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Intramolecular Diels–Alder Reactions. Synthesis of 3a-Phenylisoindolines as Analgetic Templates

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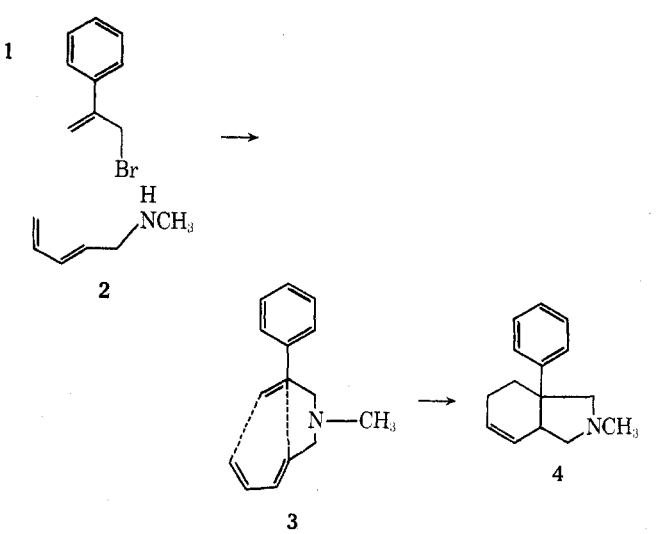
A preparatively efficient method for the synthesis of the substrate **10** is described. This undergoes an intramolecular [4 + 2] cycloaddition to give the lactam **11**. Reduction of the amide carbonyl gives **6**, the product of an extremely facile [4 + 2] cycloreversion, and no trace of the Diels–Alder adduct **7** was found. A number of transformations of **11**, including a skeletal rearrangement of **14** to **16**, are described, and the structure and relative stereochemistry of the products is elaborated largely on the basis of their NMR data. The cis stereochemistry of **20**, a product obtained from the cycloadduct **11** via hydrogenation, eliminative ether cleavage, and hydrogenation, is established by correlation with a relay compound **27**, independently synthesized via a bimolecular Diels–Alder reaction.

The application of intramolecular Diels–Alder reactions in the elaboration of substituted perhydroisoindolines, as well as kinetic aspects of these reactions, was the subject of earlier reports.[1-3] In this study we describe the use of these intramolecular cycloadditions in the synthesis of 3a-phenylisoindolines. Such compounds appeared particularly attractive to us, as this structural type incorporates some of the essential molecular features of such potent analgetics as Profadol[4] and related molecules.[5]

Our initial goal, in essence, was the preparation of a substrate **3** from α-bromomethylstyrene (**1**) and a pentadienyl amine **2**, followed by an intramolecular [4 + 2] cycloaddition to give the desired **4** (Scheme I). Our attempts to attain practical access to the amine **2** (or the corresponding halide) failed because of its inherent instability. We therefore turned our attention to alternate sources of suitable diene–methylamines, such as *N*-methylfurfurylamine (**5**). In fact we were rather encouraged by earlier reports[6,7] on the successful internal cycloaddition of the *N*-allyl derivative of **5**. The choice of **5** as the diene part added a considerable amount of flexibility, as the oxygenated character of the resulting cycloadduct provides numerous possibilities for further modifications.[8]

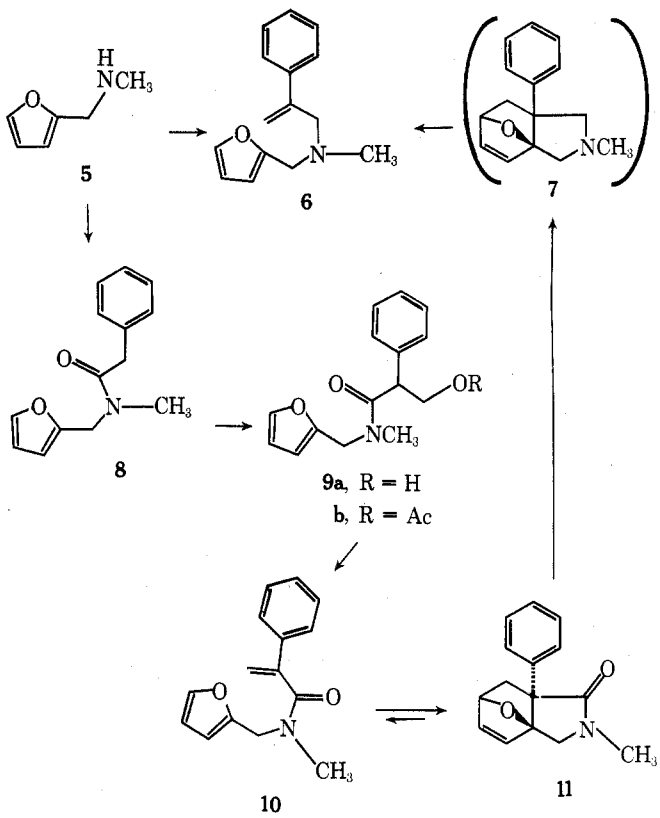
The desired substrate **6** was prepared readily and in high yield from **1** and **5**. Surprisingly, however, **6** resisted any attempt to effect the desired cycloaddition to produce **7**; in fact, compound **6**, when heated in a sealed NMR tube (C_6D_6), remained unchanged up to temperatures of 230°. Suspicions about an extremely facile retro-Diels–Alder reaction led us to lower the temperatures, but even at −60° the NMR spectrum of **6** did not reveal a trace of the elusive cycloadduct **7**. In view of the results reported with the de-

Scheme I



phenyl derivative of **6**,[6] we concluded that the phenyl substituent in **7** would sufficiently destabilize the σ bond to be formed to make **7** essentially nonexistent between −60 and 230°. That this was indeed the case will be corroborated below. Faced with these results we planned to neutralize the destabilizing effects of the phenyl group in **7** with the introduction of a carbonyl group as in **10**, i.e., to synthesize a molecule which would incorporate the "normal" electron-rich diene and an electron-deficient dienophile.[9] The synthesis outlined in Scheme II proved to be more efficient over some more obvious routes involving the highly unsta-

