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# Intra- and Intermolecular Nucleophilic Cleavage of the Amide Bond of β-Lactams[1)]

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Treatment of 4-hydroxymethyl-1-phenylazetidin-2-ones (**2a**) and (**2b**) with methanesulfonic acid afforded 4-anilino-2-oxo-tetrahydrofurans (**3a**) and (**3b**), respectively. In a similar way, 3-(2-hydroxybenzyl)-1-phenylazetidin-2-one (**8**), 1-(4-methoxyphenyl)-4-(2-piperidino)azetidin-2-one (**13**), 3-(2-aminobenzyl)-1-phenylazetidin-2-one (**16**) and 1-(4-methoxyphenyl)-3-(2-piperidinomethyl)azetidin-2-one (**19**) were subjected to cleavage of the amide bond to give the corresponding lactone and lactams (**9**), (**14**), (**17**) and (**20**), respectively. The amide bond of β-lactams was also found to be cleaved by alkyl lithium in the presence of N,N,N′,N′-tetramethylethylenediamine to give β-aminoketones.

**Keywords**——β-lactam; cleavage of amide bond of β-lactams; γ-lactone; 3,4-dihydrocoumarine; 3,4-dihydro-1*H*-2-quinolone; 2-indolizinone; 3-alkylidenation of β-lactam

It is well known that the amide bond of β-lactams is easily cleaved by nucleophilies such as amino and hydroxyl groups to form an XCO–C–C–N (X=N, O) functionality.[3,4)] This high chemical reactivity of β-lactams has been applied to a synthesis of some heterocycles in order to demonstrate clearly the synthetic utility of monocyclic β-lactams. We report here the results of our studies on the synthetic utility of active intermediate β-lactams as a synthon for the CO–C–C–N moiety through nucleophilic cleavage of the amide bond.

First, nucleophilic cleavage of the amide bond by the hydroxyl group was utilized for the formation of γ-lactone derivatives. Reduction of the acid chloride (**1a**)[5)] with sodium borohydride ($NaBH_4$) in tetrahydrofuran (THF) at −78° afforded the alcohol (**2a**). Treatment of **2a** with methanesulfonic acid in benzene at room temperature gave anilinobutyrolactone (**3a**) in 87% yield. In this way, the alcohol (**2b**), prepared by reduction of the acid chloride (**1b**)[5)] with $NaBH_4$, was converted to the butyrolactone (**3b**) in 75% yield. Bose[4)] reported the formation of 4-aminocoumarine derivatives (**5**) from the 4-(2-trimethylsilyloxyphenyl)-β-lactam (**4**) by detrimethylsilylation. This CO–N fission with a phenolic hydroxyl group was utilized for the synthesis of the 3,4-dihydrocoumarine derivative possessing an aminomethyl group at the 3-position. 3-Alkylidenation of 1-phenylazetidin-2-one (**6a**)[6)] was achieved by trimethylsilylation at the 3-position, followed by stepwise condensation of 1-phenyl-3-trimethylsilylazetidin-2-one with aldehydes or ketones.[7,8)] This procedure was improved as follows. The lithium salt of **6a**, obtained by treatment with two equivalents of lithium diisopropylamide (LDA), was treated with trimethylchlorosilane, followed by condensation of the 3-trimethylsilyl intermediate with the lithium salt of *o*-hydroxybenzaldehyde to afford

