Reactions and Syntheses with Organometallic Compounds. 7. Synthesis of Benzolactams by Palladium-Catalyzed Amidation

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o-Bromoaminoalkylbenzene **5** was heated with a catalytic amount of $Pd(OAc)_2$–PPh_3 in the presence of n-Bu_3N in a carbon monoxide atmosphere to give five-, six-, and even seven-membered benzolactams, that is, isoindolinone, isoquinolinone, and benzazepinone derivatives, in good yields.

Low-valent metal complexes can be oxidatively inserted into aryl halides to afford aryl metal complexes; this process has been developed by us as a novel synthesis for heterocyclic compounds.[1] Aryl metal complexes (**2**, M = Ni or Pd; Scheme I), which were prepared from aryl halides (**1**, X = Br or Cl) and low-valent metal complexes such as $Ni(PPh_3)_n$ or $Pd(PPh_3)_n$, react with an internal double bond to give indole, oxindole,[1a] quinoline,[1c] isoquinoline,[1b] and benzazepine derivatives.[1c] It was thus anticipated that the acyl metal complex **7** could react with an internal amino group to produce the benzolactam **8**.

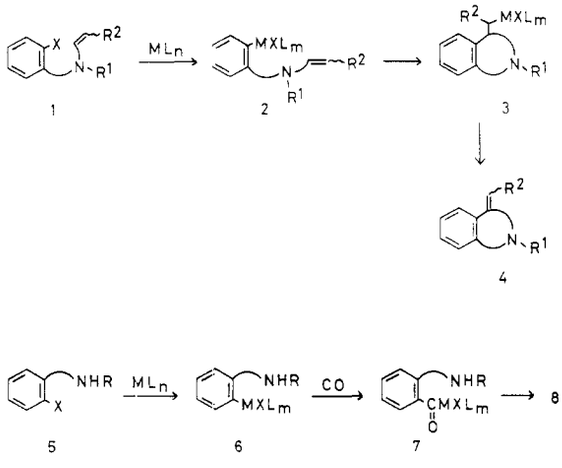
Carbonylation by means of transition metals is a useful process, but the reaction usually requires rather drastic conditions such as a high pressure of carbon monoxide and an elevated temperature.[2] However, Heck et al. reported the ingenious process of palladium-catalyzed carboalkoxylation and amidation under milder conditions at 100 °C or lower temperatures in an atmospheric pressure of carbon monoxide.[3]

$$ArX + R^1NH_2 + R^2{}_3N \xrightarrow[Pd(OAc)_2\text{–}PPh_3]{CO} ArCONHR^1 + R^2{}_3NH^+X^-$$

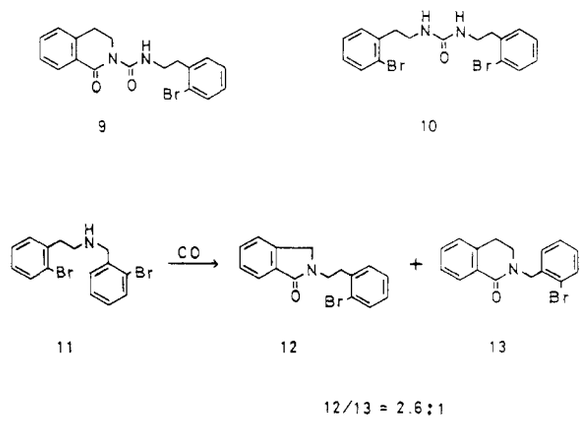
We now report a new and facile synthesis of benzolactams by utilization of this palladium-catalyzed amidation. Existing processes for these benzolactams **8** are lengthy and have serious practical limitations.

In a typical example, N-benzyl-*o*-bromobenzylamine (**5a**, Table I), n-Bu_3N, and a catalytic amount of $Pd(OAc)_2$ and PPh_3 were added to a reaction vessel connected to a balloon filled with carbon monoxide. The whole mixture was heated at 100 °C for 26 h, and a neutral substance was obtained in 63% yield. The melting point and all the spectral data of this compound indicated that the product was the expected N-benzylisoindolin-1-one (**8a**): mp 90–91 °C (lit.[4] mp 90–91 °C); IR ν 1680 cm^{-1}.

