with TLC on silica gel with dimethylformamide (R_f 0.9) or aqueous 80% methanol (R_f 0.8). Attempted recrystallization usually resulted in partial decomposition, as shown by TLC. The analytical sample was dried for 9 h at 0.1 Torr at 100 °C. The compound darkened above 240 °C but did not melt up to 400 °C; 100-MHz ^{1}H NMR (Me_2SO-d_6) δ 8.55 (s, 1, NCHN), 8.10 (s, 1, CH=CB_2), 7.64 (broadened s, 1, NH), 7.18 (broadened s, 1, NH), 3.42 (s, ~10, NH, BOH, and H_2O from solvent); on addition of methanol dropwise, the δ 7.64 peak broadened, shifted downfield, and disappeared, and the δ 7.18 peak broadened somewhat without shifting; ^{1}H NMR (CD_3OD) δ 8.31 (brd s, CH=CB_2), 8.20 (s, NCHN); IR (KBr) 3205 brd s, 1656 sh, 1587 s, 1477 s, 1456 s, 1395 sh, 1339 s, 1270 brd s, tapering off with some irregularities to 950, 909 m, 803 m, 722 s, 691 m cm^{-1}; UV (H_2O) 203 nm (ϵ 19 550), 233 (16 870), 284 (8850), 302 (10 700); UV (0.1 N HCl) 225 nm (ϵ 17 150), 283 (12 650), 300 (10 460); UV (0.1 N NaOH) 228 nm (ϵ 19 400), 288 (10 610). Anal. Calcd for $C_6H_8B_2N_4O_3$: C, 35.03; H, 3.92; B, 10.51; N, 27.22; mol wt 206. Found: C, 35.24, 35.08; H, 3.74, 3.92; B, 10.44; N, 27.15. 27.08; mol wt (dimethylformamide) 220, (methanol) 235.

4-Amino-6-trimethylenedioxyboryl-7-hydroxy-7,8-dihydro-7,8-borazaroquinazoline (8a). 4,6-Dichloro-5-[2,2-bis(trimethylenedioxyboryl)vinyl]pyrimidine (**6a**) was used in place of the ethylenedioxyboryl analogue **6b** in the procedure described for the preparation of **8b** Instead of methanol, the product was dissolved in 500 mL of chloroform, concentrated under vacuum to crystallize it, yield 70%, and recrystallized from chloroform and finally from toluene/absolute ethanol. The compound tenaciously retained 1 mol of chloroform, as shown by the persistent ^{1}H NMR peak at δ 8.35. After prolonged drying (56 °C, 30 h, 0.1 Torr) the NMR evidence of chloroform disappeared, but the analysis suggested the persistence of 7 mol % $CHCl_3$. The product did not melt at up to 300 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.92 (brd s, 1, NH), 8.44 (s, 1, NCHN), 8.05 (s, 1, CH=CB_2), 7.21 (brd s, 2, NH_2), 6.41 (s, 1, BOH), 4.07 (t, 4, OCH_2CH_2), 1.97 (m, 2, $CH_2CH_2CH_2$); IR (KBr) 3497 s, 3279 s, 3096 s, 2959 s, 1587 s, 1475 s, 1464 s, 1441 s, 1323 s, 1285 s, 1152 s, 1099 s, 1066 s, 961 m, 903 s, 838 m, 803 m, 745 s, 719 s, 692 s, 657 sh, 638 s cm^{-1}. Anal. Calcd for $C_9H_{12}B_2N_4O_3$ + 0.07 $CHCl_3$: C, 42.82; H, 4.78; B, 8.50; Cl, 3.02; N, 22.02 (calcd for $C_9H_{12}B_2N_4O_3$: C, 43.97; H, 4.92; B, 8.80; N, 22.79). Found: C, 42.44; H, 4.82; B, 8.47; Cl, 3.02; N, 21.91.

Acknowledgment. We thank Dr. James A. Magnuson for helpful discussions regarding the ^{13}C NMR spectra.

Registry No.—**2,** 5271-82-9; **3,** 64728-21-8; **4a,** 64705-53-9; **4b,** 64728-22-9; **5,** 5305-40-8; **6b,** 64705-54-0; **7a,** 64705-55-1; **7b,** 64705-56-2; **7c,** 64705-57-3; thiourea, 62-56-6; tetrakis(ethylenedioxyboryl)methane, 50485-33-1; tetrakis(trimethylenedioxyboryl)methane, 42495-90-9; tris(ethylenedioxyboryl)methane, 59278-44-3.

