set to furnish a better fit of the calculated and X-ray data. Molecular superpositioning and distance comparisons were done with the IMAGE (Interactive Modeling And Geometric Exploration) programs developed at McNeil for performing computer graphics comparisons, measurements, and manipulations.

**Acknowledgment.** The authors thank Martin Mutter for MS and NMR spectral data; Roberta Acchione and Dr. Ruth Inners for NMR spectral data; Joan Rogers for IR data; James Kalbron and Dr. Sai Chang for MS data. We also thank Dr. Harold Almond for computations and molecular modeling. Gratitude is also expressed to Samuel Nortey, Joseph Kearns, and Kent Stewart for technical assistance. We are grateful for the use of the 360-MHz NMR facilities at The Pennsylvania State University and The University of Pennsylvania (Middle Atlantic Regional NMR Lab, supported by NIH Grant RR254).

**Registry No.** **1**, 3963-62-0; **3a**, 73691-11-9; **3b**, 73691-12-0; **4a**, 73691-22-2; **4b**, 87519-47-9; **5a**, 87519-48-0; **5b**, 87519-49-1; **6**, 36756-35-1; **8a**, 73691-21-1; **8a**-$d_3$, 87532-01-2; **8b**, 87583-46-8; **9a**, 87519-50-4; **11a**, 87519-51-5; **12**, 582-22-9; **13a**, 87519-52-6; **13b**, 87519-53-7; **14**, 34611-07-9; **15a**, 87519-54-8; **15b**, 87519-55-9; **16**, 87519-56-0; **17**, 73691-13-1; **18a**, 73691-20-0; **18b**, 87519-57-1; **19**, 85336-82-9; **20a**, 87519-58-2; **20b**, 87519-59-3; **21a**, 73691-18-6; **21b**, 87519-60-6; **22**, 87519-61-7; **23a**, 73691-19-7; **23b**, 87532-02-3; **24a**, 87519-62-8; **24b**, 87519-63-9; **25a**, 87519-64-0; **25b**, 87519-65-1; **27a**, 87519-66-2; **27b**, 87519-67-3; **28a**, 87519-68-4; **28b**, 87519-69-5; **29a**, 87519-70-8; **30**, 87519-71-9; **31a**, 87519-72-0; **33a**, 87519-73-1; **33b**, 87519-74-2; **34a**, 86457-11-6; **34b**, 75688-91-4; **35a**, 87519-75-3; **35a** fumarate, 87519-76-4; **35b**, 87519-77-5; **35b** fumarate, 87519-78-6; **36a**, 87519-79-7; **36b**, 87519-80-0; **36b**–saccharin, 87519-81-1; **37a**, 87519-82-2; **37a**·HCl, 87519-83-3; **37b**, 87519-84-4; **37b** fumarate, 87519-85-5; **38a**, 87519-86-6; **38b**, 87519-87-7; **39a**, 87519-88-8; **39a** *p*-toluenesulfoante, 87519-89-9; **39b**, 87519-90-2; **39b**·$HClO_4$, 87519-91-3; **40a**, 87519-92-4; **40a**·HBr, 87519-93-5; **40b**, 87519-94-6; **40b** fumarate, 87519-95-7; **41a**, 87519-96-8; **41b**, 87583-47-9; **41b**–hexamic acid, 87637-35-2; **42a**, 58371-38-3; **42b**, 58371-36-1; **46a**, 87519-98-0; ethyl 1,4-dioxopentyl carbonate, 73691-09-5; 5-methyl-2(3*H*)-furanone, 591-12-8; etyl 2-oxocyclohexanacetate, 24731-17-7; methyl 2-oxocyclohexaneacetate, 13672-64-5; succinic anhydride, 108-30-5; 3-(1-phenyl-2-aminoethyl)indole, 5027-78-1; 1,2-diphenylethylamine, 25611-78-3; thiophene, 110-02-1; 2-amino-1-phenylethanol, 7568-93-6; 2-(thien-2-yl)phenylethylamine, 87519-99-1; 2-(thien-3-yl)phenylethylamine, 87520-00-1; 2-[2-(2,5-dioxopyrrolidin-1-yl)-1-phenylethyl]thiophene, 87520-01-2; 1-[2-(3,4-dimethoxyphenyl)-2-phenylethyl]-2,5-pyrrolidinedione, 87520-02-3; 3-[2-(2,5-dioxopyrrolidin-1-yl)-1-phenylethyl]-1*H*-indole, 87520-03-4; 1-(1,2-diphenylethyl)-2,5-pyrrolidinedione, 87520-04-5; 1-[2-(3,4-dimethoxy)-2-phenylethyl]-5-ethoxy-4,5-dihydro-2(3*H*)-pyrrolone, 73691-14-2; *N*-methylpyrrole, 96-54-8; ω-nitrostyrene, 102-96-5; 1-methyl-2-(2-nitro-1-phenylethyl)-pyrrole, 87520-05-6; 1-methyl-2-(2-amino-1-phenylethyl)pyrrole, 87520-06-7; 1-[2-(1-methylpyrrol-2-yl)-2-phenylethyl]-2,5-pyrrolidinedione, 87520-07-8; 1-[2,2-bis(3,4-dimethoxyphenyl)-ethyl]pyrrolidine-2,5-dione, 87520-08-9; 1-[2,2-bis(3,4-dimethoxyphenyl)ethyl]-5-ethoxy-3,4-dihydro-2(3*H*)-pyrrolone, 73691-15-3.

**Supplementary Material Available:** $^1H$ NMR LIS data for **3a** (Table I), **18a** and **18b** (Table II), **24a** and **24b** (Table III), and **8a** (Table V), $^1H$ and $^{13}C$ NMR chemical shift data for **18a**, **18b**, **24a** and **24b** (Table IV), $^1H$ NMR discussion for **8a**, discussion of relevant acyliminium cyclizations from the literature, Figures 1 and 3, tables of bond distances, bond angles, selected torsional angles, least-squares planes, positional and thermal parameters, and intermolecular contacts, X-ray crystallographic methods and results, discussion of least-squares planes and geometry of **18a** (27 pages). Ordering information is given on any current masthead page.

(45) Parameters used for MM2: N–CO bond, $K_s$ = 8.3, $l$ = 1.325 Å; C($sp^3$)–N–CO angle, $K_b$ = 0.6, angle = 122°; torsion angles H–C($sp^3$)–CO–N, $V_1$ = 0.167, $V_2$ = 0.0, $V_3$ = –0.1; H–C($sp^3$)–N–CO, $V_1 = V_2 = V_3$ = 0.0.

# Dealkylation of a Tertiary Amine Group by an Intramolecular Carbamyl Chloride Functionality[1]

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*Received May 26, 1983*

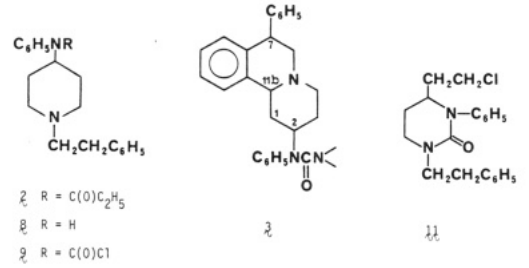
Compounds containing a 4-anilinopiperidine moiety react with phosgene to afford carbamyl chloride hydrochloride derivatives, which rearrange in the presence of nonnucleophilic amine bases. The rearrangement entails intramolecular acylation by the carbamyl chloride group of the free basic nitrogen, followed by cleavage of a carbon–nitrogen bond. Anilines **4a–4c** produce ureas **7a–7c**; so, the bicyclic ammonium ion intermediates fragment regiospecifically (one of three possible paths), presumably to maximize amide resonance in the transition state for C–N bond cleavage. In the rearrangement of **9** the piperidine ring is broken to give **11**, in preference to dealkylation of the 2-phenethyl group. Rates for the rearrangements of **6a–6c** to **7a–7c** were measured (**6c** rearranged fastest). X-ray crystallographic analyses for **7a** and **7b** are reported.