Scheme II

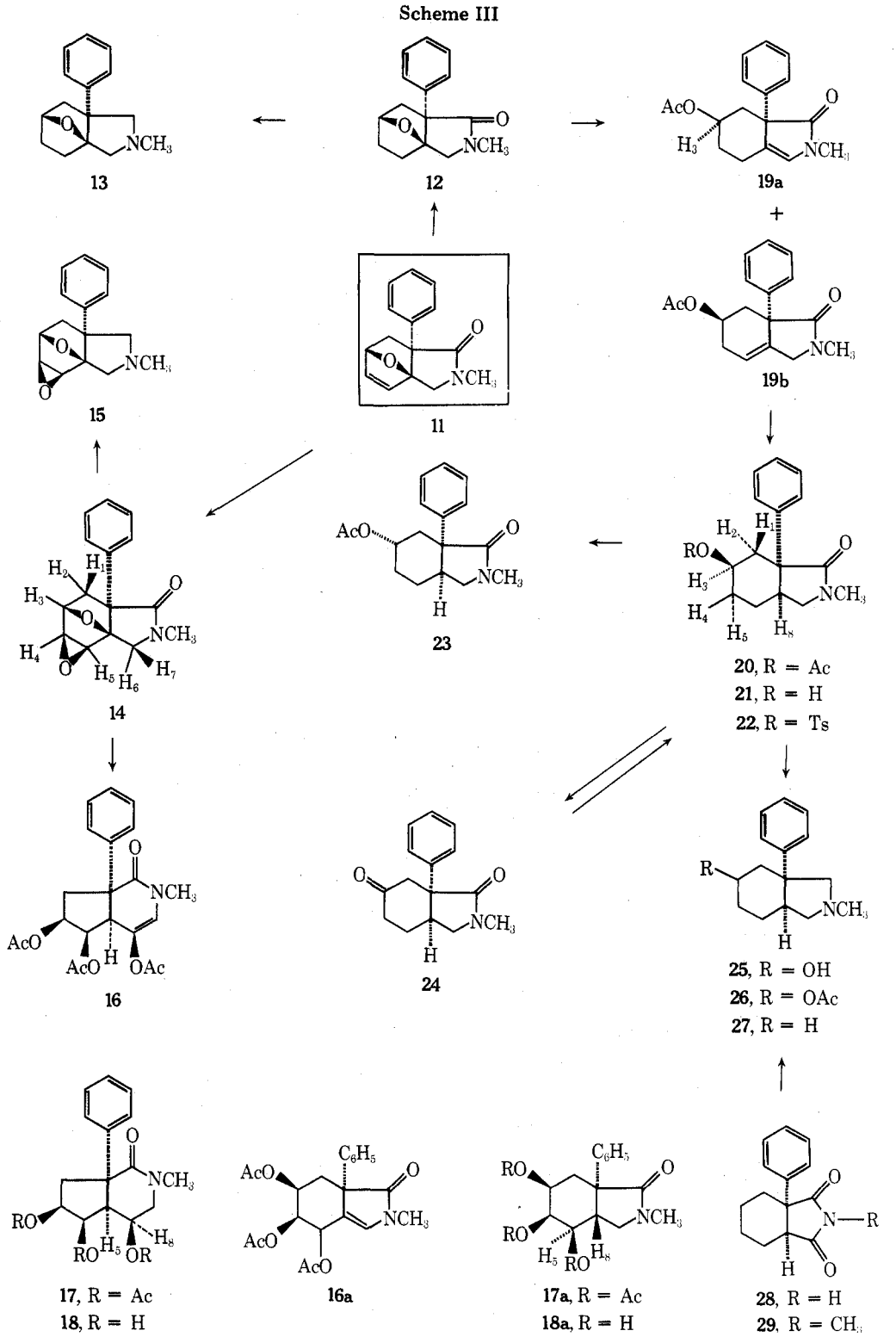


ble furfuryl chloride or atropic acid chloride. The anion of the easily accessible phenylacetamide 8, generated with lithium diisopropylamide,[10] was quenched with paraformaldehyde and the resulting alcohol **9a** was acylated with AcCl. Elimination of HOAc from **9b** with NaOEt in refluxing EtOH produced, via the substrate **10**, the crystalline cycloadduct **11**, which was isolated in a 55% overall yield based upon 8. The structure of **11**, in particular the relative configurational relationship (trans) between the ether bridge and the angular phenyl substituent, is based largely on considerations of both secondary orbital overlap during the transition state of the cycloaddition and steric strain factors. A trans-fused cycloadduct would appear to be highly strained and thus its formation rather unlikely. The extraordinarily transparent NMR spectrum supports this assignment. The propensity of **11** to undergo a $[_{\pi}4_s + {}_{\pi}2_s]$ cycloreversion was, although far less pronounced than in **7**, still evident; and the following solvent and temperature dependent equilibrium mixtures of **10** and **11** could be observed. By heating a C_6D_6 solution of pure **11** (or pure **10**) in a sealed tube at 120° for 15 hr, an equilibrium of 52% **10** and 48% **11** was attained; in a more polar solvent, such as ethanol (reflux, 15 hr), the equilibrium favored the cycloadduct **11** over the open form **10** by a ratio of 61:39. This ratio was determined by actual isolation (preparative TLC chromatography) of **10** and **11**. With the lactam **11** in hand we then set out to test the suspected instability of the elusive cycloadduct **7**. $LiAlH_4$ reduction of the lactam **11** produced an essentially quantitative yield of the styryl amine **6**, thus firmly establishing the inherent instability of the intermediate **7**.

Subsequently a number of transformations were performed in order to prepare oxygenated 3a-phenylisoindolines as originally planned (Scheme I). Catalytic hydrogenation of the dihydrofuran double bond produced the bridged ether **12** (Scheme III), which in turn was reduced to the amine **13**. Epoxidation of the double bond in **11** with *m*-chloroperbenzoic acid gave an 80% yield of an isomerically pure epoxide (**14**). The electrophilic attack of the peracid appeared to take place with high selectivity on the side opposite to the phenyl group, i.e., on the same face of the molecule already occupied by the ether bridge. The stereochemical course of this epoxidation parallels the cis stereoselectivity observed with allylic or homoallylic alcohols[11a] or the exo epoxidation of double bonds in [2.2.1] systems.[11b] This cis relationship of the oxygen functions in **14** was apparent by analyzing the NMR (100 MHz) data. With H_2 and H_3 as well as H_3 and H_4 forming practically 90° angles, the only vicinal coupling left is between H_1 and H_3. The 5-Hz coupling of H_1 collapses to the normal AB part (H_1/H_2) upon irradiation of the frequency of H_3. The assignment of H_1 and H_2 is based on the differential shift upon complexation with $Eu(fod)_3$. As H_1 is affected by the complexation at the ether oxygen, it experiences a greater paramagnetic shift than does H_2. In addition it is observed that only two out of the five aromatic protons (in positions 2 and 6, each with ortho and meta coupling) are shifted to lower field. It can thus be assumed that, with the epoxide ring on the same side as the phenyl substituent, more than just two aromatic protons would experience a downfield shift. Reduction of the lactam carbonyl in **14** with $LiAlH_4$ could be selectively achieved without hydrogenolysis of the epoxide, and the amine **15** was isolated as a crystalline malonate salt.