References and Notes

(1) Supported by Public Health Service Grant No. CA-05513 from the National Cancer Institute. Funds for the purchase of the Bruker WH-90 NMR spectrometer were provided in part by National Science Foundation Grant No. MPS75-06301.
(2) K. A. Koehler and G. E. Lienhard, *Biochemistry,* **10,** 2477 (1971).
(3) B. F. Spielvogel, L. Wojnowich, M. K. Das, A. T. McPhail, and K. D. Hargrave, *J. Am. Chem. Soc.,* **98,** 5702 (1976).
(4) S. S. Chissick, M. J. S. Dewar, and P. M. Maitlis, *J. Am. Chem. Soc.,* **83,** 2709 (1961).
(5) H. Zimmer, E. R. Andrews, and A. D. Sill, *Arzneim.-Forsch.,* **17,** 607 (1967).
(6) D. S. Matteson and T. C. Cheng, *J. Org. Chem.,* **33,** 3055 (1968).
(7) D. N. Butler and A. H. Soloway, *J. Am. Chem. Soc.,* **86,** 2691 (1964); **88,** 484 (1966).
(8) T. K. Liao, E. G. Podrebarac, and C. C. Cheng, *J. Am. Chem. Soc.,* **86,** 1869 (1964).
(9) M. J. S. Dewar, *Prog. Boron Chem.,* **1,** 235 (1964).
(10) D. S. Matteson and G. D. Schaumberg, *J. Org. Chem.,* **31,** 726 (1966).
(11) H. G. Kuivila and O. F. Beumel, Jr., *J. Am. Chem. Soc.,* **83,** 1246 (1961).
(12) D. S. Matteson and P. B. Tripathy, *J. Organomet. Chem.,* **21,** P6 (1970); **69,** 53 (1974).
(13) D. S. Matteson, L. A. Hagelee, and R. J. Wilcsek, *J. Am. Chem. Soc.,* **95,** 5096 (1973).
(14) D. S. Matteson and L. A. Hagelee, *J. Organomet. Chem.,* **93,** 21 (1975).
(15) W. Klötzer and M. Herberz, *Monatsh. Chem.,* **96,** 1567 (1965).
(16) D. S. Matteson and R. J. Wilcsek, *J. Organomet. Chem.,* **57,** 231 (1973).
(17) D. S. Matteson and P. K. Jesthi, *J. Organomet. Chem.,* **110,** 25 (1976).
(18) A. J. Jones, M. W. Winkely, D. M. Grant, and R. K. Robins, *Proc. Natl. Acad. Sci. U.S.A.,* **65,** 27 (1970).
(19) E. Breitmaier, G. Jung, and W. Voelter, *Angew. Chem., Int. Ed. Engl.,* **10,** 673 (1971).
(20) F. W. Wehrli, *Top. Carbon-13 NMR Spectrosc.,* **2,** 357 (1976).

Reaction of Tertiary Glycidamides with Boron Trifluoride Etherate. Evaluation of the Potential for Rearrangement with Amide Group Migration[1]

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Received August 8, 1977

The reaction of a series of tertiary glycidamides with boron trifluoride etherate in benzene, methylene chloride, or chloroform was studied. The major process observed with (*E*)- and (*Z*)-*N,N*-diphenyl-3-phenylglycidamides (**1a,b**) as well as (*E*)- and (*Z*)-*N,N*-diphenyl-3-methyl-3-phenylglycidamides (**1c,d**) was stereospecific intramolecular Friedel–Crafts cyclization to give the corresponding 1,4-diphenyl-3-hydroxy-2(1*H*)-quinolinones (**2**). A similar reaction was observed in the rearrangement of (*E*)-*N*-phenyl-*N*-methyl-2-methyl-3-phenylglycidamide (**1g**), although condensation with benzene solvent was also found in this case. The reaction of *N,N*-dialkyl-3-methyl-3-phenylglycidamides (**1e,f**) with boron trifluoride etherate led to formation of the corresponding *N,N*-dialkyl-2-hydroxy-3-phenyl-3-butenamides (**5d,f**). Finally (*E*)- and (*Z*)-*N,N*-dimethyl-2-methyl-3-phenylglycidamides (**1h,i**) gave fluorohydrin (**7a**) along with its BF_2 derivative (**7b**). Under more severe conditions **1i** was converted to *N,N*-dimethyl-2-phenylacetoacetamide (**9**), the product anticipated from amide group migration, along with *N,N*-dimethyl-3-phenyl-3-methylpyruvamide (**8**), formed by α-methyl migration.

Since House's[2] discovery of ketone migration in the boron trifluoride induced rearrangement of α,β-epoxy ketones, attention has been given to studies of rearrangement of various other α,β-epoxy carbonyl systems, including glycidic esters,[3] glycidic thiol esters,[4] and α,β-epoxy diazo ketones.[5] The reaction is of some mechanistic interest[2-4,6] in that it involves migration of an electron-deficient carbonyl carbon to a positive migration terminus. Recent work suggests that the

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