Scheme I



Scheme II



12/13 = 2.6:1

In a similar manner, N-benzyl-*o*-bromophenethylamine (**5b**) gave N-benzyl-1,2,3,4-tetrahydroisoquinolin-1-one (**8b**) in 65% yield. To test the suitability of a primary amine as a substrate, *o*-bromophenethylamine (**5c**) was submitted to this reaction to give 1,2,3,4-tetrahydroisoquinolin-1-one (**8c**) in 38% yield along with N-acylisoquinolinone **9** (7%) and the urea derivative **10** (15%) (Scheme II).

Moreover, *o*-bromo-N-(*o*′-bromobenzyl)phenethylamine (**11**) was an interesting substrate since it could cyclize to give a five- or six-membered ring. Thus, compound **11** furnished isoindolinone **12** and isoquinolinone **13** in a 2.6:1 ratio.

Subsequently, the possibility of generation of the seven-membered ring by this method was surveyed. The required precursor for **5d**, N-benzyl-3-(*o*-bromophenyl)propionylamide (**15**, R = CH_2Ph), was prepared by a procedure developed by Umino et al., who exploited a new reducing reagent from $NaBH_4$ and acetic acid (Scheme III).[5] This reagent reduced the amide group to the amine, leaving the bromo group on the aromatic ring intact. Compound **5d**, prepared by reduction of **15**, furnished N-benzyl-2,3,4,5-tetrahydro-1H-2-benzazepin-1-one (**8d**) in 63% yield. Compound **8d** was reduced with $LiAlH_4$ in tetrahydrofuran to give N-benzyl-2,3,4,5-tetrahydro-1H-2-benzazepine (**16**).[6] When the primary amine **5e** was used for the formation of the seven-membered ring, 2,3,4,5-tetrahydro-1H-2-benzazepin-1-one (**8e**)[7] was also obtained in 41% yield.

Scheme III

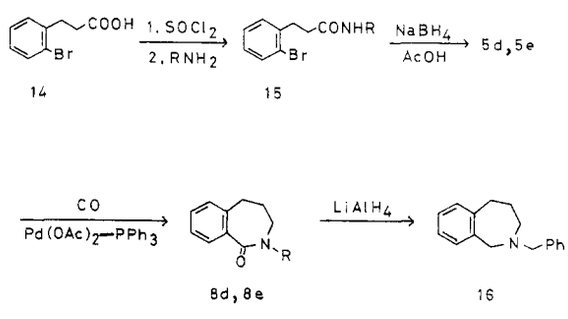


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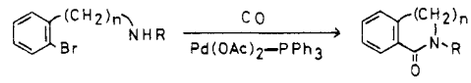
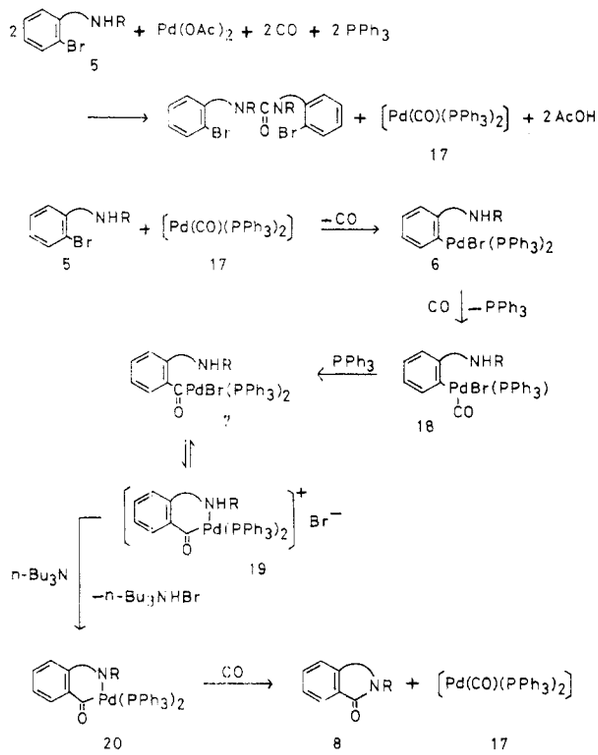
Table I. Reaction of *o*-Bromoaminoalkylbenzene 5 with Carbon Monoxide in the Presence of $Pd(OAc)_2$ and PPh_3



5a–e 8a–e

Run	Starting material	Registry no.	R	*n*	Product	Registry no.	Yield, %
1	**5a**	65185-56-0	CH_2Ph	1	**8a**	13380-32-0	63
2	**b**	65185-57-1	CH_2Ph	2	**b**	6772-61-8	65
3	**c**	65185-58-2	H	2	**c**	1196-38-9	38
4	**d**	65185-59-3	CH_2Ph	3	**d**	65185-61-7	63
5	**e**	65185-60-6	H	3	**e**	6729-50-6	41