In a extension of our work[2] on benzo[*a*]quinolizidine analogues (**1a–1d**; see Table I) of the potent analgesic fentanyl (**2**), we prepared urea derivatives having general structure **3**. Secondary ureas were readily obtained by condensation of anilines **4** with isocyanates, but tertiary ureas were not produced effectively from **4** and carbamyl chlorides. For instance, aniline **4a** did not even react with $(CH_3)_2NC(O)Cl$ to afford **5a**. As an alternative to tertiary ureas, we treated anilines **4** with phosgene, then added dialkylamines; this route was so successful that it was adopted for making secondary ureas, as well. Interestingly, use of $CF_3CH_2NH_2$ in this phosgene procedure yielded a

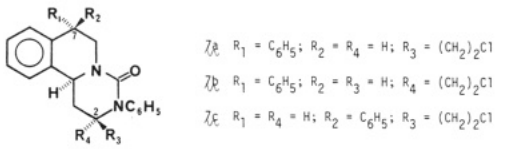
(1) Presented in part at the EUCHEM Conference on Stereochemistry, Bürgenstock, Switzerland, April 28–May 3, 1982, and the 16th Middle Atlantic Regional Meeting of the American Chemical Society, Newark, Delaware, April 24–26, 1982.

(2) Maryanoff, B. E.; McComsey, D. F.; Taylor, R. J., Jr.; Gardocki, J. F. *J. Med. Chem.* **1981**, *24*, 79.

0022-3263/83/1948-5074$01.50/0 



nonbasic, chlorine-containing substance, isomeric with carbamyl chloride **6a**, instead of the expected urea. The unusual compound was identified in our preliminary communication as pyrimidoisoquinoline **7a**, derived from



rearrangement of **6a**.[3] In that communication, we suggested that the facility of the rearrangement ($t_{1/2}$ = 2.3 h at 23 °C) may be attributable to the expected high population of cis-fused conformer in **6a**. To test this point and to extend the scope of this uncommon rearrangement, we have investigated the $COCl_2/CF_3CH_2NH_2$ reaction with two diastereomers of **4a**, anilines **4b** and **4c**, and with 4-anilinopiperidine **8**. We report herein (1) details on the conversion of **4a** to **7a**, (2) analogous reactions of **4b**, **4c**, and **8** that yield **7b**, **7c**, and **11**, respectively, (3) kinetic studies on the rearrangement of **6a–6c** to **7a–7c**, and (4) X-ray crystallographic analyses for **7a** and **7b**.

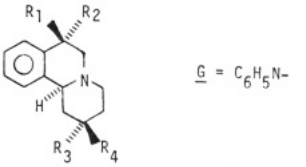
## Results and Discussion

**Rearrangement Reactions.** Aniline **4a** was treated with excess phosgene in dry $CH_2Cl_2$ to furnish intermediate **6a**·HCl, isolated as an off-white solid by evaporation of all volatile material in vacuo. An IR spectrum of this solid supported the structure by virtue of a broad $NH^+$ band centered at 2229 $cm^{-1}$ ($CHCl_3$) or 2430 $cm^{-1}$ (KBr) and a carbonyl absorption at 1727 $cm^{-1}$ ($CHCl_3$; KBr). Additionally, **6a**·HCl was readily transformed by using dimethylamine or methylamine to urea **5a** or **10a**, respectively, the latter of which was also prepared independently from **4a** and $CH_3NCO$. Reaction of **6a**·HCl with excess $CF_3CH_2NH_2$ in $CH_2Cl_2$ in a sealed vessel for 2 days (in an attempt to synthesize a trifluoroethylurea derivative of **3**) afforded **7a** in 61% isolated yield. The **7a** structural assignment, consistent with elemental analysis ($C_{26}H_{25}ClN_2O$), mass spectral ($M^+\cdot$ $m/z$ for $^{35}Cl$ 416), 270-MHz $^1H$ NMR, $^{13}C$ NMR (C=O at $\delta$ 155.3), and IR ($\nu_{max}$ for C=O at 1635 $cm^{-1}$) data, was confirmed by a single-crystal X-ray analysis (vide infra; see Figure 3 in supplementary material).[3]

Repetition of the rearrangement of **6a** to **7a** revealed that the reaction is complete in about 8 h at room temperature. Other amines were examined; pyridine and *N,N*-dimethylaniline were not effective, but triethylamine did work well. Also, when *N*-methylpiperazine (1.2 molequiv) was allowed to react with **6a**·HCl, **7a**, rather than a urea derivative (viz., **3**), was produced in good yield. Thus, release of **6a** from its HCl salt, and rearrangement of **6a** to **7a**, is much faster than nucleophilic attack of the secondary amino group of *N*-methylpiperazine on the carbamyl chloride group.

(3) Maryanoff, B. E.; Molinari, A. J.; Wooden, G. P.; Olofson, R. A. *Tetrahedron Lett.* **1982**, *23*, 2829.

Table I. Chemical Formulas for Benzo[*a*]quinolizidine Derivatives



| compd | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| 1a | H | $C_6H_5$ | $GC(O)C_2H_5$ | H |
| 1b | H | $C_6H_5$ | H | $GC(O)C_2H_5$ |
| 1c | $C_6H_5$ | H | $GC(O)C_2H_5$ | H |
| 1d | $C_6H_5$ | H | H | $GC(O)C_2H_5$ |
| 4a | H | $C_6H_5$ | GH | H |
| 4b | H | $C_6H_5$ | H | GH |
| 4c | $C_6H_5$ | H | GH | H |
| 5a | H | $C_6H_5$ | $GC(O)N(CH_3)_2$ | H |
| 5b | H | $C_6H_5$ | H | $GC(O)N(CH_3)_2$ |
| 5c | $C_6H_5$ | H | $GC(O)N(CH_3)_2$ | H |
| 6a | H | $C_6H_5$ | GC(O)Cl | H |
| 6b | H | $C_6H_5$ | H | GC(O)Cl |
| 6c | $C_6H_5$ | H | GC(O)Cl | H |
| 10a | H | $C_6H_5$ | $GC(O)NHCH_3$ | H |
| 10b | H | $C_6H_5$ | H | $GC(O)NHCH_3$ |

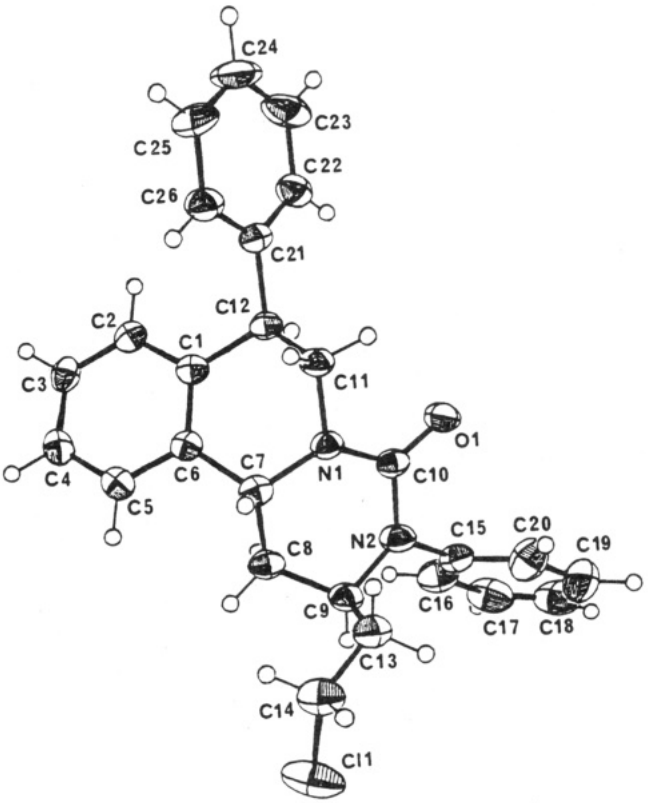



**Figure 1.** An ORTEP representation of the (chloroethyl)tetrahydrodiphenylpyrimidoisoquinolinone **7b**, giving the crystallographic numbering system used. Thermal ellipsoids for nonhydrogen atoms represent 35% probability. The epimer, **7a**, was given the same numbering system.

