100 mL of THF, and the reaction mixture was refluxed for 20 h. The excess hydride was decomposed by water and the organic layer was washed with dilute hydrochloric acid and saturated sodium chloride solution and then dried (Na_2SO_4). Evaporation of the solvent gave 0.62 g (94%) of white solid which was recrystallized from THF–methanol to give **7**: mp 237–238 °C; IR (KBr) 3550, 1700, 1075 cm^{-1}; MS *m/e* 330 (M^+), 165, 149; ^1H NMR (pyridine-d_5) δ 0.70–2.80 (m, 32 H), 4.72 (q, 1 H), 6.05 (broad s, 1 H). Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.89; H, 10.40.

To a solution of 0.360 g (1.09 mmol) of **7** in 20 mL of pyridine was added dropwise 0.57 g (5.0 mmol) of methanesulfonyl chloride and the solution was stirred at room temperature for 20 h. The solution was diluted with 150 mL of water and extracted with THF. The organic layer was washed with saturated sodium chloride solution and dried (Na_2SO_4). Evaporation of the solvent and trituration with ether gave 0.42 g (95%) of pale yellow solid which was recrystallized from THF–petroleum ether to give **8**: mp 155–156 °C with decomposition; IR (KBr) 1700, 1320, 1160 cm^{-1}. Anal. Calcd for $C_{23}H_{36}O_4S$: C, 67.61; H, 8.88; S, 7.85. Found: C, 67.23; H, 9.01; S, 7.85.

To a solution of 0.427 g (1.05 mmol) of **8** in 40 mL of dimethyl sulfoxide was added dropwise 0.38 g (2.5 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene and the solution was heated with stirring at 100–110 °C for 45 h. The solution was diluted with 200 mL of water and extracted with THF. The organic layer was washed with dilute hydrochloric acid and saturated sodium chloride solution and then dried (Na_2SO_4). Evaporation of the solvent gave brown residue, which was chromatographed on silica gel. Elution with petroleum ether–benzene (1:1) gave 0.052 g (17%) of **9**: mp 191–193 °C from THF–methanol; IR (KBr) 3030, 1700, 720 cm^{-1}; MS *m/e* 165 ($M^+ - C_{11}H_{17}$); ^1H NMR ($CDCl_3$) δ 0.80–2.60 (m, 30 H), 5.50–5.80 (m, 2 H); UV ($CHCl_3$) λ_{max} 304 nm (ϵ 43.6). Anal. Calcd for $C_{22}H_{32}O$: C, 84.56; H, 10.32. Found: C, 84.34; H, 10.51.

9 (0.102 g, 0.33 mmol) in 80 mL of acetic acid was hydrogenated with PtO_2 in the presence of hydrogen under atmospheric pressure. The catalyst was filtered off and the filtrate was diluted with 150 mL of water and extracted with chloroform. The organic layer was washed with dilute sodium carbonate solution and water. Evaporation of the solvent gave 0.098 g (94%) of white solid which was recrystallized from THF–methanol to give **10**. This material was identical with the sample synthesized by cross photocycloaddition of **4** to **11** (IR and melting point).

Bicyclo[6.3.0]undec-1(8)-ene (11). Olefin **11** was prepared according to the method of Ohloff et al.,[13] namely hydrogenation of enone **4** with Raney nickel in the presence of hydrogen at atmospheric pressure in 1% methanolic sodium hydroxide gave a mixture of saturated alcohols (90%), which was dehydroxylated with *p*-toluenesulfonic acid in boiling toluene to afford a mixture of olefins (78%). This mixture contains ~5% of undesired bicyclo[6.3.0]undec-1(2)-ene. Purification of **11** was carried out through hydroboration–oxidation (60%) according to the procedure of Benkeser et al.[14] GLC and NMR analysis showed **11** thus prepared was >99% pure. **11**: bp 88–90 °C (15 mmHg); IR (neat) 2900, 1440 cm^{-1}; MS *m/e* 150 (M^+); ^1H NMR (CCl_4) δ 1.30–2.45 (m). Anal. Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.08. Found: C, 87.55; H, 12.03.

Registry No.—**1**, 10515-92-1; **2**, 22118-00-9; **3**, 769-32-4; **4**, 38262-50-9; **5**, 66921-98-0; **6**, 67009-06-7; **7**, 66922-00-7; **8**, 66922-01-8; **9**, 66921-99-1; **10**, 66922-02-9; **11**, 25107-10-2; bicyclo[6.3.0]undecan-9-one, 40696-12-6; bicyclo[6.3.0]undec-1(2)-ene, 66922-03-0.