Scheme IV



A plausible mechanism is shown in Scheme IV. It is already known that palladium acetate is converted to zerovalent palladium **17** by treating it with a primary or secondary amine and carbon monoxide.[8] The zerovalent palladium complex **17** could be inserted into *o*-bromoaminoalkylbenzene **5** to produce the arylpalladium complex **6** (M = Pd), which should coordinate with carbon monoxide. The migration of the aryl group to carbon monoxide affords the acylpalladium complex **7** (M = Pd), which must be in equilibrium with **19**. Hydrogen bromide is eliminated from **19** with n-Bu_3N to afford **20**, which is converted to the benzolactam **8**) and a zerovalent palladium complex **17** coordinated with carbon monoxide.

The reaction is a useful synthetic method for preparation of benzolactams because the procedure is very facile and the starting material is readily available. Moreover, only a catalytic amount of transition metal of low toxicity is required. The synthesis of natural products has been accomplished by an application of this palladium-catalyzed amidation, which will be published in a forthcoming paper.

Experimental Section

Melting points were measured with a hot stage microscope (Yanaco MP-J2) and with a melting point apparatus (Yamato MP-1) and are uncorrected. Spectra reported herein were measured on a Jasco IRA-2 diffraction grating infrared spectrophotometer, a Hitachi R-20B (NMR, 60 MHz), and a Hitachi RMU-7M double focusing mass spectrometer. The preparation of $Pd(OAc)_2$ was conducted by the method previously described,[9] and all solvents were purified by established procedures.

***N*-Benzyl-*o*-bromobenzylamine (5a).** A mixture of benzylamine (4.665 g, 43.5 mmol) and *o*-bromobenzaldehyde (8.042 g, 43.5 mmol) was stirred at room temperature for 1.5 h. Benzene was added to the reaction mixture, and the supernatant phase was separated and dried over Na_2SO_4. The solvent was removed, and the residue was dissolved in 30 mL of methanol. To this methanolic solution $NaBH_4$ (1.65 g, 43.5 mmol) was added with ice cooling, and the whole mixture was stirred at room temperature overnight. After the MeOH was removed, the residue was extracted with ether. The ether layer was washed with water and dried over Na_2SO_4, and the solvent was evaporated to give a pale yellow oil (10.731 g, 89%) of *N*-benzyl-*o*-bromobenzylamine (**5a**): MS *m/e* 277, 275 (M^+), 276, 274, 186, 184 ($M^+ - CH_2Ph$), 171, 169, 91; IR ν_{max} 3300, 1600, 1570 cm^{-1}; NMR ($CDCl_3$) δ 1.9 (s, 1 H, NH), 3.8 (s, 2 H), 3.9 (s, 2 H), 6.95–7.7 (m, 9 H, aromatic).

***o*-Bromophenethylamine (5c).** *o*-Bromo-β-nitrostyrene was synthesized according to the procedure for the preparation of β-nitrostyrene.[10] A solution of NaOH (908 mg) in 0.9 mL of H_2O was added to a solution of 4 g (21.6 mmol) of *o*-bromobenzaldehyde and 1.32 g (21.6 mmol) of nitromethane in MeOH (5 mL). After 15 min, the white precipitate which had formed was dissolved in water and the aqueous solution was added to excess hydrochloric acid to deposit the crude product, which was recrystallized from ethanol to give pale yellow pillars of *o*-bromo-β-nitrostyrene (2.916 g, 59%): mp 88–91 °C; IR ν_{max} (Nujol) 1630, 1580, 1520, 1340 cm^{-1}.

To a suspension of $LiAlH_4$ (1.06 g, 27.9 mmol) in ether (20 mL) was added 1.591 g (6.98 mmol) of *o*-bromo-β-nitrostyrene in ether (40 mL) with ice cooling. After the solution was stirred at the same temperature, the excess of $LiAlH_4$ was carefully destroyed with wet ether and then with water. The undissolved material was filtered off, and the filtrate was dried and evaporated to give 1.34 g of pale yellow oil. Chromatography on silica gel eluting with benzene–ethyl acetate–methanol (1:2:3) gave 867 mg (62.0%) of *o*-bromophenethylamine (**5c**): MS *m/e* 201, 199 (M^+), 200, 198, 171, 169, 120, 90; IR ν_{max} (film) 3370, 3270, 1565, 1470 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (brd s, 2 H), 2.95 (s, 4 H), 7.0–7.4 (m, 3 H, aromatic), 7.5–7.7 (m, 1 H).