Diastereomeric aniline **4b** was reacted with $COCl_2$ to afford a solid carbamyl chloride hydrochloride, **6b**·HCl [IR (KBr) $\nu_{max}$ 2456 ($NH^+$), 1732 (CO) $cm^{-1}$]. On treatment with $CF_3CH_2NH_2$, **6b**·HCl rearranged to **7b**, the structure of which was substantiated by spectral data and, especially, X-ray crystallography (vide infra; see Figure 1). The rearrangement of **6b** to **7b** occurred at a slower rate than that observed for **6a** to **7a**; the reaction was complete in about 24 h at room temperature (ca. 3 times slower). Because the transformation of **6b** to **7b** was sluggish, it was possible in this case to isolate the carbamyl chloride free

Table II. Rate Data for Rearrangement of 6a-6c (23 °C)

| time, h[a] | | | mole fraction of 5[b] | | |
|---|---|---|---|---|---|
| 6a | 6b | 6c[c,d] | $X_{5a}$ | $X_{5b}$ | $X_{5c}$ |
| 0 | 0 | 0 | 1.00 | 1.00 | 1.00 |
| 0.25 | 5.0 | 0.17 | 0.89 | 0.88 | 0.83 |
| 0.35 | 7.0 | 0.33 | 0.84 | 0.77 | 0.74 |
| 0.50 | 9.0 | 0.67 | 0.82 | 0.64 | 0.53 |
| 0.85 | 10.0 | 0.83 | 0.70 | 0.52 | 0.46 |
| 1.35 | 11.0 | 1.00 | 0.62 | 0.48 | 0.40 |
| 2.00 | 12.0 | 1.17 | 0.54 | 0.42 | 0.29 |
| 3.00 | 14.0 | 1.42 | 0.43 | 0.34 | 0.22 |
| 3.50 | 17.0 | 1.67 | 0.32 | 0.27 | 0.17 |
| 5.00 | 20.0 | 2.00 | 0.17 | 0.20 | 0.11 |
| | 22.0 | 2.50 | | 0.18 | 0.06 |
| | 24.0 | 3.00 | | 0.16 | 0.02 |
| | 28.0 | | | 0.12 | |

[a] $t_{1/2}$ values for 6a, 6b, and 6c are 2.3, 10.8, and 0.8 h, respectively. [b] $X_5 = [5]_t/[5]_0$. The mole fraction of 7 corresponded to that expected for $X_5 + X_7 = 1$, so values for $X_7$ are not displayed. [c] Rearrangement of 6c was also measured at 3 °C; the $t_{1/2}$ was ca. 5 h. [d] A plot of log $X_{5c}$ vs. $t$ was linear for the first two half-lives.

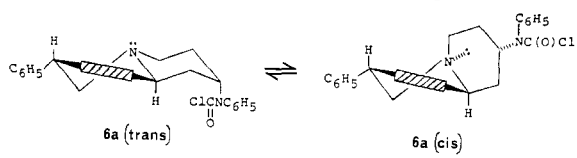
base, **6b**. An IR spectrum of **6b** (KBr) exhibited Bohlmann bands at 2817 and 2756 $cm^{-1}$, indicative of a trans-fused benzo[*a*]quinolizidine structure,[2] and a carbonyl absorption at 1745 $cm^{-1}$. The $^1H$ NMR spectrum of **6b** was consistent with the structure assigned by comparison of the spectrum with that for analogue **1b**.[2]

Aniline **4c** also underwent rearrangement on treatment with $COCl_2$, then $CF_3CH_2NH_2$, to give **7c**. The oily product, **7c**, was characterized by high-field $^1H$ and $^{13}C$ NMR, IR, and MS data.

The rearrangement reaction was also extended to piperidine **8**, underlining its inherent generality. Cyclic urea **11** ($^1H$ and $^{13}C$ NMR; MS) was the sole product from treatment of **8** with $COCl_2$ followed by $CF_3CH_2NH_2$. There was no evidence for cleavage of the phenethyl group, which is consistent with an intramolecular reaction.

**Kinetic Measurements.** Kinetic studies on the rearrangement of **6a–6c** were conducted. In these experiments, we were able to monitor with time both the disappearance of carbamyl chloride (**6**) and the appearance of pyrimidoisoquinoline (**7**). The reactions were quenched with dimethylamine, which reacted immediately with carbamyl chloride (**6**) to yield dimethylurea (**5**). The ureas (**5a–5c**) and the rearrangement products (**7a–7c**) could not be quantitated effectively by GLC because of thermal instability nor by $^1H$ NMR because of spectral complexity; thus we developed a TLC assay[4] involving densitometry on TLC spots visualized by UV fluorescence (270 nm). Reference plates for the **5a**/**7a** system established the concentration range for linear response.

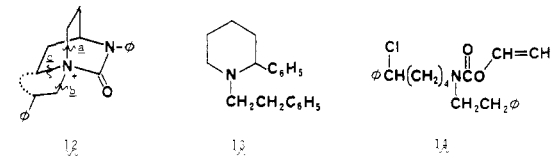
Rearrangement experiments were performed on hydrochloride salts of **6a–6c** in $CH_2Cl_2$ with excess $CF_3CH_2NH_2$ under identical conditions at 23 °C. Aliquots of known




volume, representing a known portion of the original reaction mixture, were quenched and analyzed within the concentration range for linear response, considering the presence of as much as 100% of either **5** or **7**. Data for kinetic runs on **6a–6c** are presented in Table II. Such data were plotted and curves for the amount of **5** (representing starting material **6**) and **7** vs. time were estimated. The half-life ($t_{1/2}$) for each reaction was taken as the point of intersection of the curves for **5** and **7**, at 50:50. Given the errors inherent to the sampling and TLC densitometric measurements (ca. ±5%) the data are not rigorous enough to derive kinetic expressions and accurate rate constants (k). Nevertheless, reasonable values for the reaction half-life ($t_{1/2}$) are obtainable, providing a good estimate of comparative reaction rates. The $t_{1/2}$ values for **6a**, **6b**, and **6c** are 2.3 h, 10.8 h, and 0.8 h, respectively. Thus, **6c** rearranges 3 times faster than **6a** and 14 times faster than **6b**.

**Rearrangement Mechanism.** The rearrangement of **6a–6c** and **9** hydrochlorides proceeds on release of the free bases, **6a–6c** and **9**, by an amine that is nonnucleophilic such that it does not react readily with the carbamyl chloride group. 2,2,2-Trifluoroethylamine was employed in our work because the first rearrangement (of **6a**)[3] was discovered under such conditions (not for any other special reasons).

For rearrangement to occur, a bicyclic ammonium intermediate,[5] in which the carbamyl chloride group has internally acylated the amino group, must be generated (viz., **12**). Such an acylammonium salt,[5] presumably in



equilibrium with starting carbamyl chloride, is irreversibly converted to rearrangement product by chloride-ion-induced dealkylation. The overall process for rearrangement of **6a** is illustrated in our preliminary communication.[3]

Intermediate ion **12** reacts specifically (≥98%) by cleavage mode *a*, rather than by modes *b* or *c*, as judged by failure to detect any isomeric compounds. One may suppose that benzylic fragmentation, pathway *c*, is intrinsically more favorable, since that is the preferred pathway for dealkylation of tertiary amines with acyl halide reagents, intermolecularly. Indeed, we checked this point by reacting model piperidine **13** with vinyl chloroformate,[6a] whereby only benzyl chloride **14** was formed. Thus, the regiospecificity of the rearrangement is reflective of its intramolecular nature, which imposes rigorous stereoelectronic limitations associated with maximization of amide resonance in the transition state for bond cleavage. That is to say, cleavage modes *b* or *c* in **12** are improbable because they would lead to severely strained bicyclic ureas (see scheme in ref 3).

