diluted with ether and 5% aqueous NaOH. The layers were separated, and the organic layer was extracted with 5% aqueous HCl. The combined acid-water layers were decolorized with charcoal, filtered through Celite, and made basic with 50% aqueous NaOH. The crystalline precipitate was removed by filtration, washed with water, and dried to give 31 g (57%) of **15**, mp 120-123 °C. Two recrystallizations from benzene/petroleum ether and one from ethanol/water afforded the analytical sample: mp 128-130 °C; IR (KBr) 1656 (C=O), 3380 and 3310 cm^{-1} (NH_2); NMR ($CDCl_3$) δ 1.97 (s, 2 H), 2.42 (m, 4 H), 6.22 (d, 1 H), 6.97 (m, 1 H), 7.36 (m, 4 H). The signal at δ 1.97 (s, 2 H) could be exchanged with D_2O. Anal. Calcd for $C_{12}H_{12}ClNO$: C, 65.01; H, 5.46; N, 6.32. Found: C, 64.71; H, 5.42; N, 6.21.

5-(2-Chlorophenyl)-6-(chlorosulfonyl)-6-azabicyclo-[3.2.0]heptan-7-one (16). To a solution of 14.2 g (0.1 mol) of chlorosulfonyl isocyanate (CSI) in 20 mL of CH_2Cl_2 was added all at once 17.9 g (0.1 mol) of 1-(2-chlorophenyl)cyclopentene (**7**).[12] After a 5-min induction period the reaction reached a gentle reflux which continued for ~0.5 h. The solvent was evaporated in vacuo, and the residue was diluted with ice and H_2O. After the mixture was neutralized to pH 7.0 with 10% NaOH, the precipitate was removed by filtration, washed with H_2O, and dried in vacuo to give 26.0 g (81%) of **16**: mp 108-109 °C; IR (KBr) 1811 (C=O), 1405 and 1180 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 1.92-2.59 (m, 5 H), 2.73-3.02 (m, 1 H), 4.03-4.16 (m, 1 H), 7.19-7.46 (m, 3 H), 7.50-7.68 (m, 1 H). Anal. Calcd for $C_{12}H_{11}Cl_2NSO_3$: C, 45.01; H, 3.46; N, 4.38. Found: C, 45.18; H, 3.64; N, 4.62.

5-(2-Chlorophenyl)-6-azabicyclo[3.2.0]heptan-7-one (17). A solution of 4.7 g (14.7 mmol) of **16** in 60 mL of 50% aqueous EtOH was treated with 1.0 g of KI and neutralized to pH 7.0 by the dropwise addition of 10% aqueous KOH. When the pH was constant at 7.0, the EtOH was removed at reduced pressure, and the aqueous phase and precipitate were extracted with Et_2O. The Et_2O layer was washed with H_2O, dried ($MgSO_4$), filtered, and evaporated in vacuo to give 2.7 g (84%) of **17**, mp 122-125 °C. One recrystallization from $EtOH/H_2O$ and two recrystallizations from cyclohexane afforded the analytical sample: mp 123-125 °C; IR ($CHCl_3$) 3170 (NH), 1758 and 1770 cm^{-1} (doublet, C=O); NMR ($CDCl_3$) δ 1.77-2.28 (m, 6 H), 3.60-3.75 (m, 1 H), 6.67-6.96 (m, 1 H), 7.07-7.39 (m, 4 H). Anal. Calcd for $C_{12}H_{12}ClNO$: C, 65.01; H, 5.46; N, 6.32. Found: C, 65.00; H, 5.36; N, 6.34.

5-(2-Chlorophenyl)-6-methyl-6-azabicyclo[3.2.0]heptan-7-one (3). A solution of 1.1 g (5.0 mmol) of **17** in 10 mL of THF was added dropwise to a suspension of 0.48 g (10.0 mmol) of 50% NaH in mineral oil in 20 mL of THF. The reaction was stirred until gas evolution ceased (~0.5 h) and 1 h thereafter. The flocculent suspension was treated dropwise with 1.42 g (10 mmol) of CH_3I in 5 mL of THF and then stirred at room temperature overnight. The solvent was removed in vacuo and the residue diluted with Et_2O and H_2O. The organic layer was washed with H_2O, dried ($MgSO_4$), and evaporated in vacuo to give 1.0 g (85%) of **3** (mp 64-66 °C) which had IR and NMR spectra identical with those of the material produced by the action of sodium amide in liquid ammonia on **2a**.

Acknowledgment. We are grateful to Dr. Forrest MacKellar and the personnel of the Physical and Microanalytical Sections for obtaining spectra and analyses and for helpful discussions.

Registry No. **1**, 6740-88-1; **1**·HCl, 1867-66-9; **2a**, 79548-68-8; **2a**·HBr, 79548-69-9; **2a**·HCl, 79548-70-2; **2e**, 79548-71-3; **3**, 79517-34-3; **4**, 79499-53-9; **5**, 79517-35-4; **6**, 79517-36-5; **7**, 38793-82-7; **8**, 79517-37-6; **9**, 79499-54-0; **10**, 79499-55-1; **11**, 79499-56-2; **12**, 79499-57-3; **12**·HCl, 79499-58-4; **13**, 35211-10-0; **13**·HCl, 79499-59-5; **14**, 79499-60-8; **14** (free base), 79499-61-9; **15**, 57683-62-2; **16**, 79499-62-0; **17**, 79499-63-1; (1-bromocyclopentyl)(2-chlorophenyl)methanone, 6740-86-9.