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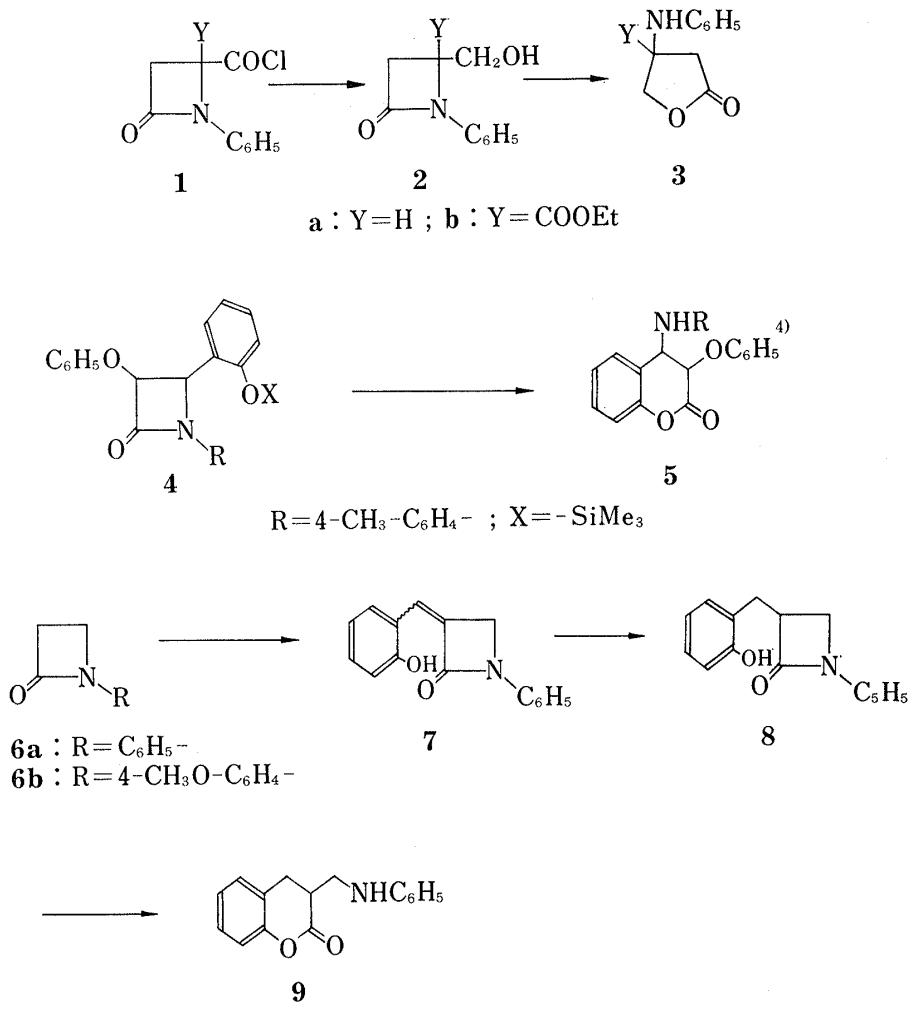


Chart 1

3-(2-hydroxybenzylidene)-1-phenyl-azetidin-2-one (**7**). Catalytic hydrogenation of **7** over platinum catalyst gave 3-(2-hydroxybenzyl)-1-phenylazetidin-2-one (**8**). Treatment of **8** with methanesulfonic acid gave 3-anilinomethyl-3,4-dihydrocoumarine (**9**).

These transformations were examined with an amino group instead of an oxygen function for the synthesis of indolizine and carbostyril derivatives. Reductive amination of ethyl 2-picolinoylacetate (**10**) with *p*-anisidine afforded ethyl 3-(4-methoxyanilino)-3-(2-pyridyl)-propionate (**11**), cyclization of which with ethylmagnesium bromide[6] gave 1-(4-methoxyphenyl)-4-(2-pyridyl)azetidin-2-one (**12**). Catalytic hydrogenation of **12** over plutinum catalyst afforded 1-(4-methoxyphenyl)-4-(2-piperidino)azetidin-2-one (**13**). Treatment of **13** with sodium ethoxide in ethanol yielded 4-(4-methoxyanilino)octahydroindolizin-2-one (**14**). Similar ring transformation was obtained in the following two cases. Reduction of 3-(2-nitrobenzylidene)-1-phenylazetidin-2-one (**15**), obtained by condensation of **6a** with *o*-nitrobenzaldehyde as described for the formation of **7**, gave 3-(2-aminobenzyl)-1-phenylazetidin-2-one (**16**). Cyclization of **16** with a catalytic amount of hydrochloric acid yielded 3-anilinomethyl-3,4-dihydro-1*H*-2-quinolone (**17**). Similarly, condensation of 1-(4-methoxyphenyl)azetidin-2-one (**6b**)[6] with pyridin-2-aldehyde yielded 1-(4-methoxyphenyl)-3-(2-picolylidene)azetidin-2-one (**18**). Catalytic hydrogenation of **18** over platinum catalyst in acetic acid–ethanol (1 : 1) gave the piperidino derivative (**19**), treatment of which with sodium ethoxide resulted in the formation of 3-(4-methoxyanilinomethyl)octahydroindolizin-2-one (**20**). Thus, intramolecular nucleophilic cleavage of the amide bond of $\beta$-lactams should be useful for the preparation of various lactam and lactone derivatives.