In the rearrangement of **9**, only two dealkylation routes are available. One involves ring breakage analogous to mode *a*, and the other involves loss of the 2-phenethyl group analogous to mode *b*. Only the former pathway leading to **11** was observed.

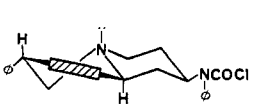
In the case of **6a**, the obligatory bicyclic ammonium intermediate can be generated directly from cis-fused quinolizidine *cis*-**6a**, but not from trans-fused conformer *trans*-**6a** (or the other, highly unfavored cis-fused con-

(4) We are very grateful to William R. Sisco and Thomas DiFeo for development of the TLC densitometric assay and for analysis of many of the samples from our kinetic reactions.

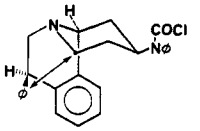
(5) *N*-Acylammonium salts have been isolated and studied: Paukstelix, J. F.; Kim, M. *J. Org. Chem.* **1974**, *39*, 1503. Also, see: Fodor, G.; Abidi, S.; Carpenter, T. C. *Ibid.* **1974**, *39*, 1507 for *N*-cyanoammonium salts.

(6) (a) Olofson, R. A.; Schnur, R. C.; Bunes, L.; Pepe, J. P. *Tetrahedron Lett.* **1977**, 1567. (b) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. "Conformational Analysis"; Wiley: New York, 1967; pp 28–31, 241–246.

former not shown).[2] The conformational equilibrium for **6a** is expected to be strongly biased (90–95%) to *cis*-**6a**, based on work with congeneric propionyl compounds.[2] Although it was originally suggested that the facility of the rearrangement may be a consequence of the high population of conformer *cis*-**6a**,[3] this violates the Curtin–Hamett principle.[6b] Indeed, diastereomer **6b**, with a strongly biasing equatorial anilido group (viz., **15**),[2] underwent the



**15**



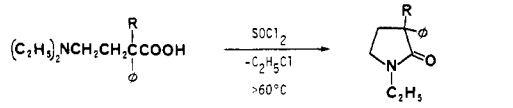
**16**

rearrangement about 5 times more slowly than **6a**; however, diastereomer **6c**, which should populate a cis conformation (viz., **16**) about 40%,[2] rearranged the fastest instead of being intermediate in rate.

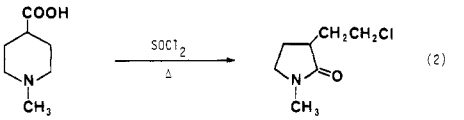
That **6c** rearranges most rapidly of the three diastereomers may be due to higher conformational (or steric) strain in **6c** relative to **6a**. For **6c**, there is adverse 1,3 diaxial interaction in the tetrahydroisoquinoline ring of conformer **16**,[2] which is relieved on rearrangement to **7c**. Carbamyl chloride **6b** would have the least conformational strain, so it rearranges most slowly.

**Reaction of Tertiary Amines with Acyl Halide Reagents.** The cleavage of tertiary amines with acyl halide reagents, such as phosgene, chloroformates, and cyanogen bromide, has been known for at least 80 years.[7,8] As far as we are aware, carbamyl chlorides have not been used in this reaction, possibly because of diminished reactivity. Our carbamyl-chloride-induced amine dealkylation probably occurs with facility because of its intramolecularity and because the *N*-phenyl group decreases the electron donation from the nitrogen into the carbonyl group.

Intramolecular dealkylations of tertiary amines by acyl halide groups have been reported in the chemical literature, albeit very infrequently.[8] Gardner et al.[8a] and Clarke et al.[8b] observed the formation of pyrrolidin-2-ones from 4-(tertiary)aminobutanoic acid chlorides on heating (e.g., eq 1). Clarke and co-workers[8b] also found that 4-

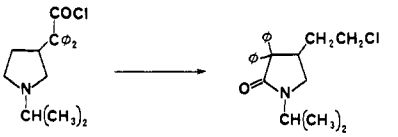


(1)



(2)

carboxy-*N*-methylpiperidines, on treatment with $SOCl_2$ followed by heating, afford rearrangement products containing chlorine, instead of bicyclic amides via loss of $CH_3Cl$ (e.g., eq 2). Lunsford, et al., reported analogous rearrangements of pyrrolidin-3-ylacetic acid chlorides to chloroethylpyrrolidin-2-ones, which are regiospecific (e.g., eq 3).[8c] The alleged bicyclic *N*-acylammonium intermediate in the Lunsford work[8c] could fragment in three different ways, similar to our benzo[*a*]quinolizidine rearrangements, but only one route is pursued. (2-Chloroethyl)pyrrolidin-2-one is generated as opposed to a bicyclic amide, by loss of RCl, or a (chloromethyl)piperidin-2-one.[8d] Dealkylation of tertiary amine groups by an intramolecular acyl halide group is a reaction that should be more widely recognized. The process can occur with great facility and high regioselectivity can be anticipated.



(3)

**X-ray Crystallography.** A single-crystal X-ray structure analysis was performed on the original rearrangement product, **7a**, to establish its structure for our preliminary communication.[3] Details on this X-ray work are furnished in the microfilm supplement.[9] Herein, we describe the X-ray analysis of **7b**. An ORTEP representation of urea **7b** giving the crystallographic numbering system (space group $P\bar{1}$, $Z = 2$, $R = 0.07$) is depicted in Figure 1 and a stereoscopic view of the triclinic unit cell is shown in Figure 2.[9]

In the crystal structure of **7b**, the three benzene rings are flat with normal bond distances and angles. While C12 is in the same plane as its phenyl substituent, N2 is 0.05 Å out of the plane of its attached phenyl, and similar minor distortions (0.11 and 0.04 Å) are found for the carbons (7 and 12, respectively) connecting the benzo unit to the middle ring. Although the four atoms of the urea function are in the same plane, the attached carbons are not (deviations from 0.07 to 0.27 Å), thus, reducing somewhat the optimum overlap for this $\pi$-system (both C10–N distances are ca. 1.38 Å). Moreover, the dihedral angle between the urea plane and the *N*-phenyl plane is 63° so there is no effective overlap between the two $\pi$ systems. The phenyl moiety attached to C12 is in a pseudoequatorial position and for evident steric reasons makes a dihedral angle of 67° with the benzo ring. The urea-containing ring looks like a skew boat with the chloroethyl group between equatorial and axial and with the electron-rich chlorine turned away from the $\pi$ cloud of the *N*-phenyl substituent.

Because of the thinness of the best available crystal (plates from 1,2-dimethoxyethane–hexane) and the presence of two independent molecules (designated A and B) in the unit cell ($P2_1/c$, $Z = 8$), the X-ray structure of epimeric urea **7a** could only be refined to $R = 0.12$. Still, this was sufficient to guarantee the stereochemistry of **7a** and provide useful conformational details. Molecules A and B are distinguished only by very minor conformational differences and are compared to urea **7b** in Figure 3.[9]

Details of the X-ray work for **7a** and **7b** are supplied in the Experimental Section; tables of bond distances and angles, selected torsional angles, least-squares planes, and positional and thermal parameters for the non-hydrogen atoms are available in the microfilm supplement.[9]

## Experimental Section

**General Information and Procedures.** Proton NMR spectra were recorded on a Perkin-Elmer R-32 (90 MHz), Varian EM-360 (60 MHz), Bruker HX-270 (270 MHz; performed at Florida State University), or Bruker WM-360 (360 MHz) spectrometer with $CDCl_3$ as solvent and $(CH_3)_4Si$ as an internal standard, unless

(7) (a) Hageman, H. A. *Org. React. (N.Y.)* **1953**, *7*, 198. (b) Moller, F. *Methoden Org. Chem. (Houben-Weyl) 4th Ed.* **1957**, *XI/1*, 982–988. (c) Kim, J. C. *Org. Prep. Proced. Int.* **1977**, *9*, 1. (d) Rice, K. C. *J. Org. Chem.* **1975**, *40*, 1850. (e) Hobson, J. D.; McCluskey, J. G. *J. Chem. Soc. C* **1967**, 2015. (f) Abdel-Monem, M. M., Portoghese, P. S. *J. Med. Chem.* **1972**, *15*, 208. (g) References cited in footnotes 6a and 7a–f.