Treatment of the epoxide **14** with $BF_3{\cdot}Ac_2O$ led to a number of products, the major and most interesting of which was the triacetate **16**, isolated in 29% yield. By analogy with the reaction **12** → **19**, described below, it was originally assumed that the five-membered ether bridge had been cleaved with the formation of the Δ^2-pyrrolenin-5-one moiety, thus leading to a compound represented by formula **16a**. However a careful analysis of the spectral data of **16** and its dihydro derivative **17** led to the conclusion that **16a** was a rather unlikely structure. After considering various alternative possibilities and mechanisms for the formation of the triacetate, the skeletal rearrangement as outlined in Scheme IV appeared particularly attractive not only from a mechanistic point of view, but, more importantly, because the resulting structure **16** could be reconciled with all the available analytical data. While the infrared spectrum in solution was not particularly conclusive, a spectrum in Nujol revealed absorptions at 1760, 1748, and 1674 cm^{-1} attributable respectively to an enol acetate, the two saturated acetates, and a lactam. Above all it was the presence of the enol acetate absorption and the frequency of the unsaturated δ-lactam (1674 vs. 1695 cm^{-1} for **19a**) which led us to favor structure **16** over **16a**. The NMR spectrum of **16** features the vinylic proton H_6 at 6.28 ppm as a singlet and only two hydrogens attached to acetoxy carbon (H_3 at 5.2 and H_4 at 5.52 ppm). The chemical shift of H_5 (d, $J_{5,4}$ = 4 Hz, 3.38 ppm) appears reasonable for structure **16** but would have to be explained by an unusually pronounced shielding influence of the axial phenyl group in **16a**. Upon catalytic hydrogenation of **16** a third downfield proton (H_8) appeared in the 5.30-ppm region, a fact which could easily be reconciled with structure **17**. Alternatively for structure **17a**, which is a trans-fused and hence conformationally immobile cyclohexane system, the unusual low field chemical shift of H_8 would have to be accounted for by a marked deshielding effect of a cis-diaxial acetyl group. In order to pursue such a possibility, **17** (or **17a**) was hydrolyzed to the triol **18** (or **18a**), on the assumption that H_8 would then appear in a more normal position (ca. 3 ppm). However, **18** (or **18a**) continued to exhibit three hydrogens in the carbinol area (ca. 4.2 ppm), thus again favoring the structure as **18**. Finally, in structure **17a** or **18a**, H_5 with its unusual high field signal would be required to exhibit a large axial–axial

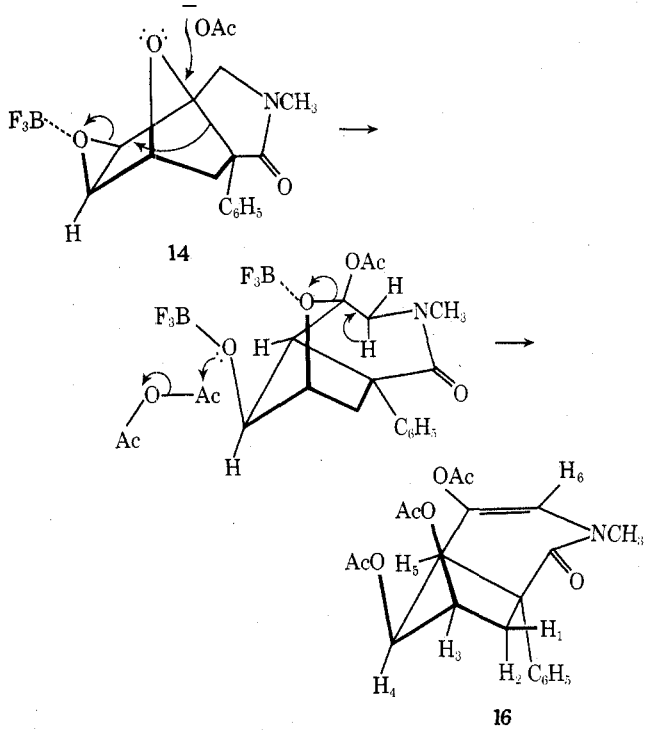
Scheme III



coupling (J = 8.6–11.5 Hz)[12] because of the conformational rigidity of the trans-fused ring system. In the NMR spectrum (in C_6D_6) of **18**, however, H_5 could be observed as a clearly separated triplet resonance with a coupling constant of 5 Hz at 2.74 ppm. The failure to exhibit a larger coupling clearly rules out the structure **18a** and thus **17a** and **16a**. On the basis of the small coupling constant it was also possible to establish the cis configurational relationship between H_5 and H_8 in **17** (and **18**). Thus, the addition of hydrogen took place on the convex side of the cis-fused molecule **16**, leading to an all-cis arrangement of the oxygen function. Additional evidence in support of the rearranged structures **16–18** could be drawn from a comparison of the ir frequencies of the lactam carbonyl in **17** (1633 cm^{-1}) and **20** (1690 cm^{-1}, see below): the rather low frequency of 1633 cm^{-1} is more adequately explained by an acetoxy-δ-lactam (**17**) than by a γ-lactam **17a**, which, after a comparison with **20**, can essentially be eliminated as a possibility. Although a number of attempts were made, we were unable to selectively hydrolyze the enol acetate functionality in **16**, which would have further corroborated its structure.

By subjecting the ether **12** to the same cleavage conditions (BF_3–Ac_2O) a mixture of **19a,b**, differing in the position of the double bond, was obtained. While this elimina-

Scheme IV



tive ether cleavage proceeded rather efficiently when judged by the 60–70% overall yield of **20,** realized by directly hydrogenating the crude mixture of **19a,b,** the pure isomers **19a,b** could only be isolated after extensive chromatography. The major product **19a** was accessible in 25% yield after such a separation. The trans relationship of phenyl and acetoxy group, which could be anticipated based on the relative configuration of the starting material **12,** is firmly corroborated by the NMR data. With the assumption of a chair conformation, the acetoxy group occupies an equatorial and the phenyl ring an axial position. H_3, which could easily be identified with double resonance experiments, exhibits two large couplings indicative of its axial nature. The isomeric lactam **19b** is clearly characterized by the presence of an ABX system assigned to the two protons between double bond and N atom. Upon hydrogenation of either **19a** or **19b** one and the same dihydro product **20** was obtained. Against normal expectations hydrogen was added to the double bond on the same face of **19a,b** already occupied by the large phenyl group, leading to the cis-fused ring system (**20**). This unusual result was initially apparent from NMR spectroscopic data and was later corroborated by an unambiguous chemical synthesis. Analysis of the NMR spectrum of **20** clearly leads to the conclusion that H_3 with no large axial–axial couplings now resides in an equatorial position. Decoupling H_4 and H_5 from H_3 supports this finding. With a trans-fused ring system, an axial position of H_3 would appear highly unlikely. Chemical proof for the cis-fused ring system was obtained by converting the acetate **20** via the alcohol **21** to the tosylate **22.** This was reduced with $LiAlH_4$ to the amine **27,** isolated and characterized as its citrate salt. An independent synthesis began with the Diels–Alder adduct of 3-phenylmaleimide with butadiene which was reported by Huebner.[13] This cis-fused tricyclic imide was then hydrogenated (**28**), N-methylated (**29**), and reduced with $LiAlH_4$ to give the bicyclic amine **27** identical by NMR spectrum, melting point, and mixture melting point of its citrate salt with **27,** obtained from **20.**