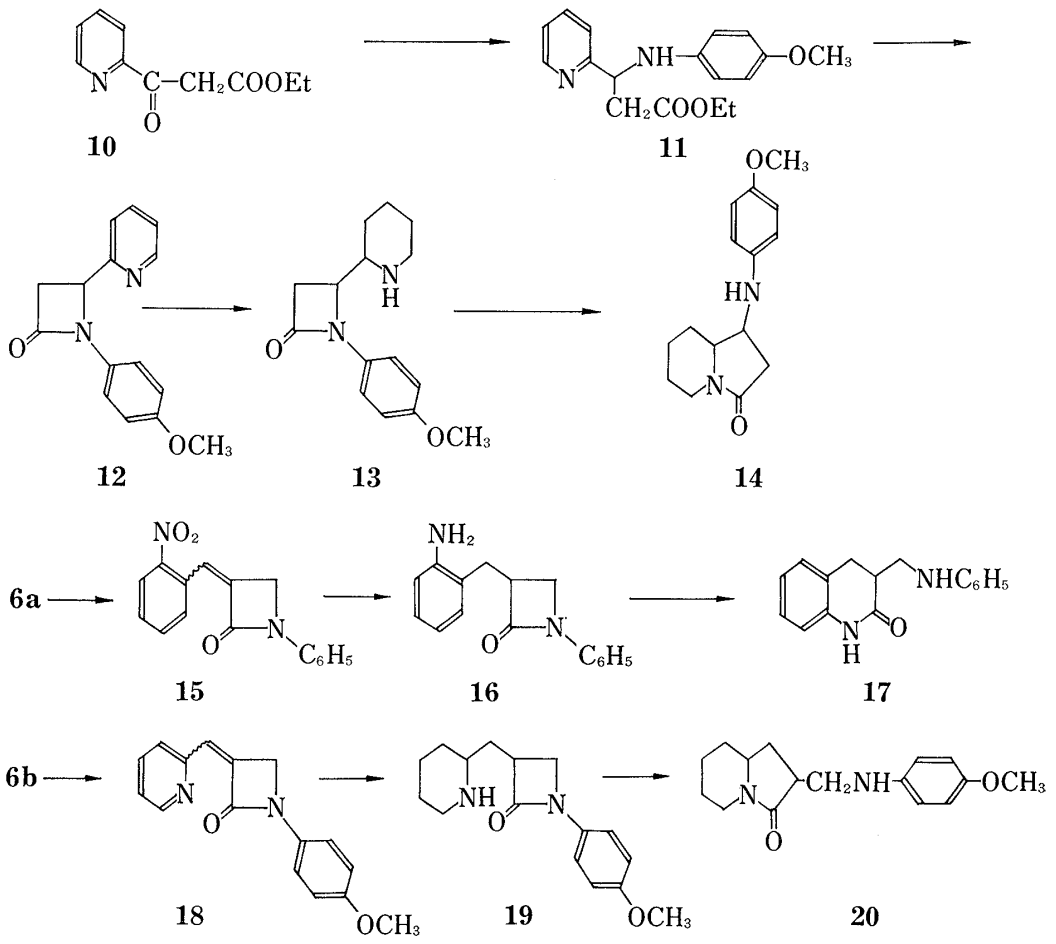


Chart 2

TABLE I. Cleavage of the Amide Bond of **6a** and **6b** with RLi

**6a** (or **6b**) + RLi ⟶ $RCOCH_2CH_2NH$-C$_6$H$_4$-X (**21a**—**21g**)

| β-Lactam | | X | R | β-Aminoketones (**21**) Yield (%) | mp (°C)[a] | IR $\nu_{max}^{Nujol}$ cm$^{-1}$ (C=O) | Mass *m/e* (M$^+$) | Formula | Analyses (%) Calcd. (Found) C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **a** | **6b** | $CH_3O$ | $C_6H_5$– | 75 | 109—111 | 1660 | 255 | $C_{16}H_{17}NO_2$ | 75.27 (75.01 | 6.71 6.69 | 5.49 5.48) |
| **b** | **6a** | H | 4-$BrC_6H_4$– | 30 | 105—107 | 1663 | 303 305 (M$^+$+2) | $C_{15}H_{14}BrNO$ | 59.21 (59.43 | 4.64 4.47 | 4.60 4.81) |
| **c** | **6a** | H | 4-$MeC_6H_4$– | 50 | 121—122 | 1662 | 239 | $C_{16}H_{17}NO$ | 80.30 (80.01 | 7.16 7.19 | 5.85 5.87) |
| **d** | **6b** | $CH_3O$ | 4-$MeC_6H_4$ | 68 | 116—117 | 1690 | 269 | $C_{17}H_{19}NO$ | 75.81 (75.67 | 7.11 7.05 | 5.20 5.71) |
| **e** | **6b** | $CH_3O$ | $C_6H_5SCH_2$– | 75 | 118—119 | 1690 | 301 | $C_{17}H_{19}NO_2S$ | 67.76 (67.55 | 6.36 6.43 | 4.65 4.71) |
| **f** | **6a** | H | $(C_6H_5(S)_2CH$– | 70 | 69— 71 | 1680 | 379 | $C_{22}H_{21}NOS_2$ | 69.64 (69.87 | 5.58 5.77 | 3.69 3.52) |
| **g** | **6a** | H |  | 65 | 80— 82 | 1692 | 226 | $C_{14}H_{14}N_2O$ | 74.31 (74.58 | 6.24 6.45 | 12.38 12.15) |

*a*) These ketones were recrystallized from MeOH-ether.

