Anal.* ($C_{19}H_{19}I_2NO_4$) C, H, N.

4-(2-Methyl-2,3-dihydrobenzofur-5-yloxy)-3,5-diiodo-L-phenylalanine (5, R″ = H). The crude dinitrodihydrobenzofuran derivative **4** (R′ = H, 3.4 g) was hydrogenated, tetrazotized, iodinated, and hydrolyzed as described for the foregoing compound. The product (1 g) was recrystallized three times from MeOH-H_2O: mp 223–226°. *Anal.* ($C_{18}H_{17}I_2NO_4$) C, H, N.

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Potential Antifertility Agents. 5. 2,3-Diphenyl-1-(*N*-methyl-*N*-propargyl)aminoindenes[1]

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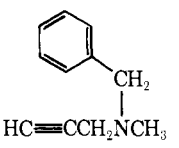
A number of inhibitors of the enzyme monoamine oxidase (MAO) are known to disrupt pregnancy at various stages in rodents.[2,3] It has been demonstrated that intrauterine instillation of the MAO inhibitor pargyline **1** in humans successfully produced interruption of pregnancy.[4]



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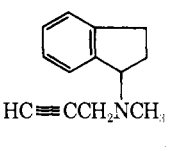

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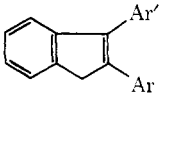


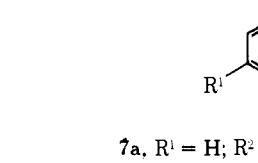
3

An indan **2** structurally related to pargyline retains potent MAO inhibitory activity[5] but apparently has not been tested for antifertility activity. Substituted 2,3-diarylindene derivatives **3**[6] are potent antifertility agents in mammals owing to their estrogenicity and/or antiestrogenicity.[6,7] These observations suggested to us synthesis of the indenes **7c** and **7f** which incorporate structural features of **2** and **3**. It seemed possible that the diarylindene portion of **7c** or **7f** might serve as a carrier to deliver to the uterine environment a moiety analogous to that present in **1** which could produce a pregnancy-inhibiting action *via* MAO inhibition[2-4] or some other effect resultant from the molecular configuration.

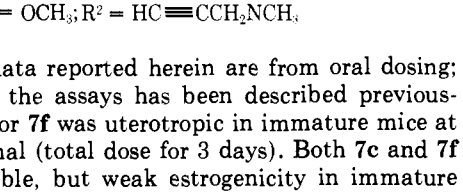
Chemistry. Ketones **4**[8] and **5** were envisioned as starting materials for the preparation of **7c** and **7f**, respective-

ly. Treatment of **5** with polyphosphoric acid readily yielded the indene **7d** which was condensed with *N*-bromosuccinimide (NBS) to provide the requisite **7e**. However, treatment of ketone **4** with PPA (180°) resulted in recovery solely of starting material, as did treatment of **4** with aluminum chloride in methylene chloride. An alternative approach to **7c** was provided from the commercially available 2,3-diphenyl-1-indone (**6**). Standard procedures were used to convert **6** to the bromo derivative **7b**. Reaction of the bromoindenes **7b** and **7e** with excess *N*-methyl-*N*-propargylamine produced **7c** and **7f**, respectively (Scheme I).

Scheme I



4, $R^1 = H$
5, $R^1 = OCH_3$



7a, $R^1 = H$; $R^2 = OH$
b, $R^1 = H$; $R^2 = Br$
c, $R^1 = H$; $R^2 = HC{\equiv}CCH_2NCH_3$
d, $R^1 = OCH_3$; $R^2 = H$
e, $R^1 = OCH_3$; $R^2 = Br$
f, $R^1 = OCH_3$; $R^2 = HC{\equiv}CCH_2NCH_3$

6

Biology. All data reported herein are from oral dosing; methodology for the assays has been described previously.[1] Neither **7c** nor **7f** was uterotropic in immature mice at 1000 μg per animal (total dose for 3 days). Both **7c** and **7f** showed comparable, but weak estrogenicity in immature rats with 1000 μg of **7c** or **7f** approximating the uterotropic response produced with 0.2 μg of diethylstilbesterol. Neither **7c** nor **7f** prevented implantation in rats dosed at 5 mg/kg/day on days 1-5 postcoitum or in mice dosed at 50 mg/kg/day on days 1-5 postcoitum. Additionally, **7f** was found to be inactive in mice dosed at 50 mg/kg/day dosed on days 3-8 postcoitum.

In summary, neither **7c** nor **7f**, which may be viewed as structural hybrids of **1-3**, disrupted pregnancy in mice or rats under the dosing regimens described.