***N*-Benzyl-*o*-bromophenethylamine (5b).** A mixture of *o*-bromophenethylamine (**5c**; 563 mg, 2.82 mmol) and benzaldehyde (300 mg, 2.82 mmol) was stirred at room temperature for 3 h. The Schiff base thus obtained was reduced with $NaBH_4$ (107 mg, 2.82 mmol) in methanol to give *N*-benzyl-*o*-bromophenethylamine (**5b**) as a pale yellow oil (674 mg, 83.0%): MS *m/e* 291, 289 (M^+), 290, 288 ($M^+ - 1$), 185, 183, 171, 169, 120, 91; NMR ($CDCl_3$) δ 1.6 (s, 1 H, NH), 2.85 (s, 4 H), 3.75 (s, 2 H), 6.8–7.6 (9 H, aromatic).

***o*-Bromo-*N*-(*o*′-bromobenzyl)phenethylamine (11).** A mixture of benzaldehyde (550 mg, 2.98 mmol) and *o*-bromophenethylamine (**5c**; 595 mg, 2.98 mmol) was stirred at room temperature for 30 min. The product was reduced with $NaBH_4$ (113 mg, 2.98 mmol) to afford the amine **11** as a pale yellow oil (942 mg, 86.0%): MS *m/e* 290, 288 (M^+), 200, 198, 171, 169, 90; IR ν_{max} (film) 3300, 1590, 1565, 1465, 1440, 1020 cm^{-1}; NMR ($CDCl_3$) δ 1.75 (brd s, 1 H, NH), 2.9 (s, 4 H), 3.87 (s, 2 H), 6.85–7.65 (m, 8 H, aromatic).

3-(*o*-Bromophenyl)propylamine (5e). 3-(*o*-Bromophenyl)propionic acid (**14**; 650 mg, 2.84 mmol)[11] was added to 1.69 g of $SOCl_2$ (14.2 mmol), and the mixture was refluxed for 3 h. The excess $SOCl_2$ was removed under reduced pressure, and the residue was dissolved in anhydrous benzene (3 mL). The benzene solution was added to 5

mL of NH_4OH (25–28%) with ice cooling and stirred for 2 h. The solution was neutralized with 10% hydrochloric acid and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, and the solvent was evaporated. The residual solid was recrystallized from *n*-hexane–ethyl acetate to give colorless plates of 3-(*o*-bromophenyl)propionylamide (**15**, R = H) (630 mg, 97%): mp 97–99 °C; IR ν_{max} (Nujol) 3470, 3330, 1670, 1620 cm^{-1}; NMR ($CDCl_3$) δ 2.3–2.7 (m, 2 H), 2.8–3.3 (m, 2 H), 5.3–6.0 (brd s, 2 H), 7.0–7.7 (4 H, aromatic).

A solution of acetic acid (633 mg, 10.5 mmol) in anhydrous dioxane (2 mL) was added to a solution of 3-(*o*-bromophenyl)propionylamide (**15**, R = H) (481 mg, 2.11 mmol) containing 401 mg (10.55 mmol) of $NaBH_4$ in anhydrous dioxane (5 mL) at 10 °C. After the whole mixture was refluxed for 9 h, dioxane was removed under reduced pressure. The residue was extracted with ether and washed with water. The ether layer was dried over $MgSO_4$, and the solvent was removed. Chromatography on alumina eluting with benzene–ethyl acetate–methanol (1:2:3) gave a colorless oil of 3-(*o*-bromophenyl)propylamine (**5e**; 155 mg, 34%): MS *m/e* 171, 169, 58; IR ν_{max} (film) 3350, 3270, 1565 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (s, 2 H), 1.5–2.1 (m, 1 H), 2.5–3.0 (m, 4 H), 7.0–7.7 (m, 4 H, aromatic).

