(25) In our hands, the reaction of 2-benzyl-1,3,4,7-tetramethylisoindole[26] with slightly less than 1 equiv of benzyne produced **57** in relatively good yield. This result is in contrast to that reported by Kricka and Vernon [*J. Chem. Soc., Perkin Trans. 1*, 766 (1973)], who obtained only mass spectral evidence for the presence of **57** in this Diels–Alder reaction. Their major product was a triptycene derivative resulting from further deaminative attack of benzyne on the anthracenimine.
(26) C. O. Bender and R. Bonnett, *J. Chem. Soc. C*, 3036 (1968).
(27) H. Gilman and L. A. Woods, *J. Am. Chem. Soc.*, **65**, 33 (1943).
(28) C. Graebe and A. Pietet, *Justus Liebigs Ann. Chem.*, **247**, 305 (1888).
(29) Henri de Diesback, *Helv. Chim. Acta*, **23**, 1232 (1940).
(30) J. Kollonitsch, H. E. Mertel, and V. F. Verdi, *J. Org. Chem.*, **27**, 3362 (1962).
(31) S. Gabriel and G. Giebe, *Chem. Ber.*, **29**, 2518 (1896).
(32) A. H. Lewin, J. Lipowitz, and T. Cohen, *Tetrahedron Lett.*, 1241 (1965).
(33) W. Borsch, K. Diacont, and H. Hanan, *Chem. Ber.*, **67B**, 675 (1934).
(34) G. C. Finger, F. H. Reed, D. M. Burness, D. M. Fort, and R. R. Blough, *J. Am. Chem. Soc.*, **73**, 145 (1951).
(35) T. H. Fife and L. K. Jao, *J. Org. Chem.*, **30**, 1492 (1965).
(36) H. Tanida, R. Muneyuki, and T. Tsumi, *Bull. Chem. Soc. Jpn.*, **37**, 40 (1964).
(37) R. Muneyuki and H. Tanida, *J. Org. Chem.*, **31**, 1988 (1966).
(38) J. F. Bunnett and C. E. Moyer, Jr., *J. Am. Chem. Soc.*, **93**, 1183 (1971).
(39) P. S. Anderson, M. E. Christy, E. L. Englehardt, G. F. Lundell, and G. S. Ponticello, *J. Heterocycl. Chem.*, **14**, 213 (1977).
(40) G. Wittig and W. Merkle, *Chem. Ber.*, **75**, 1491 (1942).
(41) G. Wittig, E. Knauss, and K. Niethammer, *Justus Liebigs Ann. Chem.*, **630**, 10 (1960), report a 54% yield using method G, mp 159–160.5 °C.
(42) L. M. Yagupolskii and M. S. Marenets, *Zh. Obshch. Khim.*, **29**, 278 (1959).
(43) J. R. Geigy, A-G., Swiss Patent 245 679, Aug 1, 1947; *Chem Abstr.*, **43**, 5802b (1949).
(44) J. B. Cohen and H. S. Roper, *J. Chem. Soc.*, 1269 (1904).
(45) B. B. Elsner and H. E. Strauss, *J. Chem. Soc.*, 583 (1957).

Synthesis of 8-Phenyl-1,2,3,4-tetrahydroisoquinolines

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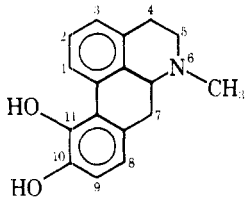
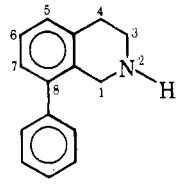
A general synthesis for the preparation of previously unreported 8-phenyl-1,2,3,4-tetrahydroisoquinolines is described. The directing properties of aryloxazolines were used for an unambiguous route to appropriate 1,2,3-trisubstituted benzenes (2,6-disubstituted aryloxazolines). Hydrolysis of the oxazolines produced 8-phenylisocoumarins, which were readily converted into the 8-phenylisoquinoline derivatives.

Although many methods[1] are available for the synthesis of isoquinolines and tetrahydroisoquinolines, none are satisfactory for the synthesis of 8-phenylisoquinoline derivatives. 8-Phenyl-1,2,3,4-tetrahydroisoquinoline is interesting because it possesses the basic structural features of the apomorphine ring system without the C-7 methylene bridge which holds the two aromatic rings in a nearly planar configuration. Only one synthesis of 8-phenylisoquinoline has appeared,[2] and no reports of its tetrahydro derivative have been described. Attempts to produce 8-phenylisoquinoline by the Pomeranz–