An SN2 transformation of the acetoxy group in **20** was achieved by nucleophilic displacement of the tosylate **22** with NaOAc in Me_2SO to produce the desired acetate **23,** isolated by preparative thin layer chromatography, together with an appreciable amount of elimination products and the ketone **24.**[14] Spin–spin decoupling experiments, ideally carried out in C_6D_6 solutions of **23,** clearly indicate that H_3 now occupies an axial position. In an attempt to realize a more efficient access to **23,** the alcohol **21** was oxidized to the ketone with CrO_3–pyridine[15] in 65% yield. $NaBH_4$ reduction of **24,** however, proceeded highly stereoselectively to give almost exclusively the axial alcohol **21** in better than 85% yield. Attempts to reduce **24** to **23** by the use of hydrogen–Pd/C[8] or $Li(O\text{-}t\text{-}Bu)_3AlH$ failed.

Final transformations consisted of the reduction of the lactam **20** to the amino alcohol **25** with $LiAlH_4$ and the acylation of the latter to **26.** All the amines described were evaluated for their potential analgetic activity. In an analogous manner our intramolecular Diels–Alder reaction, as well as the subsequently described transformations, was carried out on a substrate bearing a *m*-CH_3O-phenyl substituent.

Experimental Section

The physical data were obtained as follows: melting points in a Thomas-Hoover melting point apparatus (uncorrected); ir spectra on a Perkin-Elmer 521; uv curves on a Cary Model 14; mass spectra on a AEI MS 902 by direct insertion; NMR spectra on either a Varian A-60 or a XL-100 using tetramethylsilane as internal standard. The following abbreviations are used: (br) broad, (w) weak, (sh) shoulder, (ex) exchangeable with D_2O, (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet.

2-[(2-Furyl)methyl]-*N*-methylbenzeneacetamide (8). To an ice-cooled solution of 33.3 g (300 mmol) of **5** and 42.6 g (300 mmol) of diisopropylethylamine in 300 ml of CH_2Cl_2 was added with stirring 46.2 g (300 mmol) of phenylacetyl chloride in 300 ml of CH_2Cl_2. After the addition was complete, the reaction mixture was stirred at room temperature for 3 hr. Then the organic layer was washed with 1 *N* HCl, then with 10% Na_2CO_3 solution, water, and finally with brine. After drying the organic layer over Na_2SO_4 and removal of the solvent, the residue of 74 g was distilled (140°, 0.2 mmHg) to give 65.0 g of a yellow oil. The oil was crystallized from AcOEt–hexane to give 57.2 g (84%) of amide **8**: mp 69–71°; ir (Nujol) 1635 (br), 1609 cm^{-1}.

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.32; H, 6.73; N, 6.12.

***N*-[(2-Furyl)methyl]-α-hydroxymethyl-*N*-methylbenzeneacetamide (9a).** To an ice-cooled solution of 24.3 g of diisopropylamine in 300 ml of dry THF was added 140 ml of a 1.6 *m* solution of *n*-BuLi in hexane. The solution was then cooled under an atmosphere of N_2 to −45°, at which temperature a solution of 50 g of the amide **8** in 250 ml of dry THF was added dropwise while stirring magnetically. After the addition, during which the reaction mixture turned purplish, the temperature was allowed to rise to −20° over a 1-hr period. Subsequently, the temperature was lowered again to −45° and 9.8 g of dry paraformaldehyde was added. The mixture was then stirred at room temperature for 16 hr, cooled again in a dry ice–acetone bath, and quenched with 230 ml of 2 *N* HCl to adjust the pH to 5. The mixture was diluted with ether, the two layers separated, the aqueous phase reextracted with ether, and the organic layers washed with water and brine. After drying (Na_2SO_4) and removal of the solvent, 53.6 g of an oily residue was obtained (**9a**), ir (liquid) 3500, 1630 cm^{-1}.

Intramolecular Cycloaddition. 2,3,6,7-Tetrahydro-2-methyl-7a-phenyl-3a,6-epoxyisoindol-1-one (11). A solution of 198 g of crude hydroxy amide **9a** in 540 ml of acetyl chloride was refluxed for 1 hr. After removal of the reagent, the residue was dried under vacuum to give 220 g of a dark oil (**9b**): NMR ($CDCl_3$) δ 1.5 (s, 3 H), 2.9 (2 s, 3 H), 3.85–5.9 (m, 5 H), 6.0–6.4 (m, 2 H), 7.35 (s, 5 H).

A solution of 53 g (2.3 mol) of Na in 1.64 l. of ethanol was refluxed with 164 g (0.57 mol) of the crude acetoxy amide **9b** under N_2 for 16 hr. The solvent was then evaporated to dryness and the residue taken up in CH_2Cl_2 and washed twice with water, then with brine. After drying and removal of the solvent a residue of 134.7 g was obtained. This was dissolved in 350 ml of ether, whereupon the cycloadduct crystallized out. A first crop of 50.1 g of **11** (mp 155–156°) (36%) was collected. The mother liquor was evapo-

rated and refluxed for 1 week in 730 ml of benzene. An additional 18.2 g of **11** could be collected. Repetition of this procedure gave another 8 g of product (mp 155°), thus bringing the total yield to 76.3 g (55% overall based on crystalline phenylacetamide **8**): ir (Nujol) 1685, 750, 740, 720, 710, 700 cm^{-1}; NMR ($CDCl_3$) δ 1.85 (d, J = 12 Hz, 1 H), 2.82 (dd, J = 12 and 4.5 Hz, 1 H), 3.0 (s, 3 H), 3.83 (AB, J = 12 Hz, 2 H), 5.09 (dd, J = 4.5 and 1.9 Hz, 1 H), 6.26 (d, J = 6.1 Hz, 1 H), 6.53 (dd, J = 6.1 and 1.9 Hz, 1 H), 7.21 (m, 5 H).

Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.76; H, 6.11; N, 5.93.

Reduction and Retro-Diels–Alder. 11 → 6 (*N*-Methyl-*N*-(2-methylene-2-phenylethyl)-2-furanmethanamine. To a solution of 2.41 g (10 mmol) of isoindolone **11** in 300 ml of dry ether was added 1.68 g (30 mmol) of $LiAlH_4$. The mixture was refluxed for 24 hr. After cooling in an ice bath, excess reagent was destroyed with 1.68 ml of H_2O, 1.68 ml of 15% NaOH, and 5.04 ml of H_2O. The granular precipitate was then removed by filtration and the solvent evaporated in vacuo to give 2.1 g (93%) of an oil (**6**): ir (liquid) no >CO absorption; NMR ($CDCl_3$) identical with the one described for the independently synthesized compound (**5** + **1** → **6**).