Finally, cleavage of the amide bond with alkyl lithium was examined, since there has been no report on CO–N fission of β-lactams with any type of carbanions. Treatment of **6a** with alkyl lithium or aryl lithium (such as phenylthiomethyl lithium or phenyl lithium) in THF at −78° resulted only in the recovery of the starting material or the formation of polymerized products. However, the same reaction was carried out in the presence of N,N,N'N'-tetramethylethylenediamine (TMEDA) to yield the corresponding β-aminoethyl-ketones (**21a—g**). Phenyl lithium, 4-bromophenyl lithium, 4-methylphenyl lithium, 2-pyridyl lithium,[9] phenylthiomethyl lithium and diphenylthiomethyl lithium were used to cleave the amide bond of **6a** and **6b**. These results are summarized in Table I.

In conclusion, the amide bond of β-lactams could be cleaved not only by amino and hydroxyl groups but also by carbanions.

## Experimental[10]

**4-Hydroxymethyl-1-phenylazetidin-2-one** (**2a**)——A suspension of 450 mg of $NaBH_4$ in 30 ml of THF was added to a stirred solution of 450 mg of **1a** in 10 ml of THF at −78°. After 0.5 hr at this temperature, the mixture was poured into 100 ml of 1% AcOH and extracted with $CHCl_3$. The extract was washed with $H_2O$, dried over $Na_2SO_4$ and concentrated to leave 361 mg (95%) of **2a** as colorless needles, mp 94—95.5° (MeOH–ether). NMR ($CDCl_3$) δ: 2.91 (1H, q, $J$=3.5 and 15.5 Hz, 3-H), 3.09 (1H, q, $J$=4.5 and 15.5 Hz, 3-H), MS $m/e$: 177 ($M^+$). *Anal.* Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.77; H, 6.27; N, 7.69.

**4-Ethoxycarbonyl-4-hydroxymethyl-1-phenylazetidin-2-one** (**2b**)——The azetidin-2-one (**1b**) (500 mg) was reduced with 300 mg of $NaBH_4$ in 40 ml of THF under the conditions given above to yield 340 mg (77%) of **2b** as an oil. NMR ($CDCl_3$) δ: 3.22 (2H, s, 3-$H_2$). MS $m/e$: 249 ($M^+$).