apomorphine



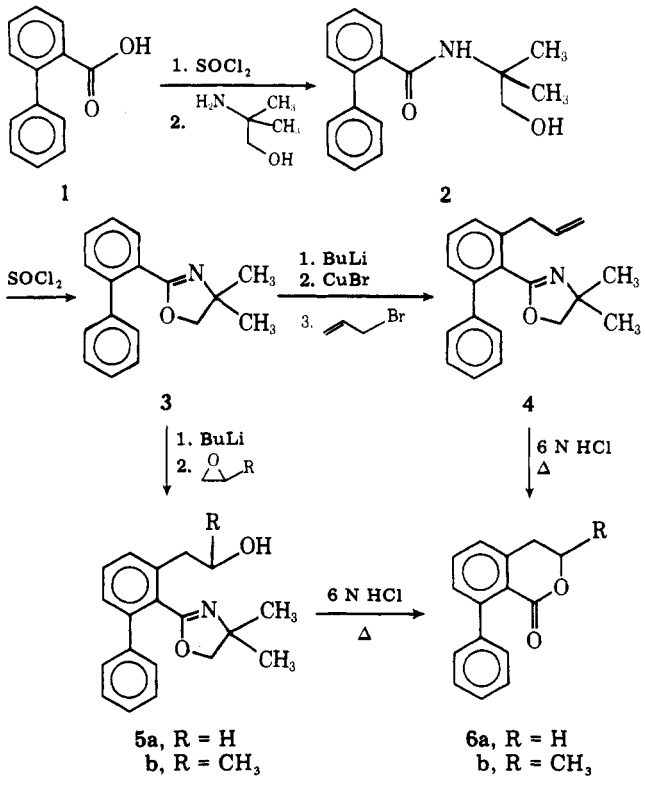
8-phenyltetrahydroisoquinoline

Fritsch reaction failed,[2] and the Bischler–Napieralski reaction gave 6- or 7-phenyl isomers but no 8-phenylisoquinoline derivatives.[3]

This report describes a general synthesis that has been successfully utilized for the preparation of 8-phenyl-1,2,3,4-tetrahydroisoquinoline and a 3-alkyl derivative, 3-methyl-8-phenyl-1,2,3,4-tetrahydroisoquinoline. Using aryloxazoline chemistry developed by Meyers[4] and Gschwend[5] et al., an unambiguous route (Scheme I) to an appropriate 1,2,3-trisubstituted benzene has been used to prepare 8-phenylisocoumarins, the key intermediates for further elaboration to tetrahydroisoquinolines.

Biphenyl-2-carboxylic acid (1) was converted to the acid chloride and reacted with 2-amino-2-methylpropanol, producing the hydroxyamide **2**, which on treatment with thionyl chloride cyclized to the aryloxazoline **3**.[6] The directing properties of the oxazoline[4,5] were used to functionalize the ortho position of the benzene ring. When **3** was metalated with *n*-

Scheme I



butyllithium followed by reaction with allyl bromide, a mixture was produced from which **4** was obtained in only 19% yield along with recovered **3** (39%) and 34% of product[7] arising from subsequent alkylation at the activated methylene of **4**. This problem was resolved when the lithiated intermediate was first converted to the organocopper reagent with cuprous bromide; alkylation with allyl bromide then gave a 71% yield of **4** after LC. Using this methodology it should be possible to

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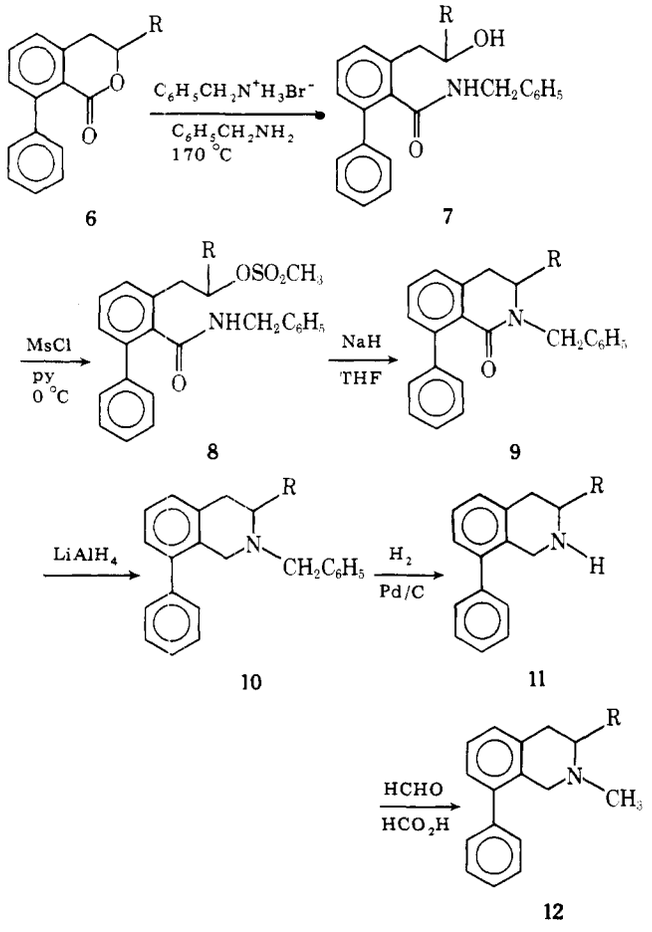
Scheme II