Tandem Alkylation-Reduction of 2-Acylpyrroles. Convenient One-Pot Syntheses of 2-Benzylpyrroles[1]

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Tandem alkylation-reduction of 2-acylpyrroles is described for the convenient one-pot syntheses of 2-benzylpyrroles. By this convenient procedure 2-(*p*-methoxybenzyl)pyrrole (**2**), 2-benzylpyrrole (**3**), 2-(*p*-methylbenzyl)pyrrole (**4**), 2-(*o*-methoxybenzyl)pyrrole (**5**), and 2-(*m*-methoxybenzyl)pyrrole (**6**) were prepared from *p*-methoxyphenyllithium, phenyllithium, *p*-tolyllithium, *o*-methoxyphenyllithium, and *m*-methoxyphenyllithium, respectively. Arylation-reduction of 2-acetylpyrrole (**7**) and 2-benzoylpyrrole (**11**) were the only entries that did not result in a direct one-pot synthesis of the corresponding α-methyl- and α-phenyl-2-benzylpyrrole. In contrast to the organolithium reagents, employment of Grignard reagents in this alkylation-reduction sequence requires N-protection of the pyrrole ring, otherwise low yields of the 2-benzylpyrroles are observed. Examples of useful synthetic procedures include the alkylation-reduction of *N*-methylpyrrole-2-carboxaldehyde (**14**), *N*-benzylpyrrole-2-carboxaldehyde (**16**), and *N*-[(β-methoxyethoxy)methyl]pyrrole-2-carboxaldehyde (**17**) with *p*-methoxyphenylmagnesium bromide to prepare *N*-methyl-2-(*p*-methoxybenzyl)pyrrole (**15**), 2-(*p*-methoxybenzyl)pyrrole (**2**), and *N*-[(β-methoxyethoxy)methyl]-2-(*p*-methoxybenzyl)pyrrole (**18**), respectively; *N*-[(β-methoxyethoxy)methyl]-2-(*p*-methylbenzyl)pyrrole (**19**) was prepared from **17** and *p*-tolylmagnesium bromide.

In our studies[1] extending the usefulness of tandem alkylation-reductions of carbonyl compounds, we have not investigated to any extent the applicability of this synthetically useful procedure to acyl heterocycles.[3] Recently, the need arose in this research group for an efficient synthesis of 2-benzylpyrroles, and 2-(*p*-methoxybenzyl)pyrrole (**2**) in particular. We envisioned the application of our tandem alkylation-reduction procedure as outlined below.

(1) Part 13 in the series "Alkylation-Reduction of Carbonyl Systems". For part 12 see: Ryan Zilenovski, J. S.; Hall, S. S. *J. Org. Chem.* **1981**, *46*, 4139-4142.

(2) Taken in part from the Ph.D Thesis of D.P.S. that was submitted to the Graduate School, Rutgers University, Newark, NJ, May 1981. H. Martin Friedman Thesis Award (Rutgers University), May 1981.

(3) Furan-2-carboxaldehyde was effectively phenylated-reduced in a survey project, while 2-acetylthiophene led to a mixture of products. See: Hall, S. S.; McEnroe, F. J. *J. Org. Chem.* **1975**, *40*, 271-275.

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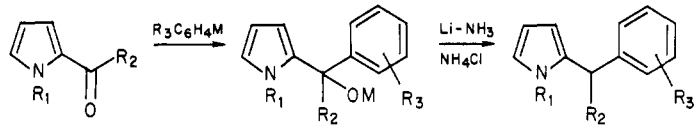
Table I. Tandem Alkylation-Reduction of 2-Acylpyrroles [a]