**4-Anilino-2-oxo-tetrahydrofuran** (**3a**)——A mixture of 210 mg of **2a**, 2 ml of benzene and 1 ml of $CH_3SO_3H$ was stirred at room temperature for 10 min. The mixture was then poured into $H_2O$, made basic with 28% $NH_4OH$ and extracted with $CHCl_3$. The extract was washed with $H_2O$ and dried over $Na_2SO_4$. Removal of the solvent afforded 183 mg (87%) of **3a**, mp 98—99° (MeOH–ether). NMR ($CDCl_3$) δ: 2.43 (1H, q, $J$=2.5 and 18.5 Hz, 3-H), 2.86 (1H, q, $J$=6 and 18.5 Hz, 3-H). MS $m/e$: 177 ($M^+$). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1735 (C=O). *Anal.* Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.66; H, 6.33; N, 7.79.

**4-Anilino-4-ethoxycarbonyl-2-oxo-tetrahydrofuran** (**3b**)——Treatment of 500 mg of **2b** with a mixture of 1 ml of $CH_3SO_3H$ and 2 ml of benzene under the above conditions gave 375 mg (75%) of **3b** as an oil. NMR ($CDCl_3$) δ: 2.82, 3.72 (2H, each d, $J$=17.5 Hz, 3-H), 4.40, 4.67 (2H, each d, $J$=9.5 Hz, 5-$H_2$). MS $m/e$: 249 ($M^+$), 249.097622 Calcd. for $C_{13}H_{15}NO_2$: 249.100089.

**3-(2-Hydroxybenzylidene)-1-phenylazetidin-2-one** (**7**)——A solution of 1.47 g of **6a** in 25 ml of THF was added to a solution of LDA in THF (prepared from 2.24 g of diisopropylamine and 14.7 ml of 1.5 M hexane solution of $n$-BuLi in THF at −78° as usual) at −78°. After 3 min, 1.08 g of trimethylchlorosilane was added. After stirring for a further 10 min, a solution of the lithium salt of $o$-hydroxybenzaldehyde (prepared from 1.22 g of $o$-hydroxybenzaldehyde and 1 equivalent of LDA in 30 ml of THF at −78°) was added to this solution at the same temperature. After 10 min, the mixture was poured into $NH_4Cl$ aqueous solution and extracted with $CHCl_3$. The extract was washed with $H_2O$, dried over $Na_2SO_4$ and concentrated. The resulting residue was recrystallized from MeOH–ether to give 1.9 g (96%) of **7** as colorless needles, mp 217—218°. NMR ($CDCl_3$–$d_6$ DMSO) δ: 4.49 (2H, broad s, 4-$H_2$). MS $m/e$: 251 ($M^+$). *Anal.* Calcd. for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22; N, 5.57. Found: C, 76.60; H, 5.36; N, 5.61.

**3-(2-Hydroxybenzyl)-1-phenylazetidin-2-one** (**8**)——A mixture of 0.5 g of **7**, 0.3 g of prereduced Pt catalyst and 100 ml of EtOH was shaken under atmospheric pressure of $H_2$ until uptake of the theoretical amount of $H_2$ (44.8 ml) had occurred. After removal of the catalyst, the solvent was evaporated and the resulting solid was recrystallized from ether–hexane to give 440 mg (87%) of **8** as colorless needles, mp 107—109°. MS $m/e$: 253 ($M^+$). *Anal.* Calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.96; H, 5.69; N, 5.39.

**3-Anilinomethyl-3,4-dihydrocoumarine** (**9**)——A mixture of 250 mg of **8**, 30 ml of benzene and 3 drops of $CH_3SO_3H$ was heated for 1 hr under reflux. The solvent was evaporated and the resulting residue was made basic with 28% $NH_4OH$, then extracted with $CHCl_3$. The extract was washed with $H_2O$ and dried over $Na_2SO_4$. Removal of the solvent left 220 mg (88%) of **9**, mp 91—93° (MeOH–ether). MS $m/e$: 253

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10) Melting points are not corrected. All reactions were carried out under a nitrogen atmosphere unless otherwise stated. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian T-60 instrument and mass spectra (MS) were determined with a Hitachi RMU-7L spectrimeter.