a, R = H; b, R = CH_3

prepare other 1,2,3-trisubstituted benzenes containing various functionalities depending on the alkylating agents used and further reactions of the oxazoline. In this case the *o*-allyloxazoline (**4**) was hydrolyzed in refluxing 6 N hydrochloric acid, producing 2-methyl-8-phenylisocoumarin (**6b**).

Alternately, the isocoumarins were prepared from hydroxylic intermediates (**5**). Lithiation of **3** with *n*-butyllithium followed by alkylation with ethylene or propylene oxide produced the *o*-(hydroxyalkyl)oxazolines (**5**). Acid hydrolysis produced the cyclic isocoumarins **6**. The functionality at the position ortho to the oxazoline in **4** and **5** presumably facilitates the hydrolysis as other 2,6-disubstituted aryloxazolines without such substituents are not hydrolyzed under similar conditions.[8] The hydroxyl compounds (**5**) gave better conversions to the isocoumarins than the allyl compound **4** (**6b** was obtained in 85% yield from **5b** vs. ~60% from **4**; see the Experimental Section). In one instance of the hydrolysis of the allylic compound **4**, a small amount (15% of the product) of the γ-lactone was found in a second crop from the recrystallization of **6b**. The only lactones observed from the hydrolysis of **5** were the isocoumarins **6**; none of the γ-lactone formation was observed.

The reactions used to proceed from the isocoumarins **6** to 8-phenyltetrahydroisoquinolines are outlined in Scheme II. Heating **6** and benzylamine hydrobromide in benzylamine at 160 °C produced the ring-opened δ-hydroxybenzamides **7**. In the absence of the benzylamine hydrobromide, reaction was only slight after 24 h; with the ammonium salt reaction was complete after several hours. The alcohols **7** were converted to the mesylates **8**, which were cyclized to dihydroisoquinolines **9** with sodium hydride. The asymmetry provided by the methyl group of **9b** produced a complex ^{1}H NMR spectrum; notably the benzylic methylene appeared as two doublets (J = 15 Hz) at 4.01 and 5.30 ppm. For **9a** the benzylic protons appeared as a singlet at 4.67 ppm.

Lithium aluminum hydride reduction of **9** produced the *N*-benzyltetrahydroisoquinolines **10**. Debenzylation by hydrogenolysis over Pd/C gave 8-phenyl-1,2,3,4-tetrahydroisoquinolines (**11**), which were converted to the *N*-methyl compounds (**12**) under Eschweiler–Clarke conditions. Again the asymmetry of the 3-methyl compound **12b** was indicated by the ^{1}H NMR spectrum, where the C-1 methylene protons appeared as two doublets (J = 16 Hz) at 3.32 and 3.69 ppm. For **12a** the C-1 methylene was a singlet at 3.36 ppm.

This synthesis provided a convenient route to 8-phenyl- and 3-alkyltetrahydroisoquinolines and adds to the utility[9] of oxazolines as useful synthetic intermediates. 1,2,3-Trisubstituted intermediates such as **4** and **5** would be virtually impossible to produce in respectable yields using classical aromatic substitution reactions. The directing properties of the oxazoline ring make such 1,2,3-trisubstituted benzenes readily accessible in satisfactory yields.

Experimental Section[10]

***N*-(2-Hydroxy-1,1-dimethylethyl)-2-biphenylcarboxamide (2).** Biphenyl-2-carboxylic acid (6.0 g, 31 mmol) and 15 mL of thionyl chloride were stirred at ambient temperature for 22 h. The thionyl chloride was distilled off; then benzene was added and distilled off, leaving an oil. The oil in 15 mL of methylene chloride was added dropwise to a solution of 5.5 g (62 mmol) of 2-amino-2-methylpropanol in 15 mL of methylene chloride at 0 °C, and the mixture was stirred at ambient temperature overnight. After filtration, the filtrate was washed with H_2O, 5% HCl, 5% NaOH and H_2O and dried. The solvent was removed by distillation, leaving 7.8 g of white solid that was recrystallized from ether, yielding 6.38 g (82%) of white crystals: mp 72.5–74 °C; IR ($CHCl_3$) 3435, 3350, 1647 cm^{-1}; NMR[11] ($CDCl_3$) δ 0.99 (s, 6 H), 3.37 (d, 2 H), 4.54 (t, 1 H), 5.40 (br, 1 H), 7.20–7.82 (m, 9 H).

Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.61; H, 7.31; N, 5.32.

2-(2-Biphenyl)-4,4-dimethyl-2-oxazoline (3). Thionyl chloride (10 mL) was added in portions with stirring to 11.8 g (43.8 mmol) of the hydroxyamide **2**. After the solid had dissolved, the solution was stirred for 20 min and poured into 125 mL of anhydrous ether. The precipitate was washed with ether and dried, yielding 12.3 g of white powder (recrystallized from EtOH/Et_2O, mp 130.5–133.5 °C. Anal. Calcd for $C_{17}H_{18}ClNO$: C, 70.95; H, 6.30; N, 4.87. Found: C, 71.00; H, 6.42; N, 4.73). An aqueous solution of the hydrochloride was treated with 50% sodium hydroxide, extracted with ether, washed with water, and dried. Distillation of the ether gave 10.8 g of a clear colorless oil that crystallized from a small amount of petroleum ether with cooling, giving 10.6 g (96%) of colorless crystals: mp 38.5–40.5 °C; IR ($CHCl_3$) 1657 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (s, 6 H), 3.76 (s, 2 H), 7.16–7.85 (m, 9 H).

Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.14; H, 6.75; N, 5.15.

2-(4,4-Dimethyl-2-oxazolin-2-yl)-3-allylbiphenyl (4). *n*-Butyllithium (43 mL of 2.4 M in hexane, 99 mmol) was added to 17.7 g (70.5 mmol) of the oxazoline **3** in 300 mL of dry tetrahydrofuran at 0 °C, and the mixture was stirred for 3.5 h. The deep red solution was transferred to an addition funnel and added to a suspension of 14.3 g (100 mmol) of cuprous bromide in 300 mL of dry tetrahydrofuran at 0 °C. The green mixture was stirred at 0 °C for 1 h, and then 12.1 g (100 mmol) of allyl bromide was added. After 1 h, water (50 mL) was added followed by 100 mL of concentrated ammonium hydroxide. The organic layer was washed with saturated aqueous NaCl and dried. Distillation of the solvent gave 20.5 g of clear amber oil that was purified by low-pressure column chromatography (LC) on Woelm silica gel using 5% ethyl acetate in benzene as the eluent, yielding 14.6 g (71%) of clear oil that was used without further purification: IR ($CHCl_3$) 1666 cm^{-1}; NMR δ 1.17 (s, 3 H), 3.80 (s, 2 H), allyl multiplets centered at 3.55 (2 H), 5.07 (2 H), and 6.04 (1 H), 7.11–7.59 (m, 8 H).

2-(4,4-Dimethyl-2-oxazolin-2-yl)-3-(2-hydroxyethyl)biphenyl (5a). *n*-Butyllithium (25 mL of 2.4 M in hexane, 60 mmol) was added to 10.0 g (39.8 mmol) of the oxazoline **3** in 200 mL of dry tetrahydrofuran at −5 °C. The deep red solution was stirred at −5 °C for 3 h; then 15 mL of ethylene oxide in 50 mL of dry tetrahydrofuran was added, and the mixture was stirred at ambient temperature overnight.

Water (50 mL) was added, the organic portion was concentrated, and the residual oil was taken up in ether, washed with water, and dried. Distillation of the solvent gave 14.1 g of clear amber oil that was purified by LC (Woelm silica gel, ethyl acetate/benzene gradient), yielding 7.3 g (62%) of oil that solidified on standing. Recrystallization from ethyl acetate/hexane gave 5.12 g (44%) of **5a** as white crystals: mp 86.5–87 °C; IR ($CHCl_3$) 3230, 1659 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (s, 6 H), 2.97 (t, 2 H), 3.72 (s, 2 H), 3.91 (t, 2 H), 4.65 (br, 1 H), 7.11–7.59 (m, 8 H).

Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.04; H, 7.32; N, 4.95.

2-(4,4-Dimethyl-2-oxazolin-2-yl)-3-(2-hydroxypropyl)biphenyl (5b) was prepared using the procedure for **5a.** From 24.0 g (95.6 mmol) of the oxazoline **3** was obtained 16.7 g (57%) of clear colorless oil after LC (Woelm silica gel, 50% ethyl acetate/toluene). The oil solidified to a waxy solid that was used for further reaction without additional purification: IR ($CHCl_3$) 3230, 1653 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (s, 6 H), 1.27 (d, 3 H), 2.85 (m, 2 H), 3.69 (q, 2 H), 3.99 (m, 1 H), 5.25 (br, 1 H), 7.10–7.61 (m, 8 H).