***N*-Benzyl-3-(*o*-bromophenyl)propylamine (5d).** 3-(*o*-Bromophenyl)propionic acid (**14**; 1.60 g, 7.0 mmol) was dissolved in 2.54 mL (35.0 mmol) of $SOCl_2$ and refluxed for 4 h. After cooling, the excess $SOCl_2$ was removed under reduced pressure and the residue was dissolved in anhydrous benzene (10 mL). When 1.87 g (17.5 mmol) of benzylamine was added to its benzene solution, a white precipitate was deposited. After 2.5 h, water was added to the reaction mixture. The organic layer was separated from the aqueous layer, washed with 10% hydrochloric acid, and dried over $MgSO_4$. The solvent was removed, and the residual solid was recrystallized from ether–petroleum ether to give colorless needles (2.25 g, 99%) of *N*-benzyl-3-(*o*-bromophenyl)propionylamide (**15**, R = CH_2Ph): mp 70–73 °C; IR ν_{max} (Nujol) 3260, 1640, 1540 cm^{-1}; NMR ($CDCl_3$) δ 2.25–2.65 (m, 2 H), 2.7–3.2 (m, 2 H), 4.25 (d, J = 5 Hz, 2 H), 7.0–7.6 (m, 10 H, aromatic and NH).

A solution of acetic acid (1.16 g, 19.3 mmol) in anhydrous dioxane (5 mL) was added to a solution of *N*-benzyl-3-(*o*-bromophenyl)propionylamide (**15**, R = CH_2Ph) (1.227 g, 3.86 mmol) containing 732 mg of $NaBH_4$ (19.3 mmol) in anhydrous dioxane (10 mL) at 10 °C. After the whole mixture was refluxed for 2 h, dioxane was removed under reduced pressure. Water was added to the residue, and the solution was extracted with $CHCl_3$. The organic layer was extracted with 10% hydrochloric acid, and the acidic layer was made strongly basic with 10% NaOH. The basic solution was extracted with ether, and the ether layer was dried over $MgSO_4$. The solvent was removed and the residual oil purified by chromatography on silica gel eluting with *n*-hexane–ether (1:1). The first fraction was a colorless oil of an amine–borane complex (198 mg) of **5d**: IR ν_{max} (film) 2300–2400 cm^{-1}.

The second fraction was a pale yellow oil (743 mg, 63.1%) of *N*-benzyl-3-(*o*-bromophenyl)propylamine (**5d**): MS *m/e* 305, 303 (M^+), 224 ($M^+ - Br$), 198, 196, 171, 169, 120, 107, 91; IR ν_{max} (film) 3300, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.4 (s, 1 H, NH), 1.6–2.1 (m, 2 H), 2.70 (t, 2 H), 2.83 (t, 2 H), 3.80 (s, 2 H, NCH_2Ph), 7.0–7.7 (9 H, aromatic).

The amine–borane complex of **5d** was dissolved in 10% hydrochloric acid and MeOH (1:1; 10 mL), and the solution was refluxed for 2 h. After the MeOH was removed, the acidic layer was made basic with 10% NaOH and the basic solution was extracted with ether. The ether layer was dried over $MgSO_4$, and the solvent was removed to give a pale yellow oil (180 mg, 15.3%) of desired amine **5d.**

General Procedure for the Synthesis of Benzolactam. A mixture of *o*-haloaminoalkylbenzene **5** or **11** (1 equiv), *n*-Bu_3N (1.1 equiv), $Pd(OAc)_2$ (0.02 equiv), and PPh_3 (0.04 equiv) was added to a reaction vessel which was connected to a balloon filled with carbon monoxide and heated at 100 °C for 26 h. After cooling, ether was added to the solution and the ether layer was washed with 10% hydrochloric acid and dried over $MgSO_4$. The solvent was removed, and the residue was purified by chromatography or recrystallization.

***N*-Benzylisoindolin-1-one (8a).** The crude product which was prepared from **5a** (336 mg, 1.22 mmol) by the general procedure was purified by chromatography on silica gel eluting with *n*-hexane–ether (1:2) to give 171 mg (63%) of colorless crystals of **8a**, which was recrystallized from *n*-hexane–ethyl acetate: mp 90–91 °C; MS *m/e* 223 (M^+), 132 ($M^+ - CH_2Ph$), 119, 91; IR ν_{max} (Nujol) 1680, 1620, 1600 cm^{-1}; NMR ($CDCl_3$) δ 4.3 (s, 2 H), 4.84 (s, 2 H), 7.4–7.6 (8 H, aromatic), 7.85–8.1 (m, 1 H, aromatic).

Anal. Calcd for $C_{15}H_{13}NO$: C, 80.63; H, 5.88; N, 6.27. Found: C, 80.69; H, 5.89; N, 6.26.

Starting material **5a** (38 mg, 11%) was recovered from the reaction mixture.