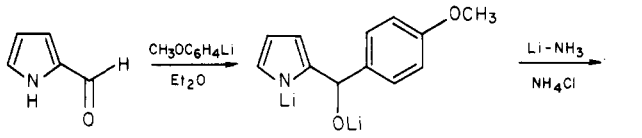


2-acylpyrrole product

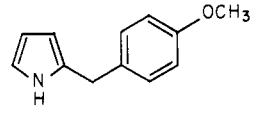
2-acylpyrrole	organometallic reagent [b] ($R_3C_6H_4M$)	product	% yield [c]
1, R_1 = H, R_2 = H	R_3 = *p*-CH_3O, M = Li	2, R_1 = H; R_2 = H; R_3 = *p*-CH_3O	98 [d]
1,	R_3 = H, M = Li [e]	3, R_1 = H; R_2 = H; R_3 = H	99 [f]
1,	R_3 = *p*-CH_3, M = Li	4, R_1 = H; R_2 = H; R_3 = *p*-CH_3	97 [g]
1,	R_3 = *o*-CH_3O, M = Li	5, R_1 = H; R_2 = H; R_3 = *o*-CH_3O	99 [g]
1,	R_3 = *m*-CH_3O, M = Li [h]	6, R_1 = H; R_2 = H; R_3 = *m*-CH_3O	57 [g]
7, R_1 = H; R_2 = CH_3	R_3 = *p*-CH_3O, M = Li	10, R_1 = H; R_2 = CH_3; R_3 = *p*-CH_3O	75 [i]
11, R_1 = H; R_2 = C_6H_5	R_3 = *p*-CH_3O, M = Li	12, R_1 = H; R_2 = C_6H_5; R_3 = *p*-CH_3O	92 [g,j]
1,	R_3 = *p*-CH_3O, M = MgBr	2,	15 [f,g,k]
14, R_1 = CH_3; R_2 = H	R_3 = *p*-CH_3O, M = MgBr	15, R_1 = CH_3; R_2 = H; R_3 = *p*-CH_3O	84 [f]
16, R_1 = $C_6H_5CH_2$; R_2 = H	R_3 = *p*-CH_3O, M = MgBr	2	83 [g]
17, R_1 = $CH_3OCH_2CH_2OCH_2$; R_2 = H	R_3 = *p*-CH_3O, M = MgBr	18, R_1 = $CH_3OCH_2CH_2OCH_2$; R_2 = H; R_3 = *p*-CH_3O	67 [f]
17	R_3 = *p*-CH_3, M = MgBr	19, R_1 = $CH_3OCH_2CH_2OCH_2$; R_2 = H; R_3 = *p*-CH_3	72 [f]

[a] See the Experimental Section for details. [b] Unless noted otherwise, the organolithium reagents were generated in situ from the aryl bromide and lithium–sodium alloy and the Grignard reagents from the aryl bromide and highly reactive magnesium metal (Rieke procedure). [c] Isolated yield after column chromatography. [d] See ref 21. [e] Commercial phenyllithium from Aldrich Chemical Co. was used. [f] Lithium wire (0.02% Na) from Alfa Products was used for the metal-ammonia reduction step. [g] Lithium wire (0.01% Na) from Foote Mineral Co. was used for the metal–ammonia reduction step. [h] Generated in situ from *m*-bromoanisole and *n*-butyllithium in hexane by transmetallation. [i] Not a one-pot synthesis. The reduction-resilient benzyl alcohol **8** was dehydrated on silica gel and the resultant 2-(α-methylbenzyl)pyrrole **9** reduced to **10** in Li–NH_3. See ref 24. [j] A 1:1 mixture of **12** and 2-(α-phenyl-3,6-dihydro-*p*-methoxybenzyl)pyrrole (**13**) was formed. Pure **13** or the mixture could be quantitatively dehydrogenated to **12**. [k] See the Discussion and ref 10.

Arylation of pyrrole-2-carboxaldehyde (**1**) with excess *p*-methoxyphenyllithium in ether would generate the intermediate benzyl alkoxide **2a**, which should reduce to



1 **2a**



2

2-(*p*-methoxybenzyl)pyrrole (**2**) after ammonia, lithium, and ammonium chloride are sequentially introduced to the reaction vessel. The pyrrole ring, under these reaction conditions, is not expected to reduce.[4]

Table I is a summary of the results of the alkylation–reduction of 2-acylpyrroles with various aromatic organometallic reagents. All of the substituted aryllithium reagents, with the exception of *m*-methoxyphenyllithium, were generated in situ in ether from the corresponding aryl bromide and lithium–sodium alloy[5] in a metal–ammonia reaction vessel.[6] Addition of pyrrole-2-carboxaldehyde (**1**) to the organolithium reagent produces the intermediate benzyl alkoxide (**2a**, for example) that is reduced to the corresponding 2-benzylpyrrole after ammonia is distilled into the reaction mixture and then lithium wire and ammonium chloride are added. The latter are conditions that protonate the alkoxide and reduce the benzyl alcohol to the 2-benzylpyrrole before all the excess reducing agent is consumed by the quench. The isolated yields after column chromatography of the 2-benzylpyrroles **2–5** in repeated runs were excellent (97–99%). The isolated yield of 2-(*m*-methoxybenzyl)pyrrole (**6**), however, was substantially less (57%). The requisite organolithium reagent *m*-methoxyphenyllithium, which in this case could not be generated by the general procedure described above with the lithium–sodium alloy, was formed from *m*-bromoanisole and *n*-butyllithium in hexane by transmetalation.[7] The lower yield of benzylpyrrole may reflect an inefficient in situ generation of the organolithium reagent or possibly solvent effects.

The arylation–reduction reactions of 2-acetylpyrrole (**7**) and 2-benzoylpyrrole (**11**) are the only entries that did not result in a direct one-pot synthesis of the corresponding α-methyl- and α-phenyl-2-benzylpyrroles. When 2-acetylpyrrole (**7**) was alkylated with *p*-methoxyphenyllithium and then the intermediate subjected to lithium–ammonia–ammonium chloride reduction, the only product isolated was the corresponding benzyl alcohol **8**. In this case, the tertiary benzyl alcohol was resilient to the metal–ammonia reducing conditions.[8] Fortuitously, during purification on silica gel, the benzyl alcohol **8** dehydrated to the 2-(α-methylenebenzyl)pyrrole **9**. This olefin was

(4) O'Brien, S.; Smith, D. C. C. *J. Chem. Soc.* **1960**, 4609–4612.