3,4-Dihydro-8-phenylisocoumarin (6a). A mixture of 10.2 g (34.6 mmol) of **5a** and 1 L of 6 N hydrochloric acid was stirred under reflux for 7 h. The semisolid that separated on cooling was washed with several portions of water and dried, yielding 7.5 g of tan solid. Recrystallization from ethyl acetate/hexane yielded 6.13 g (79%) of beige crystals: mp 105–106 °C; IR ($CHCl_3$) 1734 cm^{-1}; NMR ($CDCl_3$) δ 3.03 (t, 2 H), 4.49 (t, 2 H), 7.10–7.67 (m, 8 H).

Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39. Found: C, 80.17; H, 5.56.

3,4-Dihydro-3-methyl-8-phenylisocoumarin (6b). A. From 4. A mixture of 8.06 g (27.7 mmol) of **4** and 600 mL of 6 N hydrochloric acid was stirred under reflux overnight. The solid that separated on cooling was taken up into ether (1.63 g remained insoluble), washed with water, and dried. Distillation of the solvent gave 3.8 g of solid. The two solids were combined and recrystallized from ethanol, yielding 3.67 g (56%) of light beige crystals: mp 140–141.5 °C; IR ($CHCl_3$) 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.48 (d, 3 H), 2.92 (d, 2 H), 4.63 (m, 1 H), 7.08–7.68 (m, 8 H).

Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.60; H, 6.06.

A second crop of 0.99 g was collected after concentrating the mother liquor. NMR of this material indicated that it was approximately 28% of **6b** and 72% of the γ-lactone.

B. From 5b. Using the procedure that was used for the preparation of **6a,** 10.2 g of **5b** produced 6.69 g (85%) of crude **6b,** mp 139–141 °C. A small amount was dried in vacuo over refluxing ethanol, producing an analytical sample.

Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.57; H, 6.00.

***N*-Benzyl-3-(2-hydroxyethyl)-2-biphenylcarboxamide (7a).** A mixture of 7.84 g (35.0 mmol) of **6a** and 8 g of benzylamine hydrobromide in 40 mL of benzylamine was stirred at 160 °C for 4 h. After cooling, it was poured into 500 mL of 5% hydrochloric acid. The oil that separated was extracted into methylene chloride, washed with several portions of 5% hydrochloric acid and water and dried. Removal of the solvent gave 11.3 g of solid that was recrystallized from chloroform/hexane, yielding 9.51 g (82%) of white flocculant crystals: mp 129–130 °C; IR ($CHCl_3$) 3425, 3350, 1643 cm^{-1}; NMR (Me_2SO-d_6) δ 2.80 (t, 2 H), 3.69 (m, 2 H), 4.25 (d, 2 H), 4.65 (t, 1 H), 6.75–7.58 (m, 8 H), 9.85 (t, 1 H).

Anal. Calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.68; H, 6.36; N, 4.31.

***N*-Benzyl-3-(2-hydroxypropyl)-2-biphenylcarboxamide (7b).** A mixture of 3.58 g (15.0 mmol) of **6b** and 4 g of benzylamine hydrobromide in 20 mL of benzylamine was stirred at 165 °C overnight. The solution was cooled, poured into 250 mL of 5% hydrochloric acid, and extracted with ether. The ether extract was washed with 5% hydrochloric acid and water and dried. Removal of the solvent gave 5.9 g of clear oil that was crystallized from ethyl acetate/hexane, yielding 4.24 g (82%) of white crystals: mp 94.5–96 °C; IR ($CHCl_3$) 3425, 3350, 1645 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (d, 3 H), 2.79 (m, 2 H), 4.02 (m, 1 H), 4.02 (br, 1 H), 4.27 (d, 2 H), 5.74 (br, 1 H), 6.67–7.62 (m, 13 H).

Anal. Calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.06. Found: C, 80.32; H, 6.62; N, 4.07.

***N*-Benzyl-3-[2-(methylsulfonyloxy)ethyl]-2-biphenylcarboxamide (8a).** A solution of 15.0 g (45.3 mmol) of the alcohol **7a** and 10.5 g (91.3 mmol) of mesyl chloride in 150 mL of pyridine was left in the refrigerator overnight. The reaction mixture was diluted to 500 mL with ice water. On stirring an oil separated and solidified. The solid was washed with several portions of water and air-dried, yielding 17.7 g (95%) of light tan powder: mp 108–110 °C; IR ($CHCl_3$) 3438, 1665 cm^{-1}; NMR ($CDCl_3$) δ 2.87 (s, 3 H), 3.15 (t, 2 H), 4.26 (d, 2 H), 4.51 (t, 2 H), 5.55 (br, 1 H), 6.63–7.58 (m, 13 H). This material was used without further purification.

