were obtained as described previously, *cis*- and *trans*-propenyl methyl ether (**1c** and **1t**) were prepared in the same way as before;[3] cis/trans ~1.5, bp 45–46° (lit.[27] **1c**, 45.0° and **1t**, 48.5°). *cis*- and *trans*-propenyl *tert*-butyl ether (**4c** and **4t**) were prepared by the alcohol exchange from propenyl ethyl ether (a mixture of **2c** and **2t**).[28] The yield of a mixture of **4c** and **4t** (~4:1) was about 20%, bp 101–102° (lit.[29] **4c**, 101°).

cis- and *trans*-β-bromovinyl ethyl ether (**7c** and **7t**) were prepared from paraldehyde and bromine by the method of Jacobs, *et al.*[30] The isomeric composition (cis/trans) was ~3.5, bp 44–52° (20 mm) [lit.[30] 41–44° (19 mm)].

cis- and *trans*-propenyl methyl sulfide (**8c** and **8t**) were obtained by the rearrangement of allyl methyl sulfide,[31] bp 102–103° (lit.[32] 102°).

Geometrical structure of the ethers was assigned by pmr spectra.

Kinetic Measurements. The reaction of unsaturated ethers was carried out in 80% aqueous dioxane and the rates were measured gas chromatographically by the method described previously.[3] The hydrolysis of **8c** and **8t** was carried out in 80% aqueous tetrahydrofuran. In most cases a mixture of cis and trans isomers was subjected to hydrolysis but analyzed separately.

Acknowledgment. The authors thank Mr. Masao Nakada for his partial assistance in experimental work.

Registry No.—**1c**, 4188-68-5; **1t**, 4188-69-6; **2c**, 4696-25-7; **2t**, 4696-26-8; **3c**, 4188-64-1; **3t**, 4188-65-2; **4c**, 4188-71-0; **4t**, 4188-72-1; **5c**, 4884-01-9; **5t**, 1528-20-7; **6c**, 23679-21-2; **6t**, 23679-22-3; **7c**, 23521-49-5; **7t**, 16339-88-1; **8c**, 52195-40-1; **8t**, 42848-06-6.

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Quasi-Favorskii Rearrangement. Synthesis of 1-Phenylcycloalkanecarboxylic Acids[1]

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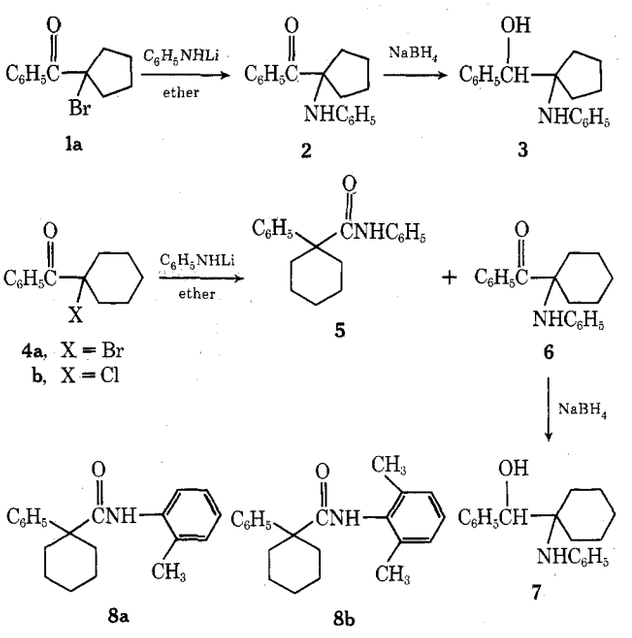
The skeletal rearrangement of α-halo ketones having an α′ hydrogen atom on treatment with certain nucleophiles such as hydroxides, alkoxides, or amines to give carboxylic acid salts, esters, or amides, respectively (Favorskii reaction) is well known and has been extensively investigated.[3,4] α-Halo ketones which do not have an α′ hydrogen atom[5,6] and certain α-halo ketones with α′ hydrogen attached to a bridgehead carbon atom[7,8] also undergo similar rearrangement, although by a different ("semibenzilic") mechanism, and may be called the "quasi-Favorskii reaction." Stevens and Farkas[5] and later Kirmann and Joschek[9] suggested that heterogeneous conditions are required for this rearrangement, as homogeneous conditions resulted in the direct replacement of the α halogen by the nucleophile. We now report a quasi-Favorskii rearrangement of α-halo ketones by the lithium salt of aromatic primary amines under homogeneous conditions. The resulting amides were hydrolyzed to the corresponding carboxylic acids, some of which are very difficultly obtained by other methods.