(M+). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1755 (C=O). *Anal.* Calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.61; H, 5.77; N, 5.35.

**Ethyl 3-(4-Methoxyanilino)-3-(2-pyridyl)propionate (11)**——A mixture of 25 g of ethyl α-picolinoylacetate (**10**), 16 g of *p*-anisidine, 200 ml of benzene and 100 mg of *p*-toluenesulfonic acid was refluxed for 12 hr. After removal of the solvent, the remaining residue was dissolved in 250 ml of EtOH and subjected to catalytic hydrogenation over 5 g of 10% Pd-C in the presence of 5 g of $NaBH_4$ under atmospheric pressure of $H_2$. After removal of the catalyst, the solvent was evaporated. The resulting residue was diluted with $H_2O$ and extracted with $CHCl_3$. The extract was washed with $H_2O$, dried over $Na_2SO_4$ and concentrated to leave 31.2 g (80%) of **11** as colorless needles, mp 72—73.5° (MeOH–ether). *Anal.* Calcd. for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.96; H, 6.68; N, 9.44.

**1-(4-Methoxyphenyl)-4-(2-pyridyl)azetidin-2-one (12)**——An ethereal solution of ethylmagnesium bromide (7.97 g, 20 ml of 3 M solution) was added to a stirred solution of 16.35 g of **11** in 250 ml of dry THF at room temperature. After stirring for 12 hr, the solvent was evaporated and the residue was diluted with $H_2O$ and extracted with $CHCl_3$. The extract was washed with $H_2O$, dried over $Na_2SO_4$ and concentrated. The remaining residue was chromatographed on silica gel using benzene as an eluent. Removal of the solvent (250 ml) afforded 10.1 g (73%) of **12**, mp 111—113° (benzene–hexane). NMR ($CDCl_3$) δ: 2.96 (1H, q, $J$=3 and 15 Hz, 3-H), 3.53 (1H, q, $J$=5.5 and 15 Hz, 3-H), 5.06 (1H, q, $J$=3 and 5 Hz, 4-H). MS *m/e*: 254 ($M^+$). *Anal.* Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.93; H, 5.60; N, 11.17.

**1-(4-Methoxyphenyl)-4-(2-piperidino)azetidin-2-one (13)**——A solution of 2 g of **12** in 150 ml of EtOH–AcOH (1: 1) was shaken in the presence of 0.5 g of Pt catalyst under atmospheric pressure of $H_2$ until uptake of the theoretical amount of $H_2$ (524 ml) had occurred. After removal of the catalyst, the solvent was evaporated and the resulting solid was recrystallized from ether–hexane to give 1.7 g (83%) of **13** as colorless needles, mp 107—108°. MS *m/e*: 260 ($M^+$). *Anal.* Calcd. for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.48; H, 7.80; N, 10.77.

**4-(4-Methoxyanilino)octahydroindolizin-2-one (14)**——A mixture of 200 mg of **13**, 100 mg of EtONa and 30 ml of EtOH was refluxed for 6 hr. After removal of the solvent, the residue was diluted with $H_2O$ and extracted with $CHCl_3$. The extract was washed with $H_2O$ and dried over $Na_2SO_4$. Removal of the solvent gave 150 mg (75%) of **14**, mp 99—101° (MeOH–ether). NMR ($CDCl_3$) δ: 1.10—3.54 (11H, m), 4.02—4.22 (1H, m, 4-H), 3.80 (3H, s, $OCH_3$), 6.55 (2H, d, $J$=9 Hz, Ar–H), 6.76 (2H, d, $J$=9 Hz, Ar–H). MS *m/e*: 260 ($M^+$). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1640 (C=O). *Anal.* Calcd. for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.01; H, 7.81; N, 10.78.