(8) (a) Gardner, J. H.; Easton, N. R.; Stevens, J. R. *J. Am. Chem. Soc.* **1948**, *70*, 2906. (b) Clarke, R. L.; Mooradian, A.; Lucas, P.; Slanson, T. J. *Ibid.* **1949**, *71*, 2821. (c) Lunsford, C. D.; Cale, A. D., Jr.; Ward, J. W.; Franko, B. V.; Jenkins, H. *J. Med. Chem* **1964**, *7*, 302. (d) Lunsford's group also described, in a patent, a carbamyl-chloride-induced amine dealkylation analogous to the rearrangement in eq 3 and to our benzo[*a*]quinolizidine rearrangements: Lunsford, C. D.; Cale, A. D., Jr. U.S. Patent 3 337 580, 1967.

(9) See the paragraph at the end of this paper regarding the microfilm supplement.

Table VI. $^{13}C$ NMR Data for 7a-7c[a]

| 7a (50.3 MHz) | | 7b (90.6 MHz) | | 7c (15.1 MHz) | |
|---|---|---|---|---|---|
| peak[b] | assignment[c] | peak[b] | assignment[c] | peak[b] | assignment[c] |
| 37.17 (2t)[d] | $C_\alpha$, $C_1$ | 34.5 (t) | $C_\alpha$[e] | 37.2 (2t)[d] | $C_\alpha$, $C_1$ |
| 40.7 (t) | $C_\beta$ | 35.8 (t) | $C_1$[e] | 40.4 (t) | $C_\beta$ |
| 45.5 (d) | $C_7$ | 41.6 (t) | $C_\beta$ | 44.4 (d) | $C_7$ |
| 47.3 (t) | $C_6$[f] | 45.2 (d) | $C_7$ | 45.8 (t) | $C_6$ |
| 53.58 (d) | $C_2$[g] | 48.1 (t) | $C_6$[f] | 53.3 (d) | $C_2$ |
| 53.90 (d) | $C_{11b}$[g] | 52.2 (d) | $C_{11b}$[e] | 53.9 (d) | $C_{11}$[b] |
| 125.0 (d) | $C_{11}$[f] | 54.8 (d) | $C_2$ | 125.7 (d) | *h* |
| 126.63 (d) | *h* | 124.6 (d) | $C_{11}$[f] | 126.4 (d) | *h* |
| 126.72 (d) | *h* | 126.10 (d) | *h* | 126.6 (d) | *h* |
| 126.94 (d) | *h* | 126.62 (d) | *h* | 127.2 (d) | *h* |
| 127.02 (d) | *h* | 126.72 (d) | *h* | 128.2 (d) | *i* |
| 128.66 (d) | *o*-C[i] | 126.93 (d) | *h* | 128.3 (d) | *i* |
| 128.70 (d) | *o*-C[i] | 127.1 (d) | *o*-C[i] | 128.5 (d) | *i* |
| 129.10 (d)[d] | *o,m*-C[i] | 128.63 (d) | *o*-C[i] | 130.5 (d) | $C_8$ |
| 129.44 (d) | $C_8$[f] | 128.95 (d) | *m*-C[i] | 136.3 (s) | $C_{7a}$[j] |
| 136.6 (s) | $C_{11a}$ | 129.05 (d) | *m*-C[i] | 136.8 (s) | $C_{11a}$[j] |
| 139.2 (s) | $C_{7a}$ | 129.7 (d) | $C_8$[f] | 140.9 (s) | 3-Ph $C_1$ |
| 141.0 (s) | 3-Ph $C_1$[k] | 137.1 (s) | $C_{11a}$ | 143.1 (s) | 9-Ph $C_1$ |
| 141.8 (s) | 7-Ph $C_1$[l] | 139.2 (s) | $C_{7a}$ | 155.9 (s) | $C_4$ |
| 155.3 (s) | $C_4$[m] | 142.0 (s) | 7-Ph $C_1$[l] | | |
| | | 143.2 (s) | 3-Ph $C_1$[k] | | |
| | | 153.7 (s) | $C_4$[m] | | |

[a] Proton-decoupled and off-resonance-decoupled spectra were recorded on samples in $CDCl_3$ at the frequencies shown. Chemical shifts are given in ppm downfield from $Me_4Si$. [b] Chemical shifts are taken from proton-decoupled spectra. Multiplicities from off-resonance spectra are provided in parentheses. [c] Assignments were made using chemical shift criteria (see Breitmaier, E.; Haas, G.; Voelter, W. "Atlas of C-13 NMR Data"; Heyden: London, 1979; Shamma, M.; Hindenlang, D. M. "Carbon-13 NMR Shift Assignments of Amines and Alkaloids"; Plenum: New York, 1979), multiplicities, and $^2J_{CH}$ splitting patterns in high-field, off-resonance spectra (so noted when employed). [d] Two isochronous resonances. [e] Axial $C_\alpha$ experiences a $\gamma$ shielding effect, as expected (see, e.g., Levy, G. C.; Nelson, G. L. "Carbon-13 NMR for Organic Chemists"; Wiley-Interscience: New York, 1972; pp 38-44). The axial group also induces a $\gamma$ shielding of $C_{11b}$ and $\beta$ shielding of $C_1$ (Levy and Nelson). [f] $^2J_{CH}$ doublet. [g] The upfield peak was assigned to $C_2$, rather than $C_{11b}$, because of its greater width and multiplicity from $^2J_{CH}$. [h] $C_9$, $C_{10}$, 3-Ph $C_4$, or 7-Ph $C_4$. [i] From 3-Ph or 7-Ph. [j] Assignments may be reversed. [k] $^2J_{CH}$ triplet. [l] $^2J_{CH}$ quartet. [m] Remained sharp singlet in off-resonance spectra.

otherwise indicated. NMR abbreviations used are as follows: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet, br = broad. Carbon-13 NMR spectra were recorded on a JEOL FX60Q (15.1 MHz), Bruker WM-360 (90.6 MHz), or Bruker WP-200 (50.3 MHz) spectrometer in $CDCl_3$ with $(CH_3)_4Si$ as an internal reference. Both proton noise-decoupled and off-resonance-decoupled $^{13}C$ spectra were determined. IR spectra were obtained on a Perkin-Elmer 283 or 727B spectrophotometer in KBr (pellets), unless otherwise noted. Mass spectra were obtained on a VG Micro Mass 7035, Finnigan GC-MS-DS Model 9500-3300-1600, or AEI MS-902 instrument. TLC separations were conducted on silica gel plates with visualization by UV fluorescence and $I_2$ staining. Melting points are uncorrected, unless noted otherwise. Chemical microanalyses were performed by Atlantic Microlab, Inc., Atlanta, GA.