***N*-Benzyl-3-[2-(methylsulfonyloxy)propyl]-2-biphenylcarboxamide (8b).** Using the procedure described for **8a,** 4.20 g of **7b** was reacted with 4 g of mesyl chloride to yield 4.68 g (91%) of white powder: mp 107–109.5 °C; IR ($CHCl_3$) 3425, 1655 cm^{-1}; NMR ($CDCl_3$) δ 1.42 (d, 3 H), 2.60 (s, 3 H), 3.00 (d, 2 H), 4.23 (d, 2 H), 5.04 (m, 1 H), 5.72 (br, 1 H), 6.67–7.54 (m, 13 H). This material was used without further purification.

2-Benzyl-3,4-dihydro-8-phenyl-1(2*H*)-isoquinolinone (9a). A mixture of 17.5 g (42.7 mmol) of the mesylate **8a** and 5 g of 50% sodium hydride dispersion in oil in 200 mL of dry tetrahydrofuran was stirred under gentle reflux overnight. After cooling, water was added dropwise to decompose the excess hydride. The solvent was removed, and the residue was taken up in methylene chloride, washed with water, and dried. Removal of the solvent gave a white solid (containing mineral oil); recrystallization from ethyl acetate/hexane gave 12.4 g (93%) of white crystals: mp 137.5–138.5 °C; IR ($CHCl_3$) 1654 cm^{-1}; NMR ($CDCl_3$) δ 2.84 and 3.48 ($A_2'B_2'$, 4 H), 4.67 (s, 2 H), 6.98–7.56 (m, 13 H).

Anal. Calcd for $C_{22}H_{19}NO$: C, 84.32; H, 6.11; N, 4.47. Found: C, 84.53; H, 6.30; N, 4.83.

2-Benzyl-3,4-dihydro-3-methyl-8-phenyl-1(2*H*)-isoquinolinone (9b). A mixture of 4.50 g (10.6 mmol) of the mesylate **8b** and 1.5 g of 50% sodium hydride suspension in oil in 65 mL of dry tetrahydrofuran was stirred at ambient temperature for 4 h. Water was added and the solvent was concentrated, producing an oil that was taken up in ether, washed with water, and dried. Removal of the solvent gave 4.3 g of a white solid that contained mineral oil. Recrystallization from cyclohexane gave 2.94 g (84%) of white crystals: mp 112–113 °C; IR ($CHCl_3$) 1645 cm^{-1}; NMR ($CDCl_3$) δ 1.18 (d, 3 H), 2.56 (dd, 1 H), 3.20 (dd, 1 H), 3.66 (m, 1 H), 4.01 (d, 1 H, J = 15 Hz), 5.30 (d, 1 H, J = 15 Hz), 6.97–7.57 (m, 13 H).

Anal. Calcd for $C_{23}H_{21}NO$: C, 84.37; H, 6.47; N, 4.28. Found: C, 84.72; H, 6.53; N, 4.61.

2-Benzyl-8-phenyl-1,2,3,4-tetrahydroisoquinoline (10a) Hydrochloride. Lithium aluminum hydride (3.6 g, 95 mmol) was added to a solution of 10.0 g (31.9 mmol) of the isoquinolinone **9a** in 225 mL of dry tetrahydrofuran, and the mixture was stirred at reflux for 5 h. The mixture was cooled in an ice bath and treated successively with (1) 7.5 mL of water in 15 mL of tetrahydrofuran, (2) 7.5 mL of 25% sodium hydroxide, and (3) 7.5 mL of water. The salts were filtered off and the filtrate was dried and concentrated, yielding 10.1 g of clear oil. The oil in ether was treated with 2-propanolic hydrogen chloride to give 11.1 g of white solid that was recrystallized from ethanol/ether, yielding 8.80 g (82%) of white crystals, mp 187–189 °C.

Anal. Calcd for $C_{22}H_{22}ClN$: C, 78.68; H, 6.60; N, 4.17. Found: C, 78.42; H, 6.70; N, 4.48.

NMR of the free amine (**10a**) ($CDCl_3$): δ 2.47–3.12 (m, 4 H), 3.57 (s, 4 H), 6.88–7.55 (m, 13 H).

2-Benzyl-3-methyl-8-phenyl-1,2,3,4-tetrahydroisoquinoline (10b) Hydrochloride. Reduction of 6.54 g (20.0 mmol) of the isoquinolinone **9b** following the procedure used for **10a** gave 5.9 g of crude hydrochloride that was recrystallized from ethanol/ether, yielding a first crop of 3.57 g of white crystals, mp 196–198 °C, and a second crop of 1.16 g (68% total), mp 194.5–197 °C.

Anal. Calcd for $C_{23}H_{24}ClN$: C, 78.95; H, 6.91; N, 4.00. Found: C, 79.01; H, 7.17; N, 3.93.

NMR of the free amine (**10b**) ($CDCl_3$): δ 1.08 (d, 3 H), 2.30–3.87 (m, 7 H), 6.81–7.46 (m, 13 H).