***N*-Methyl-*N*-(2-methylene-2-phenylethyl)-2-furanmethanamine (6).** To a solution of 1.11 g (10 mmol) of **5** in 20 ml of dry ether, cooled to −70°, was added 6.3 ml (10 mmol) of 1.6 *m* *n*-BuLi–hexane. Then 2 g (10 mmol) of α-bromomethylstyrene (**1**) in 10 ml of dry ether was added and the temperature of the reaction mixture was allowed to rise to 25°. After 3 hr of stirring at room temperature the reaction mixture became homogeneous and was quenched with H_2O. The product was extracted into 1 *N* HCl, the aqueous acidic layer basified with 20% NaOH, and the product extracted into ether. After drying and removal of the solvent 1.82 g (80%) of a yellow oil (**6**) was obtained: NMR ($CDCl_3$) δ 2.2 (s, 3 H), 3.36 (s, 2 H), 3.55 (s, 2 H), 5.26 (d, J = 1.1 Hz, 1 H), 5.43 (d, J = 1.1 Hz, 1 H), 6.07–6.35 (m, 2 H), 7.16–7.55 (m, 6 H).

Heating of a 10% solution of this amine **6** in C_6D_6 (sealed NMR tube) for extended periods of time at 85, 106, 130, 160, 180, and 230° did not result in a change of the NMR spectrum. Also at −60°, the NMR spectrum remained unchanged.

2,3,4,5,6,7-Hexahydro-2-methyl-7a-phenyl-3a,6-epoxyisoindol-1-one (12). A solution of 30 g (124 mmol) of isoindolone **11** in 750 ml of EtOH was hydrogenated over 3 g of PtO_2 and 45 lb of H_2 pressure until the theoretical amount of H_2 had been taken up. The solvent was freed from catalyst by filtration through Filtercell. After evaporation of the filtrate, the residue (28.8 g) was crystallized from benzene–hexane to give 25.4 g (85%) of **12**: mp 98–99°; ir (Nujol) 1690, 770, 740, 720, 700 cm^{-1}; NMR ($CDCl_3$) δ 1.5–2.8 (m, 6 H), 3.0 (s, 3 H), 3.64 (AB, J = 11 Hz, 2 H), 4.62 (t, br, J = 4.5 Hz, 1 H), 7.26 (s, 5 H).

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.29; H, 7.33; N, 5.53.

1,3,4,5,6,7-Hexahydro-2-methyl-7a-phenyl-3a,6-epoxyisoindole (13). To a solution of 650 mg (17 mmol) of $LiAlH_4$ in 250 ml of ether was added 2.7 g (11 mmol) of solid lactam **12** and the mixture refluxed for 16 hr. After cooling the reaction mixture, excess reagent was destroyed with a saturated solution of Na_2SO_4. After removing the inorganic solid by filtration and evaporation of the solvent, 2.4 g of an oily residue was obtained. The oil was dissolved in 50 ml of acetone and neutralized with 1.98 g of cyclohexylsulfamic acid to give 3.73 g of salt **13**, mp 152–153°.

Anal. Calcd for $C_{15}H_{19}NO{\cdot}C_6H_{13}NO_3S$: C, 61.73; H, 7.90; H, 6.86. Found: C, 61.73; H, 8.15; N, 6.83.

5-Methyl-3-phenyl-9,11-dioxa-5-azatetracyclo[5.3.1.$0^{3,7}$.$0^{8,10}$]undecan-4-one (14). To a solution of 10 g (41.5 mmol) of **11** in 200 ml of CH_2Cl_2 was added 17.6 g of solid K_2CO_3. After cooling to 0° a solution of 8.5 g of *m*-chloroperbenzoic acid in 200 ml of CH_2Cl_2 was added with vigorous stirring. The mixture was allowed to warm up to room temperature and stirred for 16 hr. The K_2CO_3 was filtered off and the organic layer washed with 10% aqueous Na_2CO_3, water, and brine and dried over Na_2SO_4. After removal of the solvent, the solid residue (11.0 g) was recrystallized from AcOEt to give a first crop of 7.6 g (mp 184–187°) and a second crop of 1.3 g (80%): ir (Nujol) 1690 cm^{-1}; NMR ($CDCl_3$) δ 2.15 (d, J = 13.5 Hz, 1 H), 2.72 (dd, J = 13.5 and 5 Hz, 1 H), 3.95 (s, 3 H), 3.27 (d, J = 3.5 Hz, 1 H), 3.47 (d, J = 3.5 Hz, 1 H), 3.8 (AB, J = 11.5 Hz, 2 H), 4.57 (d, J = 5 Hz, 1 H), 7.5 (s, 5 H).

Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.34; H, 5.97; N, 5.61.

5-Methyl-3-phenyl-9,11-dioxa-5-azatetracyclo[5.3.1.$0^{3,7}$.$0^{8,10}$]undecane (15). A solution of 12 g (46.5 mmol) of **14** in 200 ml of dry THF was added to a suspension of 7.08 g (185 mmol) of $LiAlH_4$ in 300 ml of THF. The reaction mixture was then refluxed for 16 hr and cooled in an ice bath and excess reagent was destroyed by adding 7 ml of H_2O, 7 ml of 15% NaOH, and 21 ml of H_2O. Filtration and evaporation of the filtrate gave an oily residue which was taken up in AcOEt and which was extracted with 2 *N* HCl. The acidic layer was made basic with 20% NaOH and extracted into AcOEt. After drying and evaporating the organic layer 9.8 g of an oil was obtained. Filtration through a silica gel column using benzene–ether (1:1) gave 7.8 g of an oil: NMR ($CDCl_3$) δ 1.97 (d, J = 13 Hz, 1 H), 2.3 (dd, J = 13 and 4.5 Hz, 1 H), 2.4 (s, 3 H), 2.8 (AB, J = 8.5 Hz, 2 H), 3.25 (AB, J = 12 Hz, 2 H), 3.27 (s, 2 H), 4.53 (d, J = 4.5 Hz, 1 H), 7.25 (s, 5 H). A 6.45-g portion of this oil was converted into the malonate salt which crystallized from acetone to give 6.7 g: mp 152–153°; ir (Nujol) 1730–1700, 1600 cm^{-1} (br).

Anal. Calcd for $C_{15}H_{17}NO_2{\cdot}C_3H_4O_4$: C, 62.24; H, 6.10; N, 4.03. Found: C, 62.50; H, 6.13; N, 3.99.