**2α-(2-Chloroethyl)-1,6,7,11bβ-tetrahydro-3,7β-diphenyl-2*H*-pyrimido[6,1-*a*]isoquinolin-4(3*H*)-one (7a).** Free base **4a** was obtained from 5.10 g (9.56 mmol) of its hexamate salt[2] by partitioning the salt between $CH_2Cl_2$ and a solution of 1 N NaOH. The $CH_2Cl_2$ extract was rinsed twice with water and dried ($K_2CO_3$). Excess phosgene was added at −20 °C with stirring. After 1 h, the reaction mixture was heated in a water bath to remove excess $COCl_2$, then the solvent was removed in vacuo. The flaky, off-white solid (**6a**·HCl) was dissolved in fresh, dry $CH_2Cl_2$ and treated with a solution of $CF_3CH_2NH_2$ in $CH_2Cl_2$. [$CF_3CH_2NH_2$·HCl (30.0 g) was partitioned between cold $CH_2Cl_2$ and cold 50% NaOH and the cold $CH_2Cl_2$ extract was dried ($K_2CO_3$) at 5 °C.] The reaction was allowed to stir at 23 °C for 2 days. It was filtered and the filtrate was rinsed with 0.1 N HCl, dried ($Na_2SO_4$), and evaporated to afford 4.15 g of dark solid. The solid was recrystallized twice from ethyl acetate–hexane. A solution of the material in 400 mL of warm, dry ether was concentrated to 200 mL and treated with about 10 mL of hexane. Cooling to −78 °C gave a solid, which was recrystallized from ether with slow cooling to give 2.42 g (61%) of off-white, TLC homogeneous crystals: mp 165–167 °C; MS (EI) 418 ($M^{+\cdot}$, $^{37}Cl$), 416 ($M^{+\cdot}$, $^{35}Cl$), 381 (M − Cl), 353 (M − Cl, CO), 351, 339, 225; MS (CI, $CH_4$), *m/z* (relative abundance) 459 (M + 41 adduct, $^{37}Cl$; 3%), 457 (M + 41 adduct, $^{35}Cl$; 6%), 447 (M + 29 adduct, $^{37}Cl$; 12%), 445 (M + 29 adduct, $^{35}Cl$; 17%), 420 (M + H + 1, $^{37}Cl$; 12%), 419 (M + H, $^{37}Cl$; 38%), 418 (M + H + 1, $^{35}Cl$; 31%), 417 (M + H, $^{35}Cl$; 100%), 416 (10%), 371 (M − $CH_2Cl$; 13%), 353 (M − $CH_2CH_2Cl$; 8%); IR (KBr) $\nu_{max}$ (CO) 1635 $cm^{-1}$; 270-MHz $^1H$ NMR Table III;[9] 50.3-MHz $^{13}C$ NMR Table VI. Anal. Calcd for $C_{26}H_{25}ClN_2O$: C, 74.90; H, 6.04; Cl, 8.50; N, 6.72. Found: C, 75.15; H, 6.04; Cl, 8.50; N, 6.72.

**2-(2-Chloroethyl)-1,6,7,11b-tetrahydro-3,7α-diphenyl-2*H*-pyrimido[6,1-*a*]isoquinolin-4(3*H*)-one (7b).** This compound was prepared from aniline **4b**[2] in a manner similar to that used for **7a**. The yield from 600 mg of **4b** was 400 mg (57%) of solid, TLC homogenous **7b**. Two recrystallizations from $CH_2Cl_2$, containing a small amount of hexane, furnished 300 mg of white, solid **7b**: mp 181–183 °C; MS (CI, $CH_4$), *m/z* (relative abundance) 459 (M + 41 adduct, $^{37}Cl$; 3%), 457 (M + 41 adduct, $^{35}Cl$; 6%), 447 (M + 29 adduct, $^{37}Cl$; 8%), 445 (M + 29 adduct, $^{35}Cl$; 17%), 420 (M + H + 1, $^{37}Cl$; 12%), 419 (M + H, $^{37}Cl$; 38%), 418 (M + H + 1, $^{35}Cl$; 31%), 417 (M + H, $^{35}Cl$; 100%), 416 (10%), 371 (M − $CH_2Cl$; 13%), 353 (M − $CH_2CH_2Cl$; 8%); IR (KBr) $\nu_{max}$ (CO) 1647 $cm^{-1}$; 360-MHz $^1H$ NMR Table IV;[9] 90.6-MHz $^{13}C$ NMR Table VI. Anal. Calcd for $C_{26}H_{25}ClN_2O$: C, 74.90; H, 6.04; Cl, 8.50; N, 6.72. Found: C, 74.87; H, 6.05; Cl, 8.50; N, 6.71.

The intermediate, off-white, carbamyl chloride hydrochloride powder (**6b**·HCl)[10] was converted to a free base by partitioning the salt between cold $CH_2Cl_2$ and cold 1 N NaOH. The $CH_2Cl_2$ solution was dried at 5 °C ($Na_2SO_4$) and evaporated in vacuo without heating to give an oil, **6b**: IR ($CHCl_3$) $\nu_{max}$ 3160, 3138, 2970, 2950, 2925, 2895, 2820 (Bohlmann band),[2] 2755 (Bohlmann band),[2] 1743 (NCOCl), 1640, 1595, 1493, 1453, 1400, 1360, 1280, 1238, 1228, 1110, 856/852, 810, 701 $cm^{-1}$.

**2α-(2-Chloroethyl)-1,6,7,11bβ-tetrahydro-3,7α-diphenyl-2*H*-pyrimido[6,1-*a*]isoquinolin-4(3*H*)-one (7c).** Phosgene was

(10) IR (KBr) $\nu_{max}$ 2450 ($NH^+$), 1728 (CO), 1597, 1493, 1453, 1280, 1226, 747, 715, 698 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.7–2.3 (m, 3), 2.6–3.6 (m, 7), 4.2–4.6 (m, 2, $H_2$ and $H_7$), 5.05 (br s, 1, $H_{11b}$), 6.8–7.7 (m, 15, aromatic and $NH^+$).

bubbled into a dry methylene chloride (20 mL) solution containing aniline **4c**[2] (1.00 g, 2.82 mmol) for 10 min under nitrogen at ambient temperature. After 2 h, the solution was evaporated in vacuo to give solid carbamyl chloride (**6c**·HCl). The carbamyl chloride (0.50 g, 1.1 mmol) in dry methylene chloride (10.0 mL) was stirred as excess $CF_3CH_2NH_2$ (see preparation of **7a**) in methylene chloride (30.0 mL) was added. The solution was stirred (stoppered) at 23 °C and aliquots (0.25 mL) were occasionally removed and quenched in an ethereal solution of dimethylamine (0.25 mL). The samples were evaporated under a stream of nitrogen. After the reaction stirred for 16 h, the solution was washed once with water, once with dilute NaOH, once with water, and once with saturated NaCl, dried ($Na_2SO_4$), and evaporated in vacuo to an oil (0.41 g, 82%). The product was purified via column chromatography on silica gel (ethyl acetate/hexane, 1:1) to give yellow, oily **7c**, which was homogeneous by TLC (ethyl acetate/hexane, 1:1, $R_f$ 0.45): MS (EI), $m/z$ 418/416 ($M^+$·, $^{37}Cl/^{35}Cl$), 381 (M − Cl), 353 (M − $CH_2CH_2Cl$); IR (neat) $\nu_{max}$ (CO) 1638 $cm^{-1}$; 360-MHz $^1H$ NMR Table V;[9] 15.1-MHz $^{13}C$ NMR Table VI.

***N*-(1,3,4,6,7,11b$\alpha$-Hexahydro-7$\alpha$-phenyl-2*H*-benzo[*a*]quinolizin-2$\alpha$-yl)-*N'*,*N'*-dimethyl-*N*-phenylurea (5a).** (This is a representative preparation of the dimethylureas **5a–5c**.) Aniline **4a** (2.98 g, 8.43 mmol) was treated with excess $COCl_2$ at −20 °C in dry $CH_2Cl_2$. The mixture was kept at 23 °C for 1 h to remove excess $COCl_2$ and then concentrated in vacuo to an off-white powder. The powder was combined with fresh, dry $CH_2Cl_2$ (50 mL) and treated with excess anhydrous $(CH_3)_2NH$ at 23 °C. After 16 h, the mixture was filtered, and the filtrate was washed with 10% $Na_2CO_3$ solution and then water. The organic solution was dried ($K_2CO_3$) and concentrated to dryness to give 3.76 g of yellow glass. The material was redissolved in acetone and treated with ethereal HCl until it was acidic. Anhydrous ether was added to complete precipitation of solid. Recrystallization from $CH_2Cl_2$–acetone-ether afforded 1.90 g (53%) of TLC homogeneous, white crystalline **5a**·HCl: mp 222–224 °C; IR (KBr) $\nu_{max}$ 2926 ($NH^+$), 1652 (CO) $cm^{-1}$; $^1H$ NMR $\delta$ 1.7–3.7 (m, 14; s for $NCH_3$ at $\delta$ 2.63), 4.0–4.7 (m, 2, $H_7$ + $H_6$), 5.01 (m, 1, $H_{11b}$), 6.8–7.8 (m, 14). Anal. Calcd for $C_{28}H_{31}N_3O$·HCl: C, 72.79; H, 6.98; N, 9.09. Found: C, 72.84; H, 7.03; N, 9.10.