Experimental Section

Melting points (capillary) and boiling points are uncorrected. All compounds had consistent ir and nmr spectra for assigned structures. Mass spectra (70 eV) were obtained on a LKB 9000 mass spectrometer. Where elemental analyses are indicated by symbols, analytical results were within ±0.4% of the theoretical values.

3-(*m*-Methoxyphenyl)-2-phenylpropiophenone (5). A reaction flask fitted for distillation was charged with a mixture of KOH (1.82 g, 0.032 mol) and *m*-methoxybenzyl alcohol (19.8 g, 0.127 mol). The contents were heated to 165° and about one-third of a 25.0-g (0.143 mol) quantity of molten deoxybenzoin was added. The temperature was increased to 195° at which point water began to distill. The remainder of the ketone was added slowly and the mixture was maintained at 195° for 20 min. The cooled residue was partitioned between Et_2O and water; the Et_2O layer washed with water and brine. Drying ($MgSO_4$) and evaporation of the solvent left a brown oil which was distilled to give **5**, 22.7 g (57%), which crystallized slowly: bp 200° (15 mm). An analytical sample was recrystallized from EtOH: mp 60.5-62°. *Anal.* ($C_{22}H_{20}O_2$) C, H.

2,3-Diphenyl-1-indenol (7a). A suspension of 2,3-diphenylindone (**6**, 11.3 g, 0.040 mol) in Et_2O (100 ml) was added slowly to $LiAlH_4$ (0.70 g, 0.018 mol) in Et_2O (50 ml). The mixture was refluxed for 16 hr and then treated in succession with 0.7 ml of H_2O, 0.7 ml of 4 *N* NaOH, and 2.1 ml of H_2O. The mixture was stirred for 1 hr and then was filtered. Drying and evaporation of the filtrate left an orange product which was recrystallized from toluene-Skellysolve B to give 10.4 g (91%) of **7a**, mp 122-125°, which was sufficiently pure for use. The analytical sample had mp 133.5-135° (lit.[9] mp 134-135°). *Anal.* ($C_{21}H_{16}O$) C, H.

1-Bromo-2,3-diphenylindene (7b). Phosphorus tribromide (2.0 g, 0.007 mol) was added to a solution of **7a** (5.68 g, 0.020 mol) in 200 ml dry benzene and the mixture was stirred for 17 hr. The solution was poured onto crushed ice and the organic layer washed with water and dried ($MgSO_4$). Evaporation of the solvent left an orange solid which was recrystallized (toluene-Skellysolve B) to give 4.45 g (64%) of yellow crystals: mp 160-161.5° (lit.[10] 163.5-164.5°).

2,3-Diphenyl-1-(*N*-methyl-*N*-propargyl)aminoindene (7c). A mixture of **7b** (2.61 g, 0.0075 mol) and *N*-methyl-*N*-propargylamine (10 ml) was stirred for 16 hr at 25°. The mixture was dissolved in Et_2O, washed with dilute aqueous $NaHCO_3$ and water, and then dried ($MgSO_4$). Evaporation of the Et_2O left 2.53 g (100%), mp 132-135°. Two recrystallizations (EtOH) gave 1.82 g (72%): mp 136.5-138°; *m/e* 335. *Anal.* ($C_{25}H_{21}N$) C, H, N.

2,3-Diphenyl-6-methoxyindene (7d). The ketone **5** (6.72 g, 0.212 mol) in PPA (170 g, FMC Corp.) was stirred at 150° for 2 hr. The mixture was poured onto crushed ice and extracted with Et_2O. The extracts were washed with water, dried ($MgSO_4$), and evaporated to a brown oil. Chromatography on silica gel (elution with 1:1 toluene-Skellysolve B) gave 3.9 g (62%) **7d**, which was homogeneous on tlc and sufficiently pure for use in the next step. An analytical sample was obtained by recrystallization from EtOH: mp 129-131°. *Anal.* ($C_{22}H_{18}O$) C, H.

1-Bromo-2,3-diphenyl-6-methoxyindene (7e) was prepared from the indene **7d** and NBS analogously to the procedure of Sprinzak:[10] yield 48%; mp 139-140.5° (toluene-Skellysolve B). *Anal.* ($C_{22}H_{17}BrO$) C, H, Br.

2,3-Diphenyl-6-methoxy-1-(*N*-methyl-*N*-propargyl)aminoindene (7f) was prepared from **7e** analogously to the procedure described above for **7c**: mp 119-121° (EtOH); *m/e* 365. *Anal.* ($C_{26}H_{23}NO$) C, H, N.

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