***N*-Benzyl-1,2,3,4-tetrahydroisoquinolin-1-one (8b).** The crude product obtained from **5b** (423 mg, 1.46 mmol) was purified by chromatography on silica gel eluting with benzene–ether (1:1) to give a pale yellow oil (223 mg, 64.7%) of *N*-benzyl-1,2,3,4-tetrahydroisoquinolin-1-one (**8b**): MS *m/e* 237 (M^+), 146 ($M^+ - CH_2Ph$), 133, 118, 91; IR ν_{max} (film) 1640, 1600, 1580 cm^{-1}; NMR ($CDCl_3$) δ 2.8–3.1 (m, 2 H), 3.35–3.7 (s, 2 H, NCH_2Ph), 7.1–7.6 (m, 8 H, aromatic), 8.1–8.35 (m, 1 H, aromatic).

From the acidic extract was recovered 11 mg of the starting material.

1,2,3,4-Tetrahydroisoquinolin-1-one (8c). The crude product obtained from **5c** (408 mg, 2.04 mmol) according to the general procedure was purified by chromatography on silica gel eluting with benzene–ether (1:1) to give three products. The first fraction was a pale yellow oil of 1,2,3,4-tetrahydroisoquinolin-1-one (**8c**; 113 mg, 38%): MS *m/e* 147 (M^+), 118, 90; IR ν_{max} (film) 3250, 1660, 1600, 1580 cm^{-1}; NMR ($CDCl_3$) δ 2.95 (t, 2 H), 3.4–3.75 (m, 2 H), 7.05–8.0 (m, 4 H, aromatic), 7.95–8.15 (m, 1 H, aromatic).

The second fraction was colorless needles (63 mg, 15%) of *N,N'*-di(*o*-bromophenethyl)urea (**10**): mp 159–161 °C (from benzene); MS *m/e* 347, 345 ($M^+ - Br$), 257, 255, 171, 169; IR ν_{max} (Nujol) 3340, 1620, 1580 cm^{-1}; NMR (Me_2SO-d_6) δ 2.75–3.0 (m, 4 H), 3.1–3.35 (m, 4 H), 5.95 (m, 2 H), 7.05–7.75 (m, aromatic).

Anal. Calcd for $C_{17}H_{18}N_2OBr_2$: C, 47.91; H, 4.25; N, 6.57; Br, 37.50. Found: C, 47.92; H, 4.29; N, 6.56; Br, 37.11.

The last fraction was a brown oil of 2-[*N*-(*o'*-bromophenethyl)-carbamoyl]-1,2,3,4-tetrahydroisoquinolin-1-one (**9**; 26 mg, 7%): MS *m/e* 227, 225, 171, 169, 147, 146, 118, 90; IR ν_{max} (film) 3270, 1695, 1650, 1600 cm^{-1}; NMR ($CDCl_3$) δ 2.85–3.3 (m, 4 H), 3.45–3.9 (m, 2 H), 4.05–4.4 (m, 2 H), 7.0–7.8 (m, 7 H, aromatic), 8.05–8.3 (m, 1 H, aromatic), 9.65 (brd s, 1 H, NH).

The acidic extract of the reaction products was neutralized with K_2CO_3 and extracted with ether to give 30 mg (7%) of starting material **5b.**

The Reaction of *o*-Bromo-*N*-(*o'*-bromobenzyl)phenethylamine (11) with Carbon Monoxide. The crude product obtained from the preparation of **11** (428 mg, 1.16 mmol) was purified by chromatography on silica gel eluting with *n*-hexane–ether (1:1). The first fraction furnished colorless prisms (141 mg, 38.5%) of *N*-(*o'*-bromophenethyl)isoindolin-1-one (**12**), which were recrystallized from *n*-hexane–ethyl acetate: mp 105–108 °C; MS *m/e* 317, 315 (M^+), 236 ($M^+ - Br$), 171, 169, 146, 91; IR ν_{max} (Nujol) 1680, 1620, 1470 cm^{-1}; NMR ($CDCl_3$) δ 3.0–3.3 (m, 2 H), 3.75–4.1 (m, 2 H), 4.3 (s, 2 H), 6.9–7.7 (m, 7 H, aromatic), 7.8–8.0 (m, 1 H, aromatic).

Anal. Calcd for $C_{16}H_{14}NOBr$: C, 60.77; H, 4.47; N, 4.43; Br, 25.27. Found: C, 60.79; H, 4.51; N, 4.32; Br, 25.50.