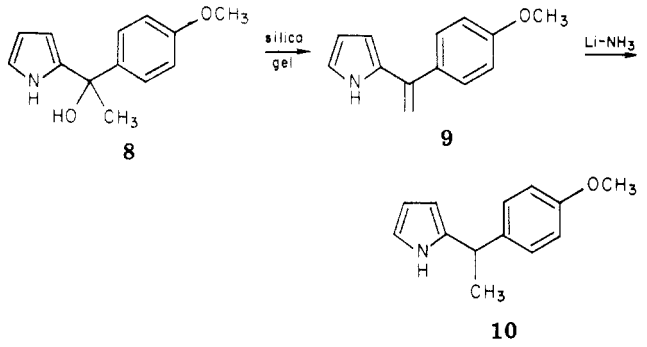
(5) The lithium–sodium alloy (2% Na) was prepared by heating a stirred mixture of the two metals in heavy oil at 190 °C in a stainless-steel beaker under an argon atmosphere tent for 1 h. The melt is then allowed to cool with slow stirring to control the size of the alloy shot, which are then stored in oil under argon. See also: Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. 1, pp 618–619 and the references cited therein.

(6) For the substituted aryllithium reagents, especially *o*- and *p*-methoxyphenyllithium, we have found that the generation of the organolithium reagent is not always reproducible unless the aryl bromide is freshly distilled, the lithium–sodium alloy is used rather than lithium metal, and a trace of ethyl acetate is present. Presumably the latter cleans the metal surface.

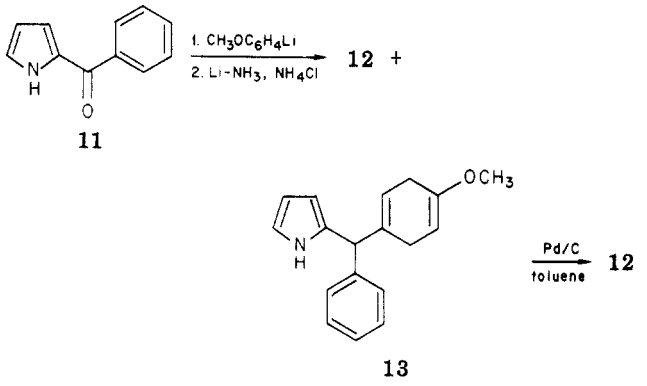
(7) (a) Gilman, H.; Wright, L.; Moore, F. W. *J. Am. Chem. Soc.* **1940**, *62*, 2327–2335. (b) Fraenkel, G.; Dayagi, S.; Kobayashi, S. *J. Phys. Chem.* **1968**, *72*, 953–961.

(8) This is not the first time we have encountered a tertiary benzyl alcohol that resists reduction under these conditions. See: Hall, S. S.; McEnroe, F. J. *J. Org. Chem.* **1975**, *40*, 271–275.

then reduced in lithium–ammonia to the desired 2-(α-methylbenzyl)pyrrole **10** in an overall isolated yield of 75% from 2-acetylpyrrole.



In the case of the alkylation–reduction of 2-benzoylpyrrole (**11**), the reduction of the intermediate tertiary benzyl alcohol went smoothly, but some overreduction of the anisole ring occurred since ca. a 1:1 mixture of the desired 2-(α-phenyl-*p*-methoxybenzyl)pyrrole (**12**) and the



1,4-dihydro compound 2-(α-phenyl-3,6-dihydro-*p*-methoxybenzyl)pyrrole (**13**) was formed. Subjecting either **13** or the mixture to 10% Pd/C in refluxing toluene converted **13** quantitatively back to **12**. The overall yield of this two-step process from 2-benzoylpyrrole was 92%.

In sharp contrast to the rather general success with aryllithium reagents, when pyrrole-2-carboxaldehyde (**1**) was added to an excess of *p*-methoxyphenylmagnesium bromide (generated in situ in THF from *p*-bromoanisole and a dark gray suspension of highly reactive magnesium metal[9]) and then subjected to the lithium–ammonia–ammonium chloride reducing conditions, the yield of 2-(*p*-methoxybenzyl)pyrrole (**2**) dropped precipitously to 15%.[10]

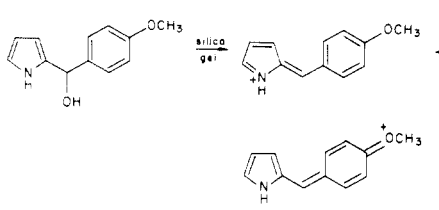
We suspected that the magnesium ion was effectively chelating to both the benzyl alkoxide and the nitrogen anion of the pyrrole, thereby efficiently interfering with the protonation of the benzyl alkoxide, which is required before the reduction sequence can occur.[11] To avoid this chelation problem, *N*-methylpyrrole-2-carboxaldehyde (**14**) was used and the isolated yield of the desired product *N*-methyl-2-(*p*-methoxybenzyl)pyrrole (**15**) improved dramatically (84%), making the procedure synthetically useful.