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A Facile Synthesis of (3-Methoxyisoquinol-7-yl)acetic Acids

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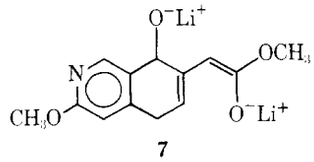
Our work on the total synthesis of 2-azasteroids necessitated the development of a synthesis of 7-aza-6-methoxy-1-tetralone (**1**).[1] While this compound has been successfully utilized for the preparation of 2-azaestrone derivatives, its potential as a precursor for the preparation of other biologically interesting molecules was apparent. We would now like to report on the use of this material for the facile preparation of (3-methoxyisoquinol-7-yl)acetic acids.[2] Previous syntheses of the carbocyclic analogues of this system have employed the Wilgerodt–Kindler reaction[3] on the appropriately substituted 2-acylnaphthalene,[2] or high temperature catalytic dehrogenation of the dihydro derivatives produced from tetralones.[4] In contrast to the rather severe conditions of these methods, the approach described herein proceeds under mild conditions and provides a method of general utility for the synthesis of a variety of systems related to **6**.

Treatment of the azatetralone **1** with glyoxylic acid monohydrate in aqueous alcoholic hydroxide solution[5] afforded the unsaturated acid **2**.[6] Following esterification to the methyl ester, sodium borohydride reduction of the ketone **3** provided the conjugated hydroxyester **4**. This ester **4** could then be conveniently converted to the isoquinoline system (**6**) by deconjugation with 2 equiv of lithium diisopropylamide (LDA)[7] and subsequent dehydration of the allylic alcohol **5** with acetic acid at room temperature. It was originally thought that the intermediate **7** generated from LDA treatment might be susceptible to side-chain alkylation during the isomerization process and provided **8** in essentially a single-pot process from



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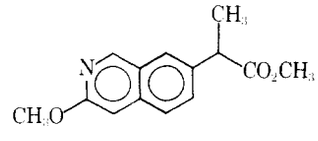

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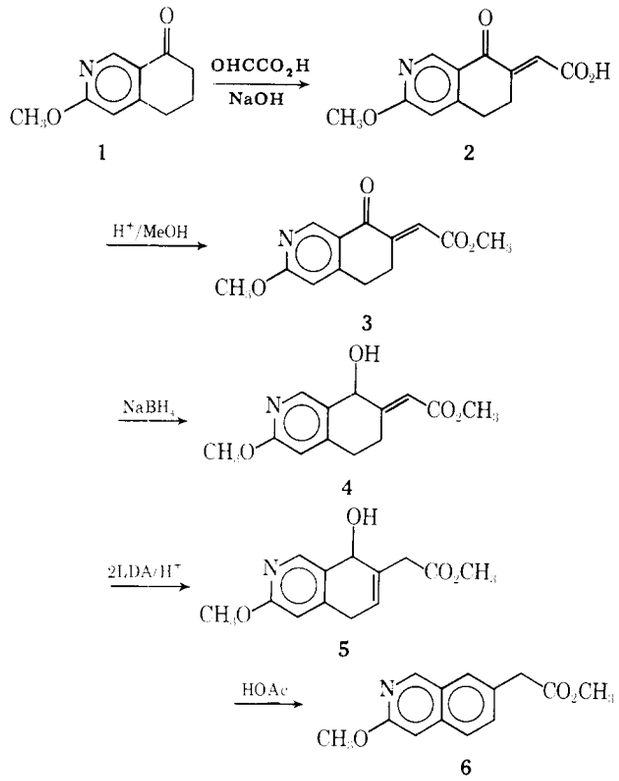
Scheme I



5.[8] Unfortunately, alkylation of 7 was not observed when methyl iodide was added to the LDA reaction mixture and 8 was ultimately prepared by LDA/MeI alkylation of 6 in a separate step.

Experimental Section

NMR spectra were obtained on a Varian A-60A or T-60 spectrometer with tetramethylsilane as the internal standard. UV spectra were obtained in MeOH on a Beckman DK-2A. TLC was on 7.6-cm microscope slides covered with Woelm F silica with a magnesium silicate binder using 5% phosphomolybdic acid–EtOH (wt/v) followed by heat for visualization. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

(3-Methoxy-8-oxo-5,6,7,8-tetrahydroisoquinol-7-ylidene)-acetic Acid (2). To 15.0 g (0.085 mol) of 1 in 100 mL of methanol was added 9.0 g (0.12 mol) of glyoxylic acid hydrate followed by 100 mL of 5% sodium hydroxide solution (0.125 mol) and the purple reaction mixture was stirred overnight at room temperature, then refluxed for 3 h. Addition of 200 mL of water was followed by extraction of the aqueous basic solution three times with chloroform. The aqueous solution was then acidified with formic acid to pH 4 whereupon the precipitate which formed was collected providing 11.2 g of product. Extraction of the filtrate three times with ethyl acetate followed by drying the extracts over sodium sulfate and solvent removal in vacuo gave 2 g of oil which upon trituration with ethyl acetate afforded an additional 0.45 g of **2** (58% total). Recrystallization from ethanol gave the pure acid: mp 221–222 °C dec; UV 297 (ε 12 600), 255 nm (ε 10 700), 235 nm (ε 11 300); NMR (C_5D_5N) δ 2.82 (2 H, m, CH_2), 3.55 (2 H, m, CH_2), 3.97 (3 H, s, OCH_3), 6.59 (1 H, brd s, 4-H), 7.38 (1 H, t, J = 1.5 Hz, vinyl-H), 9.10 (1 H, s, 1-H).

Anal. Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.70; H, 4.82; N, 5.93.

(3-Methoxy-8-oxo-5,6,7,8-tetrahydroisoquinol-7-ylidene)-acetic Acid Methyl Ester (3). To 16.6 g (0.071 mol) of **2** in 150 mL of methanol was added 4 mL of concentrated sulfuric acid and the reaction mixture was refluxed for 3 h. After cooling, water was added followed by sufficient ammonium hydroxide solution to raise the pH of the solution to 8. The precipitate which formed was collected affording 14.1 g (80%) of ester. Recrystallization from methanol gave **3**: mp 111–112 °C; UV (MeOH) 301 (ε 12 400), 252 (ε 13 300), 241 nm (ε 13 600); NMR ($CDCl_3$) δ 2.93 (2 H, brd m, CH_2), 3.42 (2 H, brd m, CH_2), 3.80 (3 H, s, CO_2CH_3), 4.00 (3 H, s, OCH_3), 6.60 (1 H, brd s, 4-H), 6.90 (1 H, t, J = 1.5 Hz, vinyl H), 8.93 (1 H, brd s, 1-H).

Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 62.85; H, 5.40; N, 5.83.

(8-Hydroxy-3-methoxy-5,6,7,8-tetrahydroisoquinol-7-ylidene)acetic Acid Methyl Ester (4). To 4.15 g (0.0167 mol) of **3** suspended in 100 mL of methanol cooled to −5 °C was added 0.4 g of sodium borohydride in portions over a 5-min period. The cooling bath was then removed and the now homogeneous reaction mixture was stirred at room temperature for 20 min after which time product began separating from the solution. Water was added and the precipitate collected providing 2.6 g of analytically pure **4**. The aqueous filtrate was extracted three times with chloroform and these extracts provided an additional 1.2 g of product (91% total): mp 141–142 °C; UV (MeOH) 220 (ε 22 900), 272 nm (ε 3600); NMR ($CDCl_3$) δ 3.72 (3 H, s, CO_2CH_3), 3.90 (3 H, s, OCH_3), 5.17 (1 H, brd s, 8-H), 6.17 (1 H, brd s, vinyl H), 6.52 (1 H, brd s, 4-H), 8.18 (1 H, brd s, 1-H).

Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.27; H, 5.87; N, 5.56.

(3-Methoxyisoquinol-7-yl)acetic Acid Methyl Ester (6). To 2.5 g (25 mmol) of diisopropylamine in 35 mL of tetrahydrofuran under a nitrogen atmosphere at room temperature was added 14 mL of 1.7 M methyllithium in ether solution (24 mmol) and the solution was then cooled to −70 °C. After addition of 2.3 g (9.25 mmol) of **4** in 25 mL of tetrahydrofuran over a 15-min period, the deep red solution was stirred at the above temperature for 90 min before a solution of 5 mL of acetic acid in 5 mL of ether was added and the cooling bath was removed. After the reaction mixture had warmed to room temperature, additional ether and saturated salt solution were added and the two phases were separated. The aqueous phase was extracted with an additional portion of ether and the combined extracts were washed with saturated salt solution and dried over sodium sulfate. Solvent removal gave an oil which by thin layer chromatography (silica; 50% ethyl acetate/50% benzene) showed two components with the more polar **5** in preponderance. The oil was taken up into 5 mL of acetic acid and let stand at room temperature overnight. Water was added to the reaction mixture followed by sufficient concentrated ammonium hydroxide solution to basify the solution (pH 8). After extracting the solution several times with pentane, the combined extracts (ca. 250 mL in volume) were washed with saturated salt solution, dried over sodium sulfate, treated with activated charcoal, and filtered through a cake of diatomaceous earth. Solvent removal in vacuo gave 1.6 g (75%) of fluffy white solid. Recrystallization from pentane gave pure **6**: mp 49.5–51 °C; UV 226 nm (ε 70 000); NMR ($CDCl_3$) δ 3.70 (3 H, s, CO_2CH_3), 3.73 (2 H, s, CH_2), 4.00 (3 H, s, OCH_3), 6.95 (1 H, brd s, 4-H), 7.50–7.70 (3 H, aromatic H's), 8.87 (1 H, brd s, 1-H).

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.72; H, 5.74; N, 5.79.

(3-Methoxyisoquinol-7-yl)-2-propionic Acid Methyl Ester (8). To 0.75 g (0.0075 mol) of diisopropylamine in 30 mL of tetrahydrofuran at room temperature under an atmosphere of nitrogen was added 4.3 mL of a 1.7 M methyllithium in ether solution. The reaction mixture was then cooled to −70 °C before the dropwise addition of 1.6 g (0.007 mol) of **6** in 10 mL of tetrahydrofuran over a 5-min period. After stirring the above for 20 min at −70 °C 1.15 g (0.081 mol) of methyl iodide in an equivalent volume of tetrahydrofuran was added and stirring was continued at the above temperature for 3 h. The reaction mixture was allowed to warm to −25 °C before addition of saturated ammonium chloride solution then ether and the layers were separated. The aqueous phase was extracted with two additional portions of ether and the combined extracts were washed with saturated salt solution and dried over sodium sulfate. Solvent removal gave 1.6 g of oil (95%). The analytically pure material was obtained by extracting the crude oil with pentane and subsequent removal of the hydrocarbon solvent to give a clear oil which crystallized upon standing: mp 35–36 °C; UV 227 nm (ε 71 500); NMR ($CDCl_3$) δ 1.63 (3 H, d, J = 7 Hz, CH_3), 3.68 (3 H, s, CO_2CH_3), 4.01 (3 H, s, OCH_3), 6.96 (1 H, brd s, 4-H), 7.60 (2 H, brd s, aromatic H's), 7.77 (1 H, brd s, aromatic H), 8.92 (1 H, brd s, 1-H).

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.30; H, 6.38; N, 5.73.

Acknowledgments. We would like to thank Ms. M. A. Oram for technical assistance, Mr. E. Zielinski and associates for microanalyses, and Mr. A. J. Damascus and associates for obtaining the spectral data.

Registry No.—**1**, 56053-58-8; **2**, 66967-20-2; **3**, 66967-21-3; **4**, 66967-22-4; **5**, 66967-23-5; **6**, 61714-84-9; **8**, 61714-85-0; glyoxylic acid, 298-12-4.

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A Direct Synthesis and Carbon-13 Nuclear Magnetic Resonance Spectral Analysis of 4-Substituted Isoquinolines[1]

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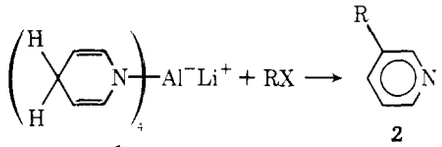
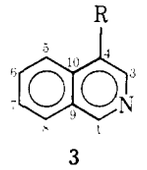
We have shown[2] that the reaction of lithium tetrakis(*N*-dihydropyridyl)aluminate (LDPA, **1**; from pyridine and lithium aluminum hydride ($LiAlH_4$))[3] with electrophilic reagents leads directly to 3-substituted pyridines, **2**, in high



1 **2**

yields. It was demonstrated[4] that the optimum yields of 3-substituted pyridines were obtained when 1 molar equiv of the appropriate alkyl halide was added per mol of LDPA. The addition of larger amounts of electrophilic reagent did not increase the yield of 3-substituted products. These results suggest that only one "dihydropyridyl" moiety per molecule of LDPA is reactive.

We now report the extension of this reaction to the synthesis of 4-substituted isoquinolines **3** from isoquinoline, $LiAlH_4$,



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and electrophilic reagents. Isoquinoline compounds with substitution in the 4 position have been shown to possess significant antispasmodic and vasodilatory properties,[5] and a tetrahydro derivative exhibited selective β_2-adrenergic agonist activity.[6] A number of synthetic studies have been directed toward these substances.[7]

Initially, the reaction of isoquinoline, $LiAlH_4$, and benzyl chloride was investigated. We first wished to ascertain if the desired reaction would occur at all and then to determine the reaction stoichiometry which is necessary for optimum yields.

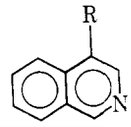
A series of reactions was carried out in tetrahydrofuran (THF) in which the molar ratio of isoquinoline to $LiAlH_4$ was kept constant at 4:1, but the number of molar equivalents of benzyl chloride was varied in increments of 1, from 1 to 4. The results of these experiments are shown in Table I and illustrate that the most efficient conversion of alkyl halide to 4-benzylisoquinoline occurs when 1 molar equiv is present (yield ≃ 90%). In contrast to the pyridine series,[4] the yield of 4-benzylisoquinoline increases as the amount of benzyl chloride increases (column 3, Table I); therefore, more than 1 of the 4 molar equiv of isoquinoline is rendered reactive by treatment with a single molar equiv of $LiAlH_4$. Since the yield increased in an irregular manner, we are as yet unable to speculate on the exact nature of the reactive species.

Table I. Effect of Various Molar Ratios of Reagents on the Yield[a] of 4-Benzylisoquinoline[b]

$PhCH_2Cl$/$LiAlH_4$	% yield based on $PhCH_2Cl$	% yield based on $LiAlH_4$
1:1	91 (88)[c]	91 (88)[c]
2:1	59 (45)	118 (91)
3:1	46 (45)	134 (128)
4:1	39 (35)	158 (142)

[a] The percent yields in this table were obtained by GLC analysis. [b] Isoquinoline (4 molar equiv) was present in THF solvent in each reaction. [c] Values in parentheses were obtained in a duplicate experiment.

Table II. Yields of 4-Substituted Isoquinolines



R	registry no.	% yield (isolated)	% yield (GLC)[a]	% yield (lit)
$PhCH_2$	10166-05-9	43[a] (56)[b]	90	34[c]
$H_2C{=}CHCH_2$	66967-18-8	24 (9)	80	
CH_3CH_2	41219-10-7	2 (13)[d]	35	<4[e]

[a] Molar ratio of isoquinoline/$LiAlH_4$/RX, 4:1:1. [b] Molar ratio of isoquinoline/$LiAlH_4$/RX, 4:1:4. [c] Reference 9. [d] Based on recovered isoquinoline. [e] Reference 10.

Subsequent reactions have been carried out using both a 4:1:1 molar ratio and a 4:1:4 molar ratio of isoquinoline/$LiAlH_4$/alkyl halide. The yields of 4-benzyl- (**4**), 4-allyl- (**5**), and 4-ethylisoquinolines (**6**) are listed in Table II. In each instance the isolated yield of purified material is less than the GLC yield, owing to nonoptimal isolation procedures. In spite of the modest isolated yields, we feel that this method is a useful one due to its simplicity and the ready availability of the inexpensive starting materials. In addition, the alkylation may be carried out using a simple aliphatic alkyl halide, which has not always been possible using other methodologies.[7,8] Work is in progress in our laboratories to optimize the yields of this process and to extend it to the preparation of more complex substances.

^{13}C NMR Spectral Analysis. As part of a thorough characterization of the 4-substituted isoquinolines prepared in this study, their ^{13}C NMR spectra were recorded. Most of the carbon resonances were readily assigned using standard chemical shift theory[11] and by comparison to a previous rigorous assignment of the spectrum of isoquinoline itself.[12] Using these data, however, it was not possible to unambiguously assign the C-7 and C-8 resonances, which are separated by about 1.5 ppm in the 4-substituted isoquinolines and by only 0.4 ppm in the parent heterocycle.

A straightforward solution to this problem results from recognition that the nonnitrogenous ring of isoquinolines can be viewed as an unsymmetrically ortho-disubstituted benzene

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