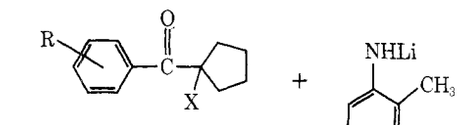
The reaction of α-bromo ketones with lithium anilide was investigated as a general method for the synthesis of α-anilino ketones. Although treatment of 1-benzoyl-1-bromocyclopentane[10] (**1a**) with lithium anilide in ether provided 87% of the amino ketone **2**, 1-benzoyl-1-bromocyclohexane[5a] (**4a**) under the same conditions gave only 30% of the corresponding amino ketone, **6**. The major product (55%) was 1-phenylcyclohexanecarboxanilide[11] (**5**), formed by a quasi-Favorskii rearrangement. When the α-chloro ketone,[5a] **4b**, was used in the place of **4a**, the proportion of the anilide[6] formed was increased to 62% at the expense of the anilino ketone, **6** (21%). This result is in agreement with an earlier observation[5a] in the rearrangement studies under heterogeneous conditions. Amino ketones **2** and **6** were further characterized by their reduction with sodium borohydride to the amino alcohols **3** and **7**, respectively.



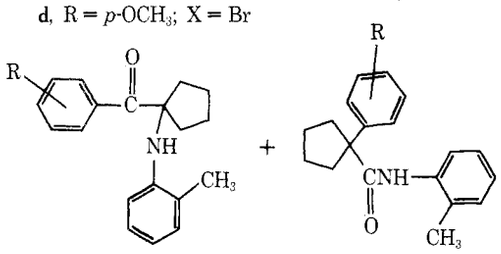
It was observed earlier that in the case of α-chloroisobutyraldehyde, rearrangement was more effective using sodium *tert*-butoxide instead of sodium methoxide under heterogeneous conditions.[9] In order to find out whether this apparent steric influence was operative in homogeneous media as well, lithium anilide was replaced by lithium salts of *o*-toluidine and 2,6-dimethylaniline. The yields of the *o*-toluidide, **8a**, and 2,6-dimethylanilide, **8b**, were 70 and 72%, respectively (the amounts of amino ketones formed in these reactions were too small to be isolated). Also, bromo ketone **1a**, which did not rearrange at all with lithium anilide, gave 59% of the rearrangement product **9a** with lithium *o*-toluidide.

In order to study the effects of substituents on the phenyl group of the halo ketone, lithium *o*-toluidide was treated with halo ketones **1a–e** and the results are summarized in Table I. It may be noted that the increase in the yield of

Table I
Reaction of Lithium *o*-Toluidide with Substituted 1-Benzoyl-1-halocyclopentanes



1a, R = H; X = Br
b, R = H; X = Cl
c, R = *m*-Cl; X = Br
d, R = *p*-OCH_3; X = Br



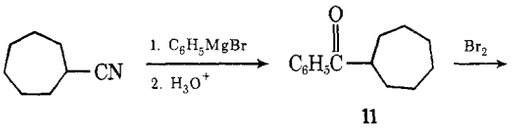
10a, R = H
b, R = *m*-Cl

9a, R = H
b, R = *m*-Cl
c, R = *p*-OCH_3

α-Halo ketone (ref)	Rearranged amide (yield, %)	Amino ketone (yield, %)
1a (10)	**9a** (59)	**10a** (20)
1b (12)	**9a** (68)	**10a** (10)
1c (13)	**9b** (13)	**10b** (50)
1d (13)	**9c** (80)	None

the rearranged product, *p*-methoxyphenyl > phenyl > *m*-chlorophenyl, is qualitatively in agreement with the relative migratory aptitudes of the three groups in pinacol-type rearrangements.[14]