8-Phenyl-1,2,3,4-tetrahydroisoquinoline (11a) Hydrochloride. A mixture of 6.20 g (18.4 mmol) of the *N*-benzyltetrahydroisoquinoline **10a** hydrochloride and 620 mg of 5% Pd/C in 100 mL of ethanol was hydrogenated in a Parr shaker at 2 psi and ambient temperature for 6 h. The filtered reaction solution was concentrated to 75 mL and ether was added, forcing 4.25 g of white crystals out of solution. Recrystallization from ethanol gave 3.36 g (74%) of white crystals, mp 268–270 °C, and a second crop of 0.69 g (15%).

Anal. Calcd for $C_{15}H_{14}ClN$: C, 73.31; H, 6.56; N, 5.70. Found: C, 73.51; H, 6.75; N, 5.86.

NMR of the free amine (**11a**) ($CDCl_3$): δ 1.87 (s, 1 H), 2.98 ($A_2'B_2'$, m, 4 H), 3.80 (s, 2 H), 6.50–7.30 (m, 8 H).

3-Methyl-8-phenyl-1,2,3,4-tetrahydroisoquinoline (11b) Hydrochloride. Hydrogenation of 10.1 g (28.9 mmol) of the *N*-benzyltetrahydroisoquinoline **10b** hydrochloride with 1 g of 5% Pd/C in 100 mL of ethanol was carried out in a Parr shaker at 2 psi and ambient temperature for 7 h. The mixture was filtered, and the catalyst was washed with warm ethanol to recover all of the product. The combined ethanolic portions were concentrated to 100 mL, producing 4.73 g of

white crystals, mp 276.5–279 °C.

Anal. Calcd for $C_{16}H_{18}ClN$: C, 73.97; H, 6.98; N, 5.39. Found: C, 74.00; H, 7.06; N, 5.64.

The filtrate was concentrated and ether was added, producing 2.19 g more of white crystals (total 92%). NMR of the free amine (**11b**) ($CDCl_3$): δ 1.18 (d, 3 H), 1.45 (br, 1 H), 2.17–3.34 (m, 3 H), 3.85 (s, 2 H), 6.83–7.54 (m, 8 H).

2-Methyl-8-phenyl-1,2,3,4-tetrahydroisoquinoline (12a) Maleate. A mixture of 2.87 g (13.7 mmol) of 8-phenyl-1,2,3,4-tetrahydroisoquinoline (**11a**), 1.8 g of 90% formic acid, and 1.35 g of 37% aqueous formaldehyde was stirred at ambient temperature overnight and then warmed on a steam bath for 2 h. Concentrated hydrochloric acid (1.5 mL) was added, and the excess formic acid and formaldehyde were distilled off. The residue was taken up in water, and the solution was made alkaline with 50% sodium hydroxide and extracted with ether. The extract was washed with water and dried and the solvent was removed, yielding 3.00 g (98%) of clear colorless oil (**12a**): NMR ($CDCl_3$) δ 2.29 (s, 3 H), 2.62 and 2.96 ($A_2'B_2'$, m 4 H), 3.36 (s, 2 H), 6.85–7.48 (m, 8 H).

The oil was taken up in ether and treated with a saturated solution of maleic acid in ether. The crystals that separated were recrystallized from acetonitrile, yielding 4.35 g (93%) of white crystals of **12a** maleate, mp 146.5–147.5 °C.

Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.57; H, 6.31; N, 4.21.

2,3-Dimethyl-8-phenyl-1,2,3,4-tetrahydroisoquinoline (12b) Hydrobromide. A mixture of 3.10 g (13.9 mmol) of 3-methyl-8-phenyl-1,2,3,4-tetrahydroisoquinoline (**11b**), 1.8 g of 90% formic acid, and 1.4 g of 37% aqueous formaldehyde was reacted under the conditions described for **12a**, yielding 3.22 g of clear colorless oil of **12b**: NMR ($CDCl_3$) δ 1.12 (d, 3 H), 2.23 (s, 3 H), 2.71 (m, 3 H), 3.32 (d, 1 H, J = 16 Hz), 3.69 (d, 1 H, J = 16 Hz), 6.66–7.45 (m, 8 H).

The oil was taken up in ether and treated with saturated hydrogen bromide in ether to give 3.48 g of white powder that was recrystallized from ethanol/ether, yielding 3.19 g (72%) of **12b** hydrobromide, mp 190–192 °C.

Anal. Calcd for $C_{17}H_{20}BrN$: C, 64.15; H, 6.33; N, 4.40. Found: C, 63.74; H, 6.32; N, 4.38.