Since the successful use of Grignard reagents in this alkylation–reduction sequence evidently requires a N-protecting group on the pyrrole ring, we examined other protecting groups that would be easier to remove than the *N*-methyl group.[12] Arylation–reduction of *N*-benzylpyrrole-2-carboxaldehyde (**16**) with *p*-methoxyphenylmagnesium bromide afforded the desired 2-(*p*-methoxybenzyl)pyrrole (**2**) in 83% yield. The *N*-benzyl protecting group is especially useful since it serves its role effectively during the alkylation step and then is conveniently cleaved during the reduction phase of the tandem sequence. The MEM group [(β-methoxyethoxy)methyl],[13] on the other hand, is inert to these conditions and can be used when subsequent N-protection of the pyrrole is desired. Thus arylation–reduction of *N*-[(β-methoxyethoxy)methyl]-pyrrole-2-carboxaldehyde (**17**) with *p*-methoxyphenylmagnesium bromide and *p*-tolylmagnesium bromide resulted in reasonable isolated yields (67% and 72%) of *N*-[(β-methoxyethoxy)methyl]-2-(*p*-methoxybenzyl)pyrrole (**18**) and *N*-[(β-methoxyethoxy)methyl]-2-(*p*-methylbenzyl)pyrrole (**19**), respectively.

This tandem arylation–reduction of 2-acylpyrroles is, in general, a very efficient method for the synthesis of 2-benzylpyrroles in excellent yield. Use of the aryllithium reagents offers the advantage that N-protection of the pyrrole is not necessary, but more organometallic reagent is consumed. The Grignard reagents, in contrast, do require N-protection of the pyrrole, but less reagent is then needed. This success with 2-acylpyrroles has encouraged us to extend this useful tandem alkyation–reduction procedure to other acyl heterocycles, and these studies are in progress in this laboratory. Finally, it has not escaped our attention that with this convenient one-pot synthesis of 2-(*p*-methoxybenzyl)pyrrole (**2**), the entire carbon skeleton of the antibiotic anisomycin[14] has been elaborated.

(9) (a) Rieke, R. D.; Bales, S. E. *J. Am. Chem. Soc.* **1974**, *96*, 1775–1781. (b) *J. Chem. Soc., Chem. Commun.* **1973**, 879–880. (c) Rieke, R. D.; Hudnall, P. M. *J. Am. Chem. Soc.* **1972**, *94*, 7178–7179.

(10) We suspected that the major product was the benzyl alcohol (corresponding to **2a**), but the only product isolated from the silica gel column was **2**. Decomposition of the alcohol on the silica gel is probable



since the columns, in this case, always turned a blood-red color when the pale pink crude oil product mixture was added to the silica gel. Such a related benzyl alcohol is an intermediate in the reaction between pyrroles and *p*-(dimethylamino)benzaldehyde. The latter reaction is used as a spot test (red-violet color) to identify pyrroles. See: Feigl, F.; Anger, V.; Oesper, R. E. "Spot Tests in Organic Analysis", 7th ed.; Elsevier Publishing Co.: Amsterdam, 1966; pp 381–382 and references cited therein.

(11) (a) Ryan Zilenovski, J. S.; Hall, S. S. *J. Org. Chem.* **1979**, *44*, 1159–1161. (b) Hall, S. S.; Lipsky, S. D.; Small, G. H. *Tetrahedron Lett.* **1971**, 1853–1854. (c) Hall, S. S.; Lipsky, S. D.; McEnroe, F. J.; Bartels, A. P. *J. Org. Chem.* **1971**, *36*, 2588–2591.

(12) Reagents that proved ineffective in removing the *N*-methyl protecting group from **15** included cyanogen bromide, 2,2,2-trichloroethyl chloroformate [(a) Reinecke, M. G.; Daubert, R. G. *J. Org. Chem.* **1973**, *38*, 3281–3287. (b) Montzka, T. A.; Matiskella, J. D.; Partyka, R. A. *Tetrahedron Lett.* **1974**, 1325–1327], vinyl chloroformate [(c) Olofson, R. H.; Yamamoto, Y. S.; Wancowicz, D. J. *Ibid.* **1977**, 1563–1566. (d) Olofson, R. H.; Schur, R. *Ibid.* **1977**, 1571–1574], and diethyl azodicarboxylate [(e) Smissman, E. E.; Makriyannis, A. *J. Org. Chem.* **1973**, *38*, 1652–1657]. With the latter reagent a substitution reaction occurred at the 5-position of the pyrrole (yield 90%). This chemistry was subsequently reported with other pyrroles [(f) Lee, C. K.; Kim, S. J.; Hahn, C. S. *J. Org. Chem.* **1980**, *45*, 1692–1693].

(13) Corey, E. J.; Gras, J. L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 1809–1812.

(14) (a) Beereboom, J. J.; Butler, K.; Pennington, F. C.; Solomons, I. A. *J. Org. Chem.* **1965**, *30*, 2334–2342. (b) Schaefer, J. P.; Wheatley, P. J. *Ibid.* **1968**, *33*, 166–169. (c) Butler, K. *Ibid.* **1968**, *33*, 2136–2141. (d) Wong, C. M. *Can. J. Chem.* **1968**, *46*, 1101–1104 and the references cited therein.