4,5,6-Triacetoxy-4a,5,6,7-tetrahydro-2-methyl-7a-phenyl-2-pyrindin-1-one (16). To a suspension of 12 g (47.5 mmol) of the epoxide **14** in 94 ml of Ac_2O was added dropwise a solution of 12.6 ml (110 mmol) of boron trifluoride etherate in 150 ml of benzene. After the mixture was refluxed for 2 hr it turned dark. The reaction mixture was cooled, diluted with AcOEt, and washed with 10% aqueous Na_2CO_3, then with H_2O and brine. After drying and removal of the solvent, a black solid (19.6 g) was obtained which was passed through a column of 400 g of alumina (activity III) using benzene–ether (1:1). The first fraction eluted 11.6 g of an oil which was crystallized from ethyl acetate to give a total of 5.4 g (29%) of **16**: mp 141–142°; ir (Nujol) 1760, 1748, 1674 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 2.0, 2.05, 2.15 (3 s, 9 H), 2.52–3.26 (ABX, J = 8 and 14 Hz, 2 H), 3.03 (s, 3 H), 3.38 (d, J = 4 Hz, 1 H), 5.2 (six lines, J = 4 and 8 Hz, 1 H), 5.52 (t, J = 4 Hz, 1 H), 6.28 (s, 1 H), 7.2–7.6 (m 5 H).

Anal. Calcd for $C_{21}H_{23}NO_7$: C, 62.83; H, 5.78; N, 3.49. Found: C, 62.79; H, 6.03; N, 3.79.

4,5,6-Triacetoxy-3,4,4a,5,6,7-hexahydro-2-methyl-7a-phenyl-2-pyrindin-1-one (17). A solution of 200 mg (0.5 mmol) of triacetate **16** in 100 ml of EtOH was hydrogenated over 200 mg of 10% Pd/C at 45 lb of H_2 pressure for 3 hr. After filtration through Filter-Cell and removal of the solvent, the residual solid was recrystallized from AcOEt to give 150 mg of dihydro compound **17**: mp 147–148°; ir (Nujol) 1745 (s), 1738, 1633 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 2.01 (s, 3 H), 2.09 (s, 6 H), 2.5–3.2 (m, 3 H), 3.05 (s, 3 H), 3.51 (ABX, J = 5 and 12 Hz, 2 H), 5.3 (m, 2 H), 6.59 (t, J = 4 Hz, 1 H), 7.31 (m, 5 H).

Anal. Calcd for $C_{21}H_{25}NO_7$: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.76; H, 6.21; N, 3.38.

4,5,6-Trihydroxy-3,4,4a,5,6,7-hexahydro-2-methyl-7a-phenyl-2-pyrindin-1-one (18). A solution of 500 mg of **17** in 50 ml of saturated methanolic ammonia was refluxed for 3 days. All solvent was then removed in vacuo and the solid residue recrystallized from CH_3OH–AcOEt to give 260 mg, mp 113–116° (**18**): ir (Nujol) 1609 cm^{-1}; mass spectrum *m/e* 277 (M^+), 259, 230, 204, 192, 186, 172, 150; NMR (100 MHz, C_6D_6) (after H → D exchange) δ 2.5 (dd, J = 7 and 14 Hz, 1 H), 2.74 (t, J = 5 Hz, 1 H), 2.90 (s, 3 H), 3.20 (dd, J = 5 Hz, 1 H), 3.22 (dd, J = 7 and 12 Hz, 1 H), 3.49 (dd, J = 7 Hz, 1 H), 4.24 (m, 3 H), 7.22 (m, 5 H).

Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 64.58; H, 7.21; N, 5.00.

6-Acetoxy-3(or 4),5,6,7-tetrahydro-2-methyl-7a-phenylisoindol-1-one (19a,b). After dissolving 25.8 g (53 mmol) of **12** in 26 ml of Ac_2O, a solution of 14.6 ml of boron trifluoride etherate in 260 ml of benzene was added and the mixture was refluxed for 2 hr. The reaction mixture was diluted with AcOEt, and the organic layer was washed to neutral with aqueous $NaHCO_3$ and water and finally dried over Na_2SO_4. After removal of the solvent 32 g of a dark oily residue was obtained which was passed through a column of neutral alumina (activity III) using benzene–ether (1:1). The eluated material was dissolved in 50 ml of ether and the crystals thus formed collected to give 6 g of **19a**, mp 112–120°. Recrystallization from AcOEt gave analytically pure material: mp 120–123°; ir (Nujol) 1730, 1695 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 1.16–1.8 (m, 2 H), 2.0 (s, 3 H), 2.0–2.7 (m, 3 H), 2.99 (s + m, 3 + 1 H), 4.71 (tt, J = 12 and 4 Hz, 1 H), 6.27 (m, 1 H), 7.3 (m, 5 H).

Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.69; H, 6.90; N, 5.10.

Careful rechromatography of 1.3 g of oily mother liquor on 39 g of alumina (III, neutral) and elution with benzene gave 260 mg of reasonably pure isomeric acetate **19b**: NMR ($CDCl_3$) δ 1.2–3.1 (m, H), 1.92 (s, 3 H), 2.74 (s, 3 H), 3.85 (ABX, 2 H), 4.7 (m, 1 H), 5.83 (m, 1 H), 7.3 (m, 5 H).

6-Acetoxy-3,3a,4,5,6,7-hexahydro-2-methyl-7a-phenylisoindol-1-one (20). A solution of 200 mg of acetate **19a** in 100 ml of ethanol was hydrogenated over 200 mg of 10% Pd/C at 45 lb H_2 pressure for 1.5 hr. After filtration through Filter-Cell, removal of the solvent, and recrystallization of the solid residue from AcOEt, 150 mg of **20** was obtained: mp 108–109°; ir (Nujol) 1728, 1690 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 1.75 (m, 4 H), 2.01 (s, 3 H), 2.14 (d, J = 5 Hz, 2 H), 2.75 (m, 1 H), 2.88 (s, 3 H), 3.04 and 3.28 [2 dd (AMX)], 4.88 (m, 1 H), 7.3 (m, 5 H).

Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37; N, 4.87. Found: C, 70.95; H, 7.46; N, 5.02.

Analogous treatment of isomer **19b** (200 mg of oily material) gave a similar yield of the same product, identical by melting point, mixture melting point, ir, and NMR spectrum.

For the preparation of larger quantities of **20**, it was more convenient to subject the crude material of the BF_3–Ac_2O treatment directly to the same hydrogenation conditions. A 60–70% overall yield (from **12**) of **20** could thus be achieved.