**4-(2-Chloroethyl)-1-(2-phenylethyl)-3-phenyltetrahydropyrimidin-2(1*H*)-one (11).** Aniline **8**[11] (280 mg, 1 mmol) in 2 mL of $CH_2Cl_2$ was treated with $COCl_2$ (130 mg, 90 $\mu$L) in 0.5 mL of dry $CH_2Cl_2$ at 0 °C. After 1 h, the mixture was evaporated to dryness. The residue was diluted with 2 mL of $CH_2Cl_2$ and a solution of $CF_3CH_2NH_2$ (3 mmol) in 10 mL of $CH_2Cl_2$ was added. The reaction was stoppered and stirred for 2 days at 23 °C. The mixture was treated with an equal volume of 2 N HCl and the organic layer was separated, rinsed with water, dried ($Na_2SO_4$), and concentrated to a tan syrup (0.22 g, 65%), which was nearly homogeneous by TLC [trace of material at origin with ethyl acetate/hexane (1:1)]: MS (CI, $CH_4$), $m/z$ (relative abundance) 385 (M + 41 adduct, $^{37}Cl$; 1%), 383 (M + 41 adduct, $^{35}Cl$; 3%), 373 (M + 29 adduct, $^{37}Cl$; 7%), 371 (M + 29 adduct, $^{35}Cl$; 18%), 346 (M + H + 1, $^{37}Cl$; 8%) 345 (M + H, $^{37}Cl$; 34%), 344 (M + H + 1, $^{35}Cl$; 29%), 343 (M + H, $^{35}Cl$; 100%), 342 (M, $^{35}Cl$; 17%), 307 (M − Cl; 20%), 279 (M − $CH_2CH_2Cl$; 15%), 253 (M − $C_6H_5CH_2$, $^{37}Cl$; 12%), 251 (M − $C_6H_5CH_2$, $^{35}Cl$; 35%); $^1H$ NMR (90 MHz) $\delta$ 1.6–2.4 (m, 4, 2 $CCH_2C$), 2.8–3.05 (m, 2, $CH_2C_6H_5$), 3.1–3.85 (m, 6, $CH_2Cl$, 2 $CH_2N$), 3.9–4.2 (m, 1, CH), 7.0–7.5 (m, 10, aromatic); $^{13}C$ NMR (15.1 MHz) $\delta$ 25.5 (t, $C_4$), 34.0 (t, $CHCH_2$ or $CH_2C_6H_5$), 35.3 (t, $CHCH_2$ or $CH_2C_6H_5$), 41.0 (t, $CH_2Cl$), 43.3 (t, $NCH_2$ or $C_5$), 50.3 (t, $C_5$ or $NCH_2$), 55.3 (d, $C_3$), 125.9 (d, 1), 126.1 (d, 1), 127.4 (d, 2), 128.3 (d, 2), 128.7 (d, 2), 128.9 (d, 2), 139.4 (s, N–$C_6H_5$), 142.8 (s, C–$C_6H_5$), 154.3 (s, $C_2$).

**N-Dealkylation of 1-(2-Phenylethyl)-2-phenylpiperidine with Vinyl Chloroformate.**[6] Vinyl chloroformate (1.76 g, 16.5 mmol) in 1,2-dichloroethane (10 mL) was added (15 min) to a cooled (0 °C), stirred solution of 1-(2-phenylethyl)-2-phenylpiperidine[9] (2.19 g, 8.25 mmol) and 1,8-bis(dimethylamino)-naphthalene (0.15 g, 0.7 mmol) in 1,2-dichloroethane (15 mL). The solution was kept at room temperature for 30 min, at 55 °C for 30 min, and then heated at reflux for 30 min. Volatiles were removed in vacuo and the residue was diluted with dichloromethane (20 mL) and then extracted with 1 N $H_2SO_4$ (3 × 10 mL). Back extracts of the aqueous layers with dichloromethane (2 × 10 mL) were combined with the original organic layer and the mixture was passed through a silica gel plug (2 in. × 2 in.) with dichloromethane–ethyl acetate (1:1) as the eluant. Evaporation of the eluate afforded a TLC homogeneous, yellow oil, identified as *N*-[(vinyloxy)carbonyl]-*N*-(2-phenylethyl)-5-chloro-5-phenylpentanamine (2.32 g, 76%; **14**): IR $\nu_{max}$ 1724 (CO) $cm^{-1}$; $^1H$ NMR ($CCl_4$) $\delta$ 1.1–3.6 (m, 12), 4.33 (dd, 1, $J$ = 6, 1 Hz), 4.52–4.93 (m, 2; t at $\delta$ 4.70, $J$ = 7 Hz; dd at $\delta$ 4.63, $J$ = 1, 14 Hz), 6.8–7.5 (m, 11); MS (EI), $m/z$ (relative abundance) 373.1627 (0.5%, $M^+$· for $^{37}Cl$; calcd, 373.1623), 371.1631 (1%, $M^+$· for $^{35}Cl$; calcd, 371.1652), 292 (74%), 145 (79%), 105 (100%).

**Kinetic Studies.** Linear response curves for **5a** and **7a** were established by spotting known amounts for each compound on channeled 250-$\mu$m silica gel GF plates. The plates were developed (ethyl acetate/hexane, 1:1) and air dried. Densitometer readings were taken with a Kratos/Schoeffel Instrument Spectrodensitometer Model SD-3000 (270 nm) and integrations were recorded with a Kratos SDC-300 Density Computer. Both **5a** and **7a** responded linearly up to about 30 $\mu$g, which was then considered the cutoff limit for examining reaction aliquots.

The following represents an example experimental procedure. A 0.50-mL syringe graduated in 0.01-mL units was used to withdraw 0.25-mL aliquots of the reaction. Aliquots were taken every few minutes and quenched in ethereal dimethylamine (0.25 mL) at 0 °C. After standing for 5 min, these samples were evaporated under a stream of nitrogen, then stored at 0 °C. For analysis, the samples were redissolved in 0.75 mL of a fresh solution of dimethylamine in methylene chloride and a 5-$\mu$L sample of each aliquot was spotted on channeled 250-$\mu$L silica gel GF plates along with two reference standards (**5** and **7**), e.g., ureas **5c** (23.3 $\mu$g) and **7c** (26.8 $\mu$g). The plates were developed and analyzed by densitometry (270 nm). The integral values for the standards were used to calculate the nanomolar percent of each urea present in each channel. The values were normalized (to 46 nmol) for each channel and plotted. The half-life of the reaction was taken as the point of intersection of the curves for **5** and **7**.

**X-ray Crystallographic Analyses.** Data were collected on an Enraf-Nonius CAD4 diffractometer (Mo K$\alpha$ radiation, $\lambda$ = 0.71073 Å) and programs were part of the Enraf-Nonius Structure Determination package as revised in 1977 and implemented on a PDP 11/34 computer or XRAY 76[12] implemented on an IBM 3081 computer.