The second fraction afforded colorless prisms (55 mg, 14.6%) of *N*-(*o'*-bromobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-one (**13**), which were recrystallized from *n*-hexane–ethyl acetate: mp 91–93 °C; MS *m/e* 317, 315 (M^+), 236 ($M^+ - Br$), 130, 118, 91, 90; IR ν_{max} (Nujol) 1650, 1600, 1580 cm^{-1}; NMR ($CDCl_3$) δ 2.85–3.2 (m, 2 H), 3.4–3.75 (m, 2 H), 4.95 (s, 2 H, NCH_2Ph), 7.0–7.75 (7 H, m. aromatic), 8.15–8.35 (m, 1 H, aromatic).

Anal. Calcd for $C_{16}H_{14}NOBr$: C, 60.77; H, 4.47; N, 4.43; Br, 25.27. Found: C, 60.88; H, 4.38; N, 4.34; Br, 25.55.

***N*-Benzyl-2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one (8d).** The product obtained from the preparation of **5d** (397 mg, 1.31 mmol) was purified by chromatography on silica gel eluting with *n*-hexane–ether (1:1) to give colorless prisms which were recrystallized from *n*-hexane–ethyl acetate to afford **8d**: mp 82–85 °C; MS *m/e* 251 (M^+), 222, ($M^+ - CH_2Ph$), 147, 131, 91; IR ν_{max} (Nujol) 1630, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.5–2.0 (m, 2 H), 2.73 (t, J = 7 Hz, 2 H), 3.18 (t, J = 7 Hz, 2 H), 4.80 (s, 2 H), 7.0–7.6 (m, 8 H, aromatic), 7.7–7.95 (m, 1 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 29.2, 30.0, 45.4, 50.1, 126.9, 127.5, 128.3, 128.6, 130.8, 136.0, 137.4, 138.1, 171.3.

Anal. Calcd for $C_{17}H_{17}NO$: C, 81.23; H, 6.83; N, 5.57. Found: C, 81.27; H, 6.81; N, 5.70.

***N*-Benzyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine (16).** To a suspension of $LiAlH_4$ (8 mg) in tetrahydrofuran (3 mL) was added 28 mg (0.11 mmol) of **8d** in tetrahydrofuran (2 mL) at room temperature. After the reaction mixture was refluxed for 67 h, excess $LiAlH_4$ was destroyed with a small amount of water. Undissolved material was filtered off and washed with ether. The combined organic layer was dried over $MgSO_4$, and the solvent was removed to give a colorless oil (16 mg, 60.7%) of **16**: MS *m/e* 237 (M^+), 146, 117, 91; IR ν_{max} (film) 1600, 1500 cm^{-1}; NMR ($CDCl_3$) δ 1.55–2.0 (m, 2 H), 2.8–3.3 (m, 4 H), 3.55 (s, 2 H), 3.9 (s, 2 H, NCH_2Ph), 6.9–7.5 (m, 9 H, aromatic); **16** picrate, mp 132 °C (yellow plates from ethanol).[6]

Anal. Calcd for $C_{23}H_{22}N_4O_7$: C, 59.21; H, 4.76; N, 12.01. Found: C, 59.03; H, 4.63; N, 11.89.

2,3,4,5-Tetrahydro-1*H*-2-benzazepin-1-one (8e). The crude product obtained from the preparation of **5e** (143 mg, 0.668 mmol) was purified by preparative chromatography on silica gel eluting with benzene–ethyl acetate (1:2) to give colorless pillars (44 mg, 41%) which were recrystallized from ether–petroleum ether, furnishing **8e:** mp 100–104.5 °C; MS *m/e* 161 (M^+), 132, 131, 104, 77; IR ν_{max} (Nujol) 3250, 1660, 1600, 1460 cm^{-1}; NMR ($CDCl_3$) δ 1.75–2.3 (m, 2 H), 2.90 (t, J = 7 Hz, 2 H), 3.20 (t, J = 7 Hz, 2 H), 7.1–7.5 (m, 5 H, aromatic).

The acidic extract of the reaction mixture was made alkaline with K_2CO_3, and the basic solution was extracted with ether. The ether layer was dried over $MgSO_4$ and concentrated to give 14 mg (10%) of the starting material.