Experimental Section[15]

General Comments. The in situ generation of the aryl organometallic reagent and subsequent alkylation sequence is performed under an inert atmosphere by connecting an argon or nitrogen gas source to a T tube that is connected to the metal–ammonia reaction assembly and to a soda lime drying trap. The latter is connected in series to an oil bubbler. Argon or nitrogen is swept through the system at a moderate flow rate. When ammonia is to be introduced, the inert gas source is disconnected and the reaction protected from moisture by attaching a soda lime drying tube to the sidearm of the Dewar condenser for the duration of the reaction. All glassware was either oven dried, cooled to room temperature in a box desiccator, and then quickly assembled or oven dried, quickly assembled, flushed with argon, and allowed to cool. Anhydrous ether (Et_2O) was used directly from freshly opened containers. Tetrahydrofuran (THF), which had been filtered through an alumina column, was freshly distilled under a nitrogen atmosphere from a dark blue THF solution containing the sodium–benzophenone ketyl radical. Lithium wire for the reduction sequence [3.2 mm in diameter, high purity, from Foote Mineral Co. (0.01% Na) and Alfa Products (0.02% Na)] was wiped free of oil, rinsed in hexane, and cut into 0.5- or 1.0-cm pieces just prior to use. The lithium wire for the alloy was from Foote Mineral Co. (0.05% Na), and the sodium metal was from Fisher Scientific Co. The potassium metal (Fisher Scientific Co.) was wiped free of oil, rinsed in hexane and cut into small pieces just prior to use. The lithium–sodium alloy[5] was rinsed in hexane, pounded to a thin foil, and cut into thin slivers directly into the reaction vessel, with argon sweeping through the flask and out the opened side-arm joint. Anhydrous magnesium chloride (Alfa Products) was quickly weighed in a dry capped vial and added to the reaction vessel to avoid uptake of moisture. Anhydrous ammonia was distilled, through a tower of potassium hydroxide pellets, directly into the reaction vessel. Melting and boiling points are uncorrected. Purification of the products by column chromatography was accomplished on silica gel (Grace, grade 62, 60–200 mesh). Thin-layer chromatography was performed on silica gel plates with ether–hexane (1:1) as the eluant. The assigned structure of each product is consistent with the spectral data. Satisfactory composition analyses (±0.4% for C, H, and N) on all products were obtained. Two experiments, one using *o*-methoxyphenyllithium and the other *p*-methoxyphenylmagnesium bromide, are described in detail to illustrate the two general tandem alkylation–reduction procedures.

Alkylation–Reduction of Pyrrole-2-carboxaldehyde (1) with *o*-Methoxyphenyllithium. 2-(*o*-Methoxybenzyl)pyrrole (5). To a cooled (3–5 °C, ice–water bath), vigorously stirred mixture containing 2.16 g (309 mmol) of lithium–sodium alloy[5] (rinsed in hexane, pounded to a foil, and cut into thin 1-cm slivers) and 60 μL (0.64 mmol) of ethyl acetate in 120 mL of Et_2O under an argon atmosphere was slowly added (1 h) a solution of 20.16 g (108 mmol) of *o*-bromoanisole in 120 mL of Et_2O. After stirring the mixture for an additional 2 h, much of the alloy was consumed and a black suspension had formed.[6] To the cooled (3–5 °C) suspension was added dropwise (ca. 30 min) a solution of 3.00 g (31.6 mmol) of pyrrole-2-carboxaldehyde (1) in 120 mL of Et_2O. After allowing the mixture to warm to ambient temperature over a 45-min period, 390 mL of THF was added. Anhydrous ammonia (ca. 750 mL) was distilled[16] into the mixture, and then 880 mg (126 mmol, 1-cm pieces) of lithium wire[17] was quickly added. Fifteen minutes after the dark blue color of the mixture was established, ca. 60 g of NH_4Cl was cautiously added[18] (ca. 5 min) to the vigorously stirred mixture to discharge the blue color, and then the ammonia was allowed to evaporate. After the residue had been partitioned between water and ether, the organic phase was dried ($MgSO_4$), filtered, concentrated at water aspirator pressure, and then analyzed (TLC). Following column chromatography (100 g of silica gel, 2% ether–98% hexane), 5.85 g (31.3 mmol, 99%) of 2-(*o*-methoxybenzyl)pyrrole (5) was obtained as a colorless oil: n^{23}_D 1.5755; IR (film) 3440 (br), 3375 (br), 3100, 3060, 3000, 2940, 2900, 2840, 1600, 1590, 1500, 1470, 1445, 1295, 1250, 1110, 1060, 1030, 800, 760, 720 cm^{-1}; UV (MeOH) λ_{max} 215 nm (ε 15 000), 271 (2355), 277 (2120); ^1H NMR (79.5 MHz, $CDCl_3$) δ 8.5–7.8 (1 H, br), 7.27–6.94 (2 H, 2 overlapping m), 6.94–6.64 (2 H, 2 overlapping m), 6.53 (1 H, dd, J = 5, 3 Hz), 6.04 (1 H, dd, J = 6, 3 Hz) overlapping 5.91 (1 H, br s, $w_{1/2}$ = 8 Hz), 3.87 (2 H, s), 3.80 (3 H, s); mass spectrum, m/e (relative intensity) 188 (10), 187 (M^+, 74), 186 (24), 172 (28), 170 (16), 156 (25), 155 (10), 154 (27), 144 (15), 128 (10), 127 (13), 117 (12), 115 (19), 109 (12), 91 (33), 81 (32), 80 (100), 78 (12), 77 (17), 65 (14), 63 (12), 53 (15), 51 (17), 43 (12), 39 (17).