Octahydro-2-methyl-7a-phenylisoindol-6-ol (25). A solution of 16 g (55.6 mmol) of acetoxy lactam **20** and 8.5 g (223 mmol) of $LiAlH_4$ in 600 ml of ether was refluxed for 16 hr. Excess reagent was then destroyed with 8.5 ml of H_2O, 8.5 ml of 15% NaOH, and 25.5 ml of water. Removal of the granular precipitate by filtration and evaporation gave 13.2 g of an oily residue (**25**): NMR ($CDCl_3$) δ 1.85–2.4 (m, 6 H), 2.6 (s, 3 H), 2.77–3.35 (m, 5 H), 3.45–3.85 (m, 1 H), 4.75 (s, 1 H), 7.45 (s, 5 H).

This oil (6 g) was dissolved in 200 ml of 2-butanone and converted to the citrate salt with 5.5 g of citric acid in 100 ml of 2-butanone. The precipitate was filtered and recrystallized from EtOH to give 8.8 g (80%): mp 193–194°; ir (Nujol) 3525, 1740 cm^{-1}.

Anal. Calcd for $C_{15}H_{21}NO \cdot C_6H_8O_7$: C, 59.56; H, 6.90; N, 3.31. Found: C, 59.17; H, 7.19; N, 3.30.

Octahydro-2-methyl-7a-phenylisoindol-6-ol Acetate (26). A solution of 7 g (30.2 mmol) of the above crude amino alcohol **25** in 200 ml of AcCl was refluxed for 1 hr. Excess reagent was then removed in vacuo, and the solid residue recrystallized from 200 ml of acetone to give 6.9 g of HCl salt (**26**), mp 228–230°, ir (Nujol) 1720 cm^{-1}.

Anal. Calcd for $C_{17}H_{23}NO_2 \cdot HCl$: C, 65.90; H, 7.80; N, 4.51. Found: C, 66.18; H, 8.07; N, 4.38.

6-Hydroxy-3,3a,4,5,6,7-hexahydro-2-methyl-7a-phenylisoindol-1-one (21). A solution of 861 mg (3 mmol) of **20** and 15 mmol of $NaOCH_3$ in 10 ml of CH_3OH was refluxed for 1 hr. The solvent was evaporated to dryness, and the residue was taken up in CH_2Cl_2 and washed with dilute HCl, water, and brine. After drying and removal of the solvent, the oily residue (640 mg) was crystallized from AcOEt–hexane to give 350 mg of **21**: mp 114–116°; ir ($CHCl_3$) 3500, 1680 cm^{-1}; NMR ($CDCl_3$) δ 1.58–2.15 (m, 6 H), 2.5–3.45 (m, 4 H), 2.85 (s, 3 H), 3.85 (t, br, J = 4 Hz, 1 H), 7.29 (s, br, 5 H).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.67; H, 7.76; N, 5.69.

3,3a,4,5,6,7-Hexahydro-2-methyl-7a-phenyl-6-(4-methylphenyl)sulfonyloxyisoindol-1-one (22). A solution of 6 g (24.5 mmol) of alcohol **21** in 72 ml of dry pyridine was cooled in an ice bath and treated with 9.3 g (49 mmol) of p-toluenesulfonyl chloride. The mixture was left in a stoppered flask at 0° for 18 hr. Then it was poured into ice water and the precipitate collected and washed with water. Recrystallization from benzene–hexane produced 7.8 g (80%) of tosylate **22**: mp 181–182°; ir ($CHCl_3$) 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.7–2.2 (m, 6 H), 2.46 (s, 3 H), 2.88 (s, 3 H), 3.1–3.4 (m, 2 H), 4.16–4.6 (m, 1 H), 7.16–7.8 (m, 9 H).

Anal. Calcd for $C_{22}H_{25}NO_4S$: C, 66.14; H, 6.30; N, 3.50. Found: C, 66.10; H, 6.56; N, 3.82.

Octahydro-2-methyl-7a-phenylisoindole (27). A solution of 3.99 g (10 mmol) of tosylate **22** in 200 ml of ether was refluxed with 1.52 g of $LiAlH_4$ for 16 hr. Excess hydride was then destroyed by adding 1.5 ml of H_2O, 1.5 ml of 15% NaOH, and 4.5 ml of H_2O. After filtering off the granular inorganic precipitate and evaporation of the solvent, 2.05 g of an oily residue were obtained, NMR ($CDCl_3$) δ 1.2–3.1 (m, 13 H), 2.4 (s, 3 H), 7.25 (s, 5 H).

The crude product was dissolved in 2-butanone and neutralized with citric acid. Recrystallization of the salt thus formed from CH_3OH gave 2.5 g (81%), 189–190°.

Anal. Calcd for $C_{15}H_{21}N \cdot C_6H_8O_7$: C, 61.90; H, 7.17; N, 3.44. Found: C, 61.82; H, 7.27; N, 3.51.

3,3a,4,5-Tetrahydro-2-methyl-7a-phenylisoindol-1,6(7*H*)-dione (24). To a magnetically stirred solution of 9.49 g (120 mmol) of dry pyridine in 150 ml of CH_2Cl_2 was added 6 g (60 mmol) of CrO_3. The mixture was allowed to stir at room temperature for 15 min. To this solution was then added a solution of 2.45 g (10 mmol) of alcohol **21** in 10 ml of CH_2Cl_2. The reaction mixture turned dark, and after an additional 15 min of stirring at room temperature the solvent was decanted, washed with 5% aqueous NaOH, then with 5% HCl, with saturated $NaHCO_2$, and finally with brine. After drying over Na_2SO_4, the solvent was evaporated to give 2.1 g of an oily residue. Crystallization from AcOEt–ether gave 1.6 g of ketone **24** (65%): mp 64–66°; ir ($CHCl_3$) 1720, 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.75–3.31 (m, 8 H), 2.92 (s, 3 H), 3.62 (dd, J = 10 and 7 Hz, 1 H), 7.2 (s, 5 H).

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.37; H, 7.14; N, 5.73.

6-Hydroxy-3,3a,4,5,6,7-hexahydro-2-methyl-7a-phenylisoindol-1-one (21 ← 24). A solution of 486 mg (2 mmol) of ketone **24** in 10 ml of EtOH was stirred for 2 hr with 148 mg of $NaBH_4$ at 5°. The mixture was then concentrated to dryness, excess hydride destroyed with 2 *N* HCl, and the product extracted into CH_2Cl_2. After washing the organic layer with brine, drying it over Na_2SO_4, and removal of the solvent, 430 mg of solid alcohol **21** was obtained, mp 107–109°; ir and NMR spectra, as well as TLC (silica, ether–benzene, 1:1) were identical with those of the alcohol described earlier (**20 → 21**).