**3-(2-Nitrobenzylidene)-1-phenylazetidin-2-one (15)**——A solution of 1.47 g of **6a** in 25 ml of THF was added to a stirred solution of LDA in THF (prepared from 2.24 g of diisopropylamine and 14.7 ml of 1.5 M hexane solution of *n*-BuLi in THF) at −78°. After 3 min, 1.18 g of trimethylchlorosilane was added to this solution, then after a further 10 min, a solution of 1.5 g of *o*-nitrobenzaldehyde in 20 ml of THF was added at the same temperature. After stirring at the same temperature for 10 min, the mixture was poured into $NH_4Cl$ aqueous solution. After warming the mixture at 40° for 1 hr with stirring, the mixture was extracted with $CHCl_3$. The extract was washed with $H_2O$ and dried over $Na_2SO_4$. Removal of the solvent afforded 2.16 g (77%) of **15**, mp 150—150.5° (MeOH–ether). NMR ($CDCl_3$) δ: 4.24 (2H, broad s, 4-$H_2$), 7.05 (1H, broad s, olefinic H). MS *m/e*: 280 ($M^+$). *Anal.* Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 10.00. Found: C, 68.47; H, 4.35; N, 10.20.

**3-(2-Aminobenzyl)-1-phenylazetidin-2-one (16)**——A mixture of 560 mg of **15**, 300 mg of prereduced Pt catalyst and 100 ml of EtOH was shaken under atmospheric pressure of $H_2$ until uptake of the theoretical amount of $H_2$ (359 ml) had occurred. After removal of the catalyst, the solvent was evaporated and the resulting solid was recrystallized from MeOH–ether to give 444 mg (88%) of **16**, mp 98—99.5°. MS *m/e*: 252 ($M^+$). *Anal.* Calcd. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.36; H, 6.44; N, 11.17.

**3-Anilinomethyl-3,4-dihydro-1*H*-2-quinolone (17)**——A mixture of 250 mg of **16**, 30 ml of EtOH and 3 drops of conc. HCl was refluxed for 1 hr. After removal of the solvent, the residue was made basic with 28% $NH_4OH$ and extracted with $CHCl_3$. The extract was washed with $H_2O$ and dried over $Na_2SO_4$. The solvent was evaporated and the residue was recrystallized from MeOH–ether to give 200 mg (80%) of **17**, mp 153—154.5°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1655 (C=O). MS *m/e*: 252 ($M^+$). *Anal.* Calcd. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.33; H, 6.51; N, 11.13.

**1-(4-Methoxyphenyl)-3-(2-picolylidene)azetidin-2-one (18)**——The azetidin-2-one (**18**) was prepared from 1.77 g of **6b** by treatment with LDA, 1.08 g of trimethylchlorosilane and 1.07 g of pyridin-2-aldehyde as described for **15**. Recrystallization of the product from benzene–hexane gave 1.8 g (68%) of **18**, mp 165—168°. NMR ($CDCl_3$) δ: 4.17 (2H, broad s, 4-$H_2$). MS *m/e*: 266 ($M^+$). *Anal.* Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.19; H, 5.10; N, 10.41.

**3-(4-Methoxyanilinomethyl)octahydroindolizin-2-one (20)**——A mixture of 532 mg of **18**, 300 mg of prereduced Pt catalyst, 50 ml of AcOH and 50 ml of EtOH was shaken under atmospheric pressure of $H_2$ and worked up as above to give 510 mg of 1-(4-methoxyphenyl)-3-(2-piperidinomethyl)azetidin-2-one (**19**); this was, without purification, treated with 260 mg of EtONa in 30 ml of EtOH under reflux for 1 hr. The solvent was evaporated and the residue was extracted with $CHCl_3$. The extract was washed with $H_2O$, dried over $Na_2SO_4$ and concentrated to leave 423 mg (77%) of **20**, mp 91—92° (ether–hexane). MS *m/e*:

274 ($M^+$). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1655 (C=O). *Anal.* Calcd. for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.11; H, 7.97; N, 9.96.

**Cleavage of the Amide Bond of 6a (or 6b) with Aryl and Alkyl lithium; General Procedure**——A stirred solution of 0.73 g (0.05 mol) and **6a** (or 0.90 g of **6b**) in 20 ml of THF was added to a solution of aryl lithium (0.05 mol) and TMEDA (0.06 mol) in 35 ml of ether at −78°. After stirring for 15 min at the same temperature, the mixture was poured into 100 ml of $NH_4Cl$ aqueous solution and extracted with $CHCl_3$. The extract was washed with $H_2O$, dried over $Na_2SO_4$ and concentrated to afford the corresponding ketones (**21a—g**) (see Table I).