Alkylation–Reduction of *N*-Benzylpyrrole-2-carboxaldehyde (16) with *p*-Methoxyphenylmagnesium Bromide. 2-(*p*-Methoxybenzyl)pyrrole (2). A stirred mixture containing 1.82 g (19.2 mmol) of magnesium chloride and 1.36 g (34.9 mmol) of potassium in 50 mL of THF was refluxed (oil bath, 80 °C) for 2 h under a nitrogen atmosphere. After the dark gray suspension was allowed to cool to ambient temperature (ca. 30 min), a solution of 1.60 g (8.60 mmol) of *p*-bromoanisole in 5 mL of THF was slowly added. After 30 min, the stirred dark gray suspension was cooled to −50 °C (dry ice/2-propanol bath), and then a solution of 1.40 g (7.60 mmol) of *N*-benzylpyrrole-2-carboxaldehyde (16) in 10 mL of THF was added dropwise (ca. 20 min). After 30 min, the mixture was diluted with an additional 150 mL of THF. Ammonia (ca. 250 mL) was then distilled[16] into the mixture, and 312 mg (44.6 mmol, 1-cm pieces) of lithium wire[17] was quickly added. Twenty minutes after the dark blue-black color of the mixture was established, ca. 12 g of NH_4Cl was cautiously added[18] (ca. 5 min) to discharge the color, and then the ammonia was allowed to evaporate. After the residue was partitioned between ether and water,[19] the organic phase was dried ($MgSO_4$), filtered, concentrated at water aspirator pressure, and then analyzed (TLC). Following column chromatography (30 g of silica gel, 2% ether–98% hexane), 1.18 g (6.31 mmol, 83%) of 2-(*p*-methoxybenzyl)pyrrole (2) was obtained as a colorless oil:[14a,20] n^{21}_D 1.5776;

(15) Melting points were determined with a Fisher-Johns apparatus. Refractive indices were determined with an American Optical ABBE Model 10450 refractometer. The IR spectra were determined with a Perkin-Elmer Model 180 infrared spectrophotometer. The UV spectra were determined with a Cary Model 118 ultraviolet spectrophotometer. The ^1H NMR spectra were determined at 79.5 MHz with a Varian Model CFT-20 Fourier transform NMR spectrometer, at 90 MHz with a Varian Model EM 390 NMR spectrometer, and at 100 MHz with either a Varian Model XL-100 Fourier transform NMR spectrometer or a JEOL Model JNM-PS-FT-100 fast Fourier transform NMR spectrometer. The chemical shifts are expressed in δ values (parts per million) relative to a Me_4Si internal standard. The mass spectra were determined with a Varian Associates Model MAT CH-5 single-focusing mass spectrometer with an SS-100C data system. Phenyllithium (1.9 M, cyclohexane–ether), *n*-butyllithium (1.6 M, hexane), methylmagnesium bromide (3 M, ether), potassium *tert*-butoxide, *p*-bromoanisole (redistilled), *o*-bromoanisole (redistilled), *m*-bromoanisole (redistilled), *p*-bromotoluene (redistilled), pyrrole-2-carboxaldehyde, *N*-methylpyrrole-2-carboxaldehyde, pyrrole, ethyl benzoate, α-chlorotoluene, and (β-methoxyethoxy)methyl chloride were from Aldrich Chemical Co.

(16) To increase the efficiency of the condensing process, the reaction vessel was cooled (dry ice/2-propanol bath), and to prevent splattering, the apparatus was tilted slightly to allow the condensing ammonia to run down the walls of the flask.

(17) Lithium wire from Foote Mineral Co. (0.01% Na).

(18) The NH_4Cl is most conveniently introduced by attaching a glass bulb filled with the salt to a side arm by means of Tygon tubing. When the NH_4Cl is to be added, the bulb is raised and tapped gently to smoothly introduce the quenching agent. Should this step start to become violent, the addition and sometimes even the vigorous stirring should be momentarily stopped to avoid an eruption.

(19) Caution should be observed when water is added to the residue since occasionally a small ball of potassium is concealed in the bottom of the flask. The best precaution is to add ca. 25 mL of 2-propanol to the residue before the workup.

(20) Salmon, M.; Diaz, E.; Walls, F. *Bol. Inst. Quim. Univ. Nacl. Auton. Mex.* **1969**, *21*, 7–65.

(21) High-purity lithium wire (0.011% Na, 0.012% Ca, 0.007% K) from Foote Mineral Co. was used for the metal–ammonia reduction step. For reasons that we cannot explain, when either lithium wire (0.02% Na) from Alfa Products or lithium wire (0.05% Na) from Foote Mineral Co. was used for the reduction step in this synthesis of 2, the yield dropped to ca. 50%.