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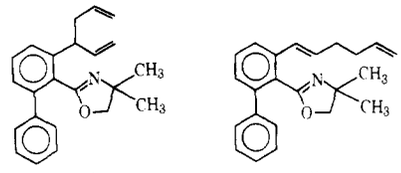
Registry No.—**2,** 69381-38-0; **3,** 57598-40-0; **3** HCl, 69381-39-1; **4,** 69381-40-4; **5a,** 69381-41-5; **5b,** 69381-42-6; **6a,** 69381-43-7; **6b,** 69381-44-8; **7a,** 69381-45-9; **7b,** 69381-46-0; **8a,** 69381-47-1; **8b,** 69381-48-2; **9a,** 69381-49-3; **9b,** 69381-50-6; **10a,** 69381-51-7; **10a** HCl, 69381-52-8; **10b,** 69381-53-9; **10b** HCl, 69381-54-0; **11a,** 69381-55-1; **11a** HCl, 69381-56-2; **11b,** 69381-57-3; **11b** HCl, 69381-58-4; **12a,** 69381-59-5; **12a** maleate, 69381-60-8; **12b,** 69381-61-9; **12b** HBr, 69381-62-0; biphenyl-2-carboxylic acid, 947-84-2; 2-amino-2-methylpropanol, 124-68-5; allyl bromide, 106-95-6; 3-ethyl-7-phenyl-1(3*H*)-isobenzofuranone, 69381-63-1; 2-(4,4-dimethyl-2-oxazolin-2-yl)-3-(1,5-hexadien-3-yl)biphenyl, 69381-64-2; ethylene oxide, 75-21-8; propylene oxide, 75-56-9.

References and Notes

(1) For examples, see (a) W. M. Whaley and T. R. Govendachari, *Org. React.*, **6,** Chapters 2 and 3 (1951); W. J. Gensler, *ibid.*, Chapter 4 (1951); (b) W. J. Gensler, *Heterocycl. Compd.*, **4,** Chapter 2 (1952).
(2) Y. Ahmad and D. H. Hey, *J. Chem. Soc.*, 3882 (1961).
(3) J. Sam, R. M. Shafik, and K. Aparajithan, *J. Pharm. Sci.*, **59,** 59 (1970).
(4) A. I. Meyers and E. D. Mihelich, *J. Org. Chem.*, **40,** 3158 (1975).
(5) H. W. Gschwend and A. Hamden, *J. Org. Chem.*, **40,** 2008 (1975).
(6) This biphenyloxazoline has been reported previously: A. I. Meyers and E. D. Mihelich, *J. Am. Chem. Soc.*, **97,** 7383 (1975). It was prepared by a different method, and no properties were given.
(7) This product (i) was further confirmed by Cope rearrangement to the linear 1,5-diene (ii). The NMR spectra were consistent for both structural assignments.



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(8) (a) A. I. Meyers, Colorado State University, personal communication, 1978. (b) Similar methodology was recently reported [M. S. Newman, J. M. Khanna, K. Kanakarajan, and S. Kumar, *J. Org. Chem.*, **43,** 2553 (1978)] for the hydrolysis of a γ-hydroxyozazoline to a γ-lactone.
(9) For a review, see A. I. Meyers and E. D. Mihelich, *Angew. Chem., Int. Ed. Engl.*, **15,** 270 (1976).
(10) Melting points were taken in open capillaries on a Mel-Temp apparatus and are uncorrected. Spectra were recorded with a Beckman IR 12 infrared spectrometer and a Varian A-60d NMR spectrometer. Solvents were distilled off under reduced (aspirator) pressure, and anhydrous $MgSO_4$ was used as the drying agent. No attempts were made to maximize the yields of the reactions.
(11) NMR signals are indicated as s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet, and br = broad signal.

Convergent Approaches to Indoloquinones: Additions to Quinone Monoimides

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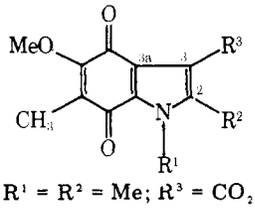
Indoloquinone **1a,** a model for more complex mitomycin analogues, was prepared by Michael addition of ethyl acetoacetate to quinone monoimide **12,** dehydration of the adduct **13** to indole **14,** and elaboration of the quinone functionality. The final oxidation step of **16b** to **1a** was accomplished with argentic oxide and aqueous nitric acid. Al alternative scheme failed in a model sequence when the amino benzofurans **6** could not be converted to indoles **7.**

A variety of synthetic endeavors have been directed toward mitomycins[1] and mitosenes,[2] as well as toward simple analogues[3] of these antibiotics. The challenge of developing a convergent synthesis of such functionalized indoloquinones (**1**) led us to consider an approach in which the key carbon–carbon bond (C-3,C-3a) is formed by the addition of an enol to a highly substituted benzoquinone derivative. Closure of the N,C-2 bond would complete the formation of the indole nucleus.[4]

Initial model work based on the addition of ethyl acetoac-



1a, $R^1 = R^2 = Me$; $R^3 = CO_2Et$

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