SN2 on Tosylate 22 → 23 + 24. A solution of 798 mg of tosylate **22** and 650 mg of anhydrous NaOAc in 10 ml of Me_2SO were stirred in an oil bath of 120° for 5 hr. The mixture was then cooled, diluted with CH_2Cl_2, and washed with brine. After drying the organic layer over Na_2SO_4 and removal of all solvents, 450 mg of a yellow oil was obtained. Preparative TLC (silica, $CHCl_3$–AcOEt, 4:1) gave **24** (59 mg, R_f 0.20), **23** (143 mg, R_f 0.4), and 210 mg (R_f 0.55) of elimination products. **23**: NMR (100 MHz, $CDCl_3$) δ 1.2–1.6 (m, 2 H), 1.68 (dd, J = 11 and 13 Hz, 1 H), 1.92 (s, 3 H), 2.02 (m, 2 H), 2.59 (m, 2 H), 2.72 (d, J = 9 Hz, 1 H), 2.86 (s, 3 H), 3.22 (dd, J = 5 and 9 Hz, 1 H), 4.68 (m, 1 H), 7.3 (m, 5 H). **24**: NMR identical with that of oxidation product from **21 → 24**.

Independent Synthesis of Octahydro-2-methyl-7a-phenylisoindole (27 ← 28). To a solution of 460 mg (2 mmol) of imide **28** in 5 ml of DMF was added 100 mg of NaH (55%, washed twice with ether). After 10 min 300 mg of CH_3I was added and the mixture stirred at ambient temperature for 1.25 hr. The mixture was then poured onto ice–water and the product extracted into ether. After drying (Na_2SO_4) and evaporating the organic layer, the residue of 500 mg was crystallized from ether to give 340 mg of **29**, mp 95°. This imide (220 mg) was dissolved in 25 ml of ether and reduced with 100 mg of $LiAlH_4$. After 2 hr at 25°, excess reagent was destroyed, the inorganic material filtered, and the ether evaporated to give an oil (200 mg) whose NMR spectrum was superimposable on the one of **27**. The melting point of its citrate salt was 189° and a mixture melting point with **27** (obtained from **22**) gave no depression.

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2-(3-Aryl-5-pyrazolyl)benzoic Acid Chemistry

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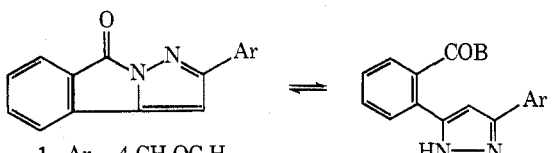
The nucleophilic ring-cleavage reactions of 2-(4-methoxyphenyl)-8*H*-pyrazolo[5,1-*a*]isoindol-8-one (1) and its analogues with aqueous base, alcohols, and primary and secondary amines are convenient syntheses of 2-[3-(4-methoxyphenyl)-5-pyrazolyl]benzoic acid (4), its esters (5), and amides (6), and their analogues. These reactions may be reversed by heat and by dehydrating agents such as $SOCl_2$, $POCl_3$, and Ac_2O. The derivative chemistry of 4 is discussed.

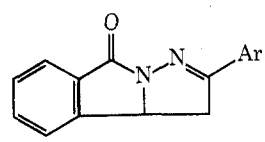
We have described[1] the synthesis of 2-(4-methoxyphenyl)-8*H*-pyrazolo[5,1-*a*]isoindol-8-one (1) from its 3,3a-dihydro derivative (9), which was prepared from phthalaldehydic acid, 4-methoxyacetophenone, and hydrazine. We now wish to report the further chemistry of these interesting plant growth regulants,[2-9] which concerns their conversion to 2-[3-(4-methoxyphenyl)-5-pyrazolyl]benzoic acid (4), its esters (5), and amides (6) by reaction with aqueous base, alcohols, and amines. These new compounds are also plant growth regulants.[10,11] In solution at 25°, the pyrazoloisoindolone 1 and its analogues are very susceptible to nucleophilic attack at the γ-lactam function to form 4–6 and their analogues. The progress of these reactions is readily followed by the rapid disappearance of the bright yellow color of 1, an observation which appears to have escaped Leclerc,[12] who reported the uv spectrum of the phenyl analogue 2 in ethanol as λ_{max} 248 nm (ε 36000) and 335 (1480). The true spectrum of 2, obtained in an unreactive solvent such as THF, has λ_{max} 337 nm (ε 10960), 323 (10880), 290 (13890), and 254 (35950), showing clearly that Leclerc's sample had partly decayed in solution to ester 7 after preparation. The ring-opened ester 7 has λ_{max} (EtOH) 252 nm (ε 25140), a value which is typical of this class of compounds.



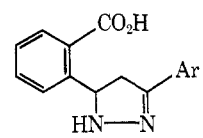
1, Ar = 4-$CH_3OC_6H_4$
2, Ar = C_6H_5
3, Ar = 4-HOC_6H_4

4, Ar = 4-$CH_3OC_6H_4$; B = OH
5, Ar = 4-$CH_3OC_6H_4$; B = OR
6, Ar = 4-$CH_3OC_6H_4$; B = NR_1R_2
7, Ar = C_6H_5; B = OC_2H_5
8, Ar = 4-HOC_6H_4; B = OH

The 3,3a-dihydro derivative 9 behaves similarly to 1 toward nucleophiles, but the resulting 2,3-dihydropyrazole derivatives (e.g., 11) are oxidatively unstable, and the usual product after atmospheric isolation is a mixture of 11 and 4. An exception is the phenol 12, which can be isolated pure in good yield by treating the phenol 10 with aqueous base.



9, Ar = 4-$CH_3OC_6H_4$
10, Ar = 4-HOC_6H_4



11, Ar = 4-$CH_3OC_6H_4$
12, Ar = 4-HOC_6H_4

Although dihydropyrazole 10 may be prepared most conveniently by the demethylation of 9 with 48% HI, the corresponding pyrazole 1 is converted to the ring-opened phenol 8 by this treatment.[13] Table I lists the compounds prepared by these methods, using the general procedures described in the Experimental Section.

Spectra. The fused γ-lactam structure of 1 and 2 gives their spectra characteristic ir bands at 1780 and 1760 (1), 1790 and 1760 cm^{-1} (2), and a pair of intense uv bands at 346 and 331 (1) and 337 and 323 nm (2). The compounds in Table I have entirely different spectra, with the ir carbonyl frequencies expected for aromatic acids (1670–1690 cm^{-1}), their esters (1705–1720 cm^{-1}), and amides (1610–1670 cm^{-1}), and uv absorptions near 260 nm with slight variations in extinction coefficient for the acids (30000–36000), esters (26000–29000), and amides (31000–33000). The position of the singlet pyrazole proton signal (δ 6.60–7.00 ppm) in the proton NMR spectra of the ring-opened compounds does not distinguish them from the cyclic forms where the signal is at 6.63 ppm in 1 and 6.68 ppm in 2. The spectral differences between the cyclic dihydro form 9 [1690 cm^{-1}, 323 nm (ε 18070), 277 (9080), and 268 (9150)] and its cleavage product 12 [1700 cm^{-1}, 282 nm (ε 17400)] are less pronounced, but do reflect the differences between these structures.