2$\alpha$-(2-Chloroethyl)-1,6,7,11b$\alpha$-tetrahydro-3,7$\alpha$-diphenyl-2*H*-pyrimido[6,1-*a*]isoquinolin-4(3*H*)-one (**7b**): $C_{26}H_{25}ClN_2O$; $M_r$ 416.95; triclinic, $a$ = 8.721 (5) Å, $b$ = 9.876 (4) Å, $c$ = 14.697 (3) Å, $\alpha$ = 97.64 (2)°, $\beta$ = 101.93 (2)°, $\gamma$ = 115.15 (3)°, $V$ = 1086 (2) Å$^3$; $d_o$ = 1.28 g/cm$^3$, $d_c$ = 1.275 g/cm$^3$ for $Z$ = 2 molecules/unit cell, space group $P\bar{1}$. Of the 3580 reflections collected up to 2$\Theta$ = 48°, 2378 had $I > 2\sigma(I)$ and were used for the subsequent structure analysis (data corrected for Lorentz and polarization factors but not for absorption). Starting positions for all non-hydrogen atoms were determined from a MULTAN 78[13] calculation and refinement was carried out by the full-matrix least-squares method. Final anisotropic refinement of non-hydrogen atoms (H's put in calculated positions assuming a C–H length of 0.97 Å with $B$ = 5 Å$^2$) gave $R$ = 0.070 and $R_w$ = 0.074 where $R = (\sum||F_o| - |F_c||)/\sum|F_o|$, $R_w = [\sum(|F_o| - |F_c|)^2/\sum F_o^2]^{1/2}$, and the function minimized was $(\sum|F_o| - |F_c|)^2$. The final difference map was smooth with maxima and minima of ±0.22 e/Å$^3$. Tables of atomic positional parameters, bond distances and angles, useful least-squares planes, and thermal parameters are available as supplementary material.[9]

2$\alpha$-(2-Chloroethyl)-1,6,7,11b$\beta$-tetrahydro-3,7$\beta$-diphenyl-2*H*-pyrimido[6,1-*a*]isoquinolin-4(3*H*)-one (**7a**): $C_{26}H_{25}ClN_2O$; $M_r$ 416.95; monoclinic, $a$ = 32.367 (5) Å, $b$ = 13.250 (2) Å, $c$ = 11.294

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(14) Å, $\beta$ = 99.25 (3)°, V = 4781 (9) Å$^3$, $d_0$ = 1.20 g/cm$^3$, $d_c$ = 1.163 g/cm$^3$ for $Z$ = 8 molecules/unit cell, space group $P2_1/c$ (the 2 unique molecules denoted A and B). Anisotropic refinement of non-hydrogen atoms (H's put in calculated positions as above) over 3878 statistically significant [$I > 2\sigma(I)$] reflections converged at $R$ = 0.118 and $R_w$ = 0.160 where $R$ is as above, $R_w = [\sum w(|F_o| - |F_c|)^2/\sum wF_o^2]^{1/2}$, $w = 1/[\sigma(F_o)^2]$, and $\sigma(F_o)^2 = [\sigma(I)^2 + (0.07F^2)^2]^{1/2}/(\mathrm{Lp})$ where $F_o^2 = F^2/(\mathrm{Lp})$. The final difference map was featureless with maxima and minima ranging down from ±0.80 e/Å$^3$. The poor quality of the best available crystal and the large number of independent atoms in the unit cell vs. the number of significant reflections limited the structure solution to a demonstration of stereochemistry and gross conformation (shown for molecules A and B in Figure 3).[9]

**Acknowledgment.** We express our appreciation to Martin Mutter, Joan Rodgers, Dr. Sai Chang, James Kalbron, and Dr. Ruth Inners for spectroscopic analysis. We also thank William Sisco and Thomas DiFeo for TLC densitometry.

**Registry No.** **4a**, 75715-72-9; **4a**·hexamate, 75688-93-6; **4b**, 75715-73-0; **4c**, 75715-68-3; **5a**, 87680-29-3; **5a**·HCl, 87640-70-8; **5b**, 87680-30-6; **5c**, 87680-31-7; **6a**, 87680-23-7; **6b**, 87680-24-8; **6c**, 87680-25-9; **7a**, 87680-26-0; **7b**, 87680-27-1; **7c**, 87680-28-2; **8**, 21409-26-7; **9**, 87640-68-4; **10a**, 87680-32-8; **10b**, 87680-33-9; **11**, 87640-69-5; **13**, 87640-72-0; **14**, 87640-71-9; $CF_3CH_2NH_2$, 753-90-2; phosgene, 75-44-5; dimethylamine, 124-40-3; vinyl chloroformate, 5130-24-5; 1,8-bis(dimethylamino)naphthalene, 20734-58-1.

**Supplementary Material Available:** Tables of positional and thermal parameters, bond distances and angles, selected least-squares planes, Figures 2 and 3, Tables III–V containing high-field $^1$H NMR data for **7a–7c**, and experimental procedures for the preparation of **10a**, (**10b**), and **13** (12 pages). Ordering information is given on any current masthead page.

# Hydroboration. 65. Relative Reactivities of Representative Alkenes and Alkynes toward Hydroboration by Catecholborane

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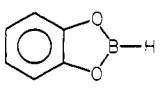
*Received June 21, 1983*

The relative reactivities of a number of alkenes and alkynes toward hydroboration by catecholborane were determined in refluxing THF and were compared with data available for other monofunctional hydroborating agents such as 9-borabicyclo[3.3.1]nonane, disiamylborane, thexylchloroborane–methyl sulfide, and dibromoborane–methyl sulfide. Catecholborane is less selective than the other reagents, even though the trend is the same as that for the dialkylboranes. This may be attributed, in part, to the inherent low steric and electrophilic properties of this reagent and, in part, to the relatively high temperture (65 °C) required to achieve a reasonable rate of hydroboration.

Catecholborane ((1,2-phenylenedioxy)borane, 1) is a mild hydroborating agent.[2,3] It hydroborates alkynes cleanly



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to the monohydroborated products.[2b] It has been effectively used in the preparation of alkyl- and alkenylboronic acids. It has been employed in the synthesis of vinylmercurials[4] and haloalkenes of controlled stereochemistry.[5] In spite of its synthetic importance,[6] its selectivity in the hydroboration of alkenes and alkynes is not yet known.

Moreover, catecholborane has unique structural features. Due to electron donation from the adjacent oxygen, it is a much weaker Lewis acid than dialkylboranes and dihaloboranes. The boron atom is part of a planar five-membered ring and hence its steric requirements are much less than those of bulky reagents such as disiamylborane. We have long been interested in establishing the effects of variation of the structural features of hydroborating agents on their selectivities for hydroboration.[7–10] Consequently, we determined the relative rates of hydroboration of representative alkenes and alkynes by catecholborane in refluxing THF by the competition method in order to compare the data with the analogous data available for other monofunctional hydroborating agents such as 9-borabicyclo[3.3.1]nonane[8] (9-BBN), disiamylborane[7] ($Sia_2BH$), thexylchloroborane–methyl sulfide[9] ($ThxBHCl{\cdot}SMe_2$) and dibromoborane–methyl sulfide[10] ($Br_2BH{\cdot}SMe_2$). We report out results in this paper.

## Results and Discussion

**Competitive Hydroboration of Alkenes and Alkynes by Catecholborane.** Catecholborane does not hydroborate alkenes and alkynes at 25 °C. Consequently, we determined the relative reactivities of alkenes and alkynes toward hydroboration by catecholborane in refluxing THF by the competition method. Two alkenes (1 equiv each) were treated with catecholborane (1 equiv) in THF so that the concentrations were ~1.0 M. The reaction mixture was refluxed until at least 50% of the reaction was over.[11] An aliquot was then quenched with excess aqueous NaOH,

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(11) With some alkene pairs, the reaction was very slow; since the Ingold–Shaw expression is to be obeyed at any point in a reaction, we analyzed the reaction mixtures after 50% of the catecholborane was consumed.

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