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Registry No.—**9,** 65185-62-8; **10,** 65185-63-9; **11,** 65185-64-0; **12,** 65185-65-1; **13,** 65185-66-2; **14,** 15115-58-9; **15** (R = H), 55223-26-2; **15** (R = CH_2Ph), 65185-67-3; **16,** 54311-89-6; **16** picrate, 54311-90-9; benzylamine, 100-46-9; *o*-bromobenzaldehyde, 6630-33-7; nitromethane, 75-52-5; *o*-bromo-β-nitrostyrene, 65185-68-4; benzaldehyde, 100-52-7; $Pd(OAc)_2$, 33571-36-7.

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Synthesis of Thiols and Polysulfides from Alkyl Halides, Hydrogen Sulfide, Ammonia, and Sulfur

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Alkyl thiols and silyl-substituted alkyl thiols have been synthesized from the corresponding alkyl halides by the action of hydrogen sulfide and ammonia or alkyl amines under autogenous pressures in methanol. Alkyl halides converted to thiols in greater than 90% yield include hexyl, dodecyl, benzyl, trimethoxysilylpropyl, and methyldimethoxysilylpropyl chlorides, and 1,2-dibromoethane. Exceptionally low yields (~1%) of dialkyl sulfides were observed. Cyclohexyl bromide gave chiefly cyclohexene with a low yield of thiol. Dialkyl disulfides and polysulfides were prepared from hexyl and trimethoxysilylpropyl chlorides by the action of hydrogen sulfide, sulfur, and ammonia.

The reaction of alkyl halides and alkali metal hydrogen sulfides to prepare alkyl thiols is well known and industrially important.[1,2] In some cases, this route gives an acceptable yield of thiol, although it always leads to formation of sulfides. Even with excess hydrogen sulfide under pressure the formation of sulfides is not completely suppressed. For example, the amount of sulfides formed from dihalides is usually such that dithiols are best prepared otherwise.[1]

The reaction of alkyl halides with hydrogen sulfide and ammonia was studied as a more economical route to anhydrous preparations of alkyl thiols than the use of relatively expensive anhydrous sodium hydrosulfide. The procedure was easily extended to the preparation of disulfides and mixtures of polysulfides by adding sulfur to the mixture of reagents.

Ammonia and hydrogen sulfide combine to form unstable salts, ammonium hydrosulfide and ammonium sulfide. While these salts have received little attention in recent literature, early reports indicate that ammonium sulfide melts at −18 °C and has a vapor pressure of 760 mm at 0 °C. The more stable ammonium hydrosulfide melts at 118 °C and has a vapor pressure of 80 mm at 0 °C.[3,4] The reaction of ammonium hydrosulfide with dihalides to prepare dithiols was reported in 1947 by Simpson.[5] The yields of dithiols were poor (10–47%) and no better than those obtained with sodium hydrosulfide, so the reaction apparently received no further study.

Dodecyl thiol, $(MeO)_3Si(CH_2)_3SH$ (**1**), and $(MeO)_2MeSi(CH_2)_3SH$ (**2**) were prepared in high yield by heating the corresponding chlorides in an autoclave with a 10–20% molar excess of hydrogen sulfide and ammonia. Normally 15–25% methanol was used as solvent. For example, thiol **1** was obtained in 88.3% isolated yield by heating the corresponding chloride with hydrogen sulfide and ammonia in a molar ratio of 1:1.2:1.2 for 18.5 h at 100 °C. The rate of reaction increased with greater excess ammonia. Thiol **2** was obtained in 90.3% yield after 4 h at 100 °C when the molar ratio of chloride, hydrogen sulfide, and ammonia was 1:1:1.8. With a large excess of ammonia the yield of $[(MeO)_2MeSi(CH_2)_3]_2S$ (**3**) was only 1%.

Very little alkylation of ammonia occurred. Only 1–2% of $(MeO)_2MeSi(CH_2)_3NH_2$ (**4**) was detected in the products. Amine **4** was separated by distillation. Some loss of thiol resulted from oxidation of the thiol by air to disulfide. Oxygen must be excluded as far as possible during the reaction and workup since ammonia and amines catalyze the oxidation of thiols.

Amines and hydrogen sulfide also reacted with alkyl halides to form thiols. Conversion of 1-chlorohexane to the corresponding thiol was 80% after 6 h at 95 °C in a sealed tube with a solution of hydrogen sulfide, triethylamine, and methanol. The yield of thiol was 99% with only 0.9% of sulfide.

1,2-Dibromoethane in a solution of dipropylamine, hydrogen sulfide, and methanol at room temperature and at-

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