Because of the significant difference in the yields of the rearranged amides from cyclohexyl and cyclopentyl ring systems, it was decided to study the influence of the ring size on the rearrangement. For this purpose, α-bromo ketones with seven- and eight-membered rings were synthesized as follows. Cycloheptyl phenyl ketone[15] (**11**) was prepared in 73% yield by treating phenylmagnesium bromide with cycloheptanecarbonitrile followed by acid hydrolysis. Bromination of **11** with bromine in carbon tetrachloride provided the required 1-benzoyl-1-bromocycloheptane (**12**). Similarly, conversion of cyclooctyl chloride[16] to the Grignard reagent followed by treatment with benzonitrile and hydrolysis gave cyclooctyl phenyl ketone (**13**) which was subsequently brominated to bromo ketone (**14**).



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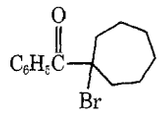

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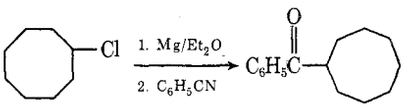

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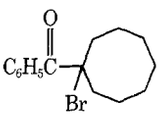

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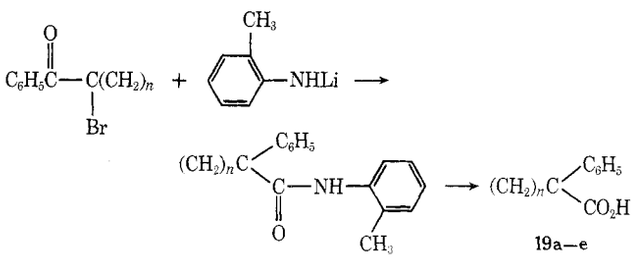
Rearrangements of bromo ketones with five- and six-membered rings have been discussed previously. Treatment of 1-benzoyl-1-bromocyclobutane[17] (**15**) with lithium *o*-toluidide gave only 19% of the rearranged amide, **16**. Several by-products formed in this reaction were not identified. Bromo ketones **12** and **14** yielded 62 and 48% of the *o*-toluidides, **17** and **18**, respectively. The formation of these rearranged amides in good yields from the α-bromo ketones could serve as an attractive synthetic pathway for the preparation of 1-phenylcycloalkanecarboxylic acids, some of which are very difficultly synthesized by alternate methods.[18,19] Because of the extremely hindered position of the amide carbonyl in the molecule, hydrolysis to the carboxylic acid was difficult. However, heating the toluidide with concentrated hydrochloric acid in a sealed tube at a temperature higher than its melting point offered a satisfactory method for the cleavage of the amide linkage in most cases. Results of these experiments are summarized in Table II.

Table II
Conversion of α-Bromo Ketones to Carboxylic Acids



19a–e

n	α-Bromo ketone	*o*-Toluidide (yield, %)	Carboxylic acid (yield, %)	Ref
3	**15**	**16** (19)	**19a** (79)	18
4	**1a**	**9a** (59)	**19b** (73)	18
5	**4a**	**8a** (70)	**19c** (66)	5
6	**12**	**17** (62)	**19d** (85)	19
7	**14**	**18** (48)	**19e** (50)	

The availability of *exo*-2-bromo-*endo*-2-benzoylnorbornane[20] (**20**) made it possible to carry out the rearrangement with lithium anilide on a bromo ketone of known stereochemistry. Only one anilide, *endo*-2-phenylnorbornane-*exo*-2-carboxanilide (**21**), was obtained (67%), as might be expected from a concerted "semibenzilic rearrangement" mechanism.[21] Traces of amino ketone **22** were also formed.

Table III
Physical Properties of α-Amino Ketones and α-Amino Alcohols

Compd	Mp, °C	Molecular formula	Anal., % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
2	147	$C_{18}H_{19}NO$	81.48	7.22	5.28	81.55	7.12	5.48[a]
3 (HCl)	208 dec	$C_{18}H_{22}ClNO$	71.18	7.31	4.61	71.27	7.23	4.46
6	139–140	$C_{19}H_{21}NO$	81.68	7.58	5.05	81.64	7.64	5.04[b]
7 (HCl)	200 dec	$C_{19}H_{24}ClNO$	71.68	7.61	4.41	71.70	7.61	4.45
10a	120–121	$C_{19}H_{21}NO$	81.68	7.58	5.05	81.52	7.75	5.07
10b	99–100	$C_{19}H_{20}ClNO$	72.73	6.42	4.46	72.59	6.18	4.41[c]
22	200–201	$C_{20}H_{21}NO$	82.44	7.26	4.81	82.66	7.52	5.10[d]

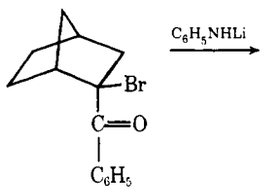
[a] Uv λ_{max} 285 nm (ε 2650), 248 (22,850); ir ($CHCl_3$) 3356 (NH), 1665 cm^{-1} (C=O). [b] Uv λ_{max} 287 nm (ε 2950), 248 (23,500); ir ($CHCl_3$) 3390 (NH), 1670 cm^{-1} (C=O). [c] Calcd: Cl, 11.30. Found: Cl, 11.27. [d] Uv λ_{max} 285 nm (ε 2820), 248.5 (23,300).

Table IV
Physical Properties of the Rearranged Amides

Compd	Mp, °C	Molecular formula	Anal., % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
8a	138	$C_{20}H_{23}NO$	81.87	7.90	4.77	82.08	7.86	4.87
8b	246–247	$C_{21}H_{25}NO$	82.04	8.20	4.56	82.28	8.24	4.57
9a	129–130	$C_{19}H_{21}NO$	81.68	7.58	5.05	81.79	7.55	5.12
9b	129–130	$C_{19}H_{20}ClNO$	72.73	6.42	4.46	72.55	6.39	4.56[a]
9c	111–112	$C_{20}H_{23}NO_2$	77.64	7.49	4.53	77.84	7.47	4.60
16	131–132	$C_{18}H_{19}NO$	81.48	7.22	5.28	81.43	7.17	5.41
17	82–83	$C_{21}H_{25}NO$	82.04	8.20	4.56	82.22	8.44	4.85
18	126–127	$C_{22}H_{27}NO$	82.20	8.47	4.36	82.39	8.67	4.56
21	144–145	$C_{20}H_{21}NO$	82.44	7.26	4.81	82.70	7.07	4.94

[a] Calcd: Cl, 11.30. Found: Cl, 11.22.

The structure of **21** was proved by its hydrolysis to the known *endo*-2-phenylnorbornane-*exo*-2-carboxylic acid[22] (**23**) and conversion of **23** back to **21** by standard procedures.



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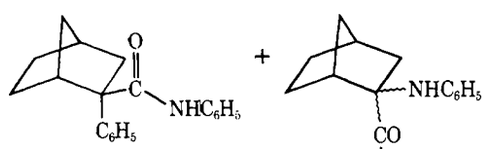
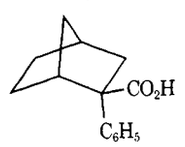


21 **22**



23

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Thin layer chromatography was performed on 5 × 15 cm glass plates coated with silica gel H from Brinkmann Instruments using a hexane–ether (1:1) solvent system for developing unless otherwise mentioned. Compounds were detected by iodine vapor. Gas chromatographic analyses were performed on an F & M Model 810 instrument fitted with a flame ionization detector. A 3 ft × 0.25 in. 3% Carbowax 20M on Chromosorb W column was used. Nmr spectra were obtained in $CDCl_3$ using a Varian A-60 spectrometer with TMS as an internal standard. Infrared spectra were determined on a Perkin-Elmer Model 237B grating spectrophotometer. Ultraviolet spectra were obtained with a Cary Model 14 spectrophotometer in absolute ethanol. Elemental analyses were performed by Midwest Microlabs, Inc., Indianapolis, Ind.

General Procedure for the Reaction of α-Halo Ketones with the Lithium Salt of Aromatic Primary Amines. A solution of 20 mmol of the freshly distilled amine in 30 ml of anhydrous ether was stirred at room temperature under a nitrogen atmosphere and 20 mmol (12.5 ml of a 1.6 *M* solution) of butyllithium in hexane was added drop by drop. This homogeneous solution of the lithium salt of the amine was cooled to room temperature and a solution of 10 mmol of the bromo ketone in 20 ml of anhydrous ether was added dropwise with stirring. In most cases the reaction mixture remained homogeneous and the reaction was complete in 30 min as shown by tlc. The mixture was poured into cold water and extracted with ether. The ether layer was washed with 0.5 *N* HCl to remove the unreacted amine. If the ether solution showed only one product (either amino ketone or amide) by tlc, it was washed with water, dried (Na_2SO_4), and evaporated to dryness to give that single compound. If tlc indicated two products, the ether solution was washed repeatedly with 6 *N* HCl until all the amino ketone was separated from the amide. The ether layer was then washed with water, dried (Na_2SO_4), and evaporated to dryness to obtain the rearranged amide. The 6 *N* HCl solution was diluted with water and neutralized with $NaHCO_3$, the liberated amino ketone was extracted with ether and dried (Na_2SO_4), and the solvent was removed. The products were usually recrystallized from hexane for analysis. The melting points and analytical data of the amino ketones are given in Table III and those of the amides in Table IV.

Reduction of Amino Ketones to Amino Alcohols. A solution of 100 mg of **2** in 10 ml of CH_3OH was stirred with 200 mg of $NaBH_4$ for 12 hr at room temperature. The solvent was removed under reduced pressure, water was added, and the mixture was ex-

tracted with ether. The ether solution was dried (K_2CO_3) and evaporated to dryness and the gummy residue as redissolved in ether and treated with HCl in isopropyl alcohol. The product was recrystallized from ethanol–ether to give 90 mg (78%) of **3** as its HCl salt. Similarly 100 mg of **6** was converted to 110 mg (95%) of **7**, also characterized as its HCl salt. The physical properties of **3** and **7** are included in Table III.

General Procedure for the Hydrolysis of the Rearranged Amide. A mixture of 500 mg of the amide and 20 ml of concentrated HCl was heated in a sealed tube at 130–150° (about 10° above the melting point of the amide) for 24 hr. The reaction mixture was diluted with water and extracted several times with ether. The ether layer was extracted with a saturated solution of $NaHCO_3$. The bicarbonate solution was acidified with HCl, reextracted with ether, dried (Na_2SO_4), and evaporated to dryness. The residue was usually recrystallized from hexane to give the carboxylic acid in good yield. (See Table II.)

Cycloheptyl Phenyl Ketone (11). Freshly distilled bromobenzene (157 g, 1.0 mol) was converted to phenylmagnesium bromide using 24.0 g of magnesium. A solution of 61.5 g (0.5 mol) of cycloheptanecarbonitrile in 250 ml of dry ether was added drop by drop to the Grignard reagent while the mixture was mechanically stirred. After the addition was complete, the mixture was heated under reflux for 36 hr. It was cooled and 125 ml of 4 *N* HCl was carefully added followed by 250 ml of 4 *N* H_2SO_4. The ether was expelled by warming the mixture on a steam bath and the residue was heated under reflux with stirring for 24 hr. The cooled mixture was extracted with ether, washed with water followed by $NaHCO_3$ solution, and dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was fractionated at 0.1 mm. The fraction boiling at 100–110° (86 g) showed 3% impurities by gc. It was refractionated to give 75.2 g (75%) of **11**: bp 97–100° (0.05 mm); $n^{24}D$ 1.5410; 2,4-dinitrophenylhydrazone, mp 168–170° [lit.[15] bp 115–117° (0.2 mm); $n^{25}D$ 1.5405; 2,4-dinitrophenylhydrazone, mp 170–171°].

1-Benzoyl-1-bromocycloheptane (12). A solution of 3.2 g (20 mmol) of bromine in 25 ml of CCl_4 was added dropwise to a magnetically stirred solution of 4.04 g (20 mmol) of **11** in 25 ml of CCl_4. After the addition of bromine, stirring was continued for 2 hr. The solvent was removed *in vacuo* and the residue was evaporatively distilled (bath temperature 75°, 0.0005 mm) to give 5.06 g (90%) of **12**, $n^{24}D$ 1.5718, λ_{max} 251.5 nm (ϵ 7660).

Anal. Calcd for $C_{14}H_{17}BrO$: C, 60.02; H, 6.12; Br, 28.53. Found: C, 60.04; H, 6.06; Br, 28.47.

Cyclooctyl Phenyl Ketone (13). Cyclooctyl chloride[16] (103.5 g, 0.7 mol) was converted to cyclooctylmagnesium chloride in ether using 17.0 g of magnesium. A solution of 51.5 g (0.5 mol) of benzonitrile in 200 ml of ether was added dropwise and the mixture was stirred at room temperature for 3 hr and then heated under reflux for 12 hr. The mixture was cooled and 100 ml of 6 *N* H_2SO_4 was added carefully. The ether was boiled off and the residue was heated on a steam bath with stirring for 8 hr. The cooled mixture was extracted with ether, the ether layer was washed with water followed by $NaHCO_3$ solution and dried (Na_2SO_4), and the solvent was removed. The residue was fractionated at 0.02 mm. The fraction boiling at 112–115° (46.2 g) showed 2% impurities by gc. It was refractionated to give 30.3 g (28%) of **13**, bp 102° (0.01 mm). A sample was evaporatively distilled for analysis, $n^{25}D$ 1.5438.

Anal. Calcd for $C_{15}H_{20}O$: C, 83.29; H, 9.32. Found: C, 83.51; H, 9.38.

A portion of **13** was converted to its semicarbazone, mp 136–137°.

Anal. Calcd for $C_{16}H_{23}N_3O$: C, 70.30; H, 8.48; N, 15.37. Found: C, 70.03; H, 8.76; N, 15.48.

1-Benzoyl-1-bromocyclooctane (14). Ketone **13** (4.32 g, 20 mmol) was brominated as described for the preparation of **12**. The product was evaporatively distilled (bath temperature 110°, 0.01 mm) to give 4.7 g (80%) of **14**, $n^{25}D$ 1.5699.

Anal. Calcd for $C_{15}H_{19}BrO$: C, 61.05; H, 6.49; Br, 27.07. Found: C, 60.76; H, 6.62; Br, 26.66.

1-Phenylcyclooctanecarboxylic Acid (19e). A mixture of 500 mg of **18** and 10 ml of concentrated HCl was heated in a sealed tube at 110° for 12 hr and then at 135–140° for 12 hr. The mixture was diluted with water and extracted with ether. The ether layer was extracted with $NaHCO_3$ solution. From the neutral ether solution was isolated 210 mg (42%) of the starting amide, **18**. The bicarbonate solution was acidified with concentrated HCl, reextracted with ether, and dried (Na_2SO_4) and the solvent was removed. The residue was recrystallized from hexane to give 105 mg (50% based on the hydrolyzed amide) of **19e**, mp 103°.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.39; H, 8.63.

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Registry No.—**1a,** 6740-66-5; **1b,** 52217-42-2; **1c,** 52123-79-2; **1d,** 6728-52-5; **2,** 52123-80-5; **3** HCl, 52123-81-6; **4a,** 7500-66-5; **4b,** 1135-71-3; **6,** 52123-82-7; **7** HCl, 52217-43-3; **8a,** 52123-83-8; **8b,** 52123-84-9; **9a,** 52123-85-0; **9b,** 52123-86-1; **9c,** 52123-87-2; **10a,** 52123-88-3; **10b,** 52123-89-4; **11,** 6004-52-0; **12,** 52217-44-4; **13,** 6004-59-7; **13** semicarbazone, 52123-90-7; **14,** 52123-91-8; **15,** 51175-78-1; **16,** 52123-92-9; **17,** 52123-93-0; **18,** 52123-94-1; **19e,** 52123-95-2; **20,** 34546-66-2; **21,** 52123-99-6; **22,** 52123-96-3; lithium *o*-toluidide, 52217-45-5; bromobenzene, 108-86-1; cycloheptanecarbonitrile, 32730-85-1; cyclooctyl chloride, 1556-08-7; benzonitrile, 100-47-0; lithium anilide, 20732-26-7.

References and Notes

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The Selenium Analogs of Biuret

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Although the sulfur analogs of biuret (**1**), namely 2-thiobiuret (**2**)[1] and 2,4-dithiobiuret (**3**),[2] were prepared in 1886 and 1945, respectively, the only selenium analog of **1** which is known is 2-seleno-4-thiobiuret (**4**),[3] the synthesis of which was reported comparatively recently from this labo-