(22) Lithium wire from Alfa Products (0.02% Na).

(23) Bean, G. P. *J. Heterocycl. Chem.* **1965**, *2*, 473–476.

(24) Since the benzyl alcohol 8 was resilient to the reducing conditions of the tandem alkylation–reduction sequence, the metal–ammonia step was omitted in all subsequent syntheses of benzylpyrrole 10 and is so described here.

(25) Eloy, F.; Deryckere, A. *Helv. Chim. Acta* **1970**, *53*, 645–648.

IR (film) 3400 (br), 3100, 3000, 2960, 2940, 2910, 2850, 1620, 1520, 1260, 1180, 1040, 800, 720 cm^{-1}; UV (MeOH) λ_{max} 224 nm (ϵ 15600), 276 (1900), 284 (1600); ^1H NMR (100 MHz, $CDCl_3$) δ 8.1-7.4 (1 H, br s, exchanges with D_2O), 7.13 (2 H, d with further fine splitting, J = 9 Hz), 6.85 (2 H, d with further fine splitting, J = 9 Hz), 6.65 (1 H, dd with further fine splitting, J = 4, 2 Hz), 6.15 (1 H, dd, J = 5, 3 Hz), 5.99 (1 H, br s with fine splitting, $w_{1/2}$ = 8 Hz), 3.92 (2 H, s), 3.78 (3 H, s); mass spectrum, m/e (relative intensity) 187 (M^+, 26), 186 (19), 156 (9), 80 (23), 58 (25), 43 (100).

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Supplementary Material Available: Experimental details and characterization data for the 2-benzylpyrroles 2-4, 6, 10, 12, 15, 18, and 19 and the 2-acylpyrroles 7, 11, 16, and 17 (12 pages). Ordering information is given on any current masthead page.

Codeine Analogues. Synthesis of Spiro[benzofuran-3(2*H*),4'-piperidines] and Octahydro-1*H*-benzofuro[3,2-*e*]isoquinolines

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A synthesis of highly functionalized spiro[benzofuran-3(2*H*),4'-piperidines] and octahydro-1*H*-benzofuro-[3,2-*e*]isoquinolines, analogues of codeine containing the benzofuran/piperidine and benzofuran/decahydroisoquinoline ring fragments, has been developed. The process extends to the dimethoxyphenyl series earlier work in the synthesis of 4a-aryldecahydroisoquinolines involving the α-methylene lactam rearrangement and utilizes a novel α-chloro ortho ester Claisen rearrangement to establish the requisite functionality for oxide ring closure. Selective ether cleavage is achieved with methanesulfonic acid/methionine to afford a spiro[chromone-piperidinone], and base-promoted rearrangement then yields the desired spiro[benzofuran-piperidinone]. The C ring is closed by Michael addition of a β-keto ester to the α-methylene lactam moiety, subsequently affording a protected benzofuroisoquinolone. Finally, amide reduction followed by ketone deprotection gives the desired *cis*- and *trans*-benzofuroisoquinolines. The entire synthesis can be performed by starting from o-vanillin with six purifications in 10% overall yield, and the various intermediates additionally provide entries into the synthesis of 4-arylpiperidines, benzomorphans, and 4a-aryldecahydroisoquinolines. Functionality is built in to allow preparation of typical morphine patterns.

The synthesis of novel codeine analogues has been pursued for many years in the hope of finding analgesics with fewer undesirable side effects. One strategy has been to dissect the pentacyclic codeine molecule **1b** into various partial ring structures. For efficiency in designating the various ring combinations and for ease in recognition, we have adopted a nomenclature system in which the hydrophenanthrene rings are indicated as A-C in the usual way, the furan ring is referred to as O (for oxygen ring), and the piperidine ring is referred to as N (for nitrogen ring). Thus codeine (**1b**) contains the ABCNO rings, and partial structures to which considerable synthetic activity has been directed are the bicyclic (AN) arylpiperidines **2**, the tricyclic (ACN) aryldecahydroisoquinolines **3**, and the tricyclic (ABN) benzomorphans **4**. Three classes of analogues which have received meager attention are the ANO spiro[benzofuran-3(2*H*),4'-piperidines] **5**, the ACNO octahydro-1*H*-benzofuro[3,2-*e*]isoquinolines **6**, and the ABNO 3*H*-2a,6-methano-2*H*-furo[4,3,2-*f*,*g*][3]benzazocines **7** (Chart I).

The first synthesis of an ANO system was reported[1] in 1944 and utilized *gem*-dialkylation of arylacetonitriles with bis(2-chloroethyl)methylamine, closing the oxide ring by ether cleavage and nitrile attack to form a lactone. Subsequent workers[2-5] have used the same approach with subtle variations, but none has reported the preparation of ANO compounds containing functionality in the C-2 side chain or the nitrogen ring. Some of these compounds have shown analgesic activity in spite of this lack of functionality.[3-6] The first synthesis of an ACNO system was reported[7] in 1976 and used a heteroatom-directed photoarylation route. Recently an intramolecular Diels-Alder route to this system has appeared.[8] The former method does provide C-ring functionalization, with additional substituents at C-4a and C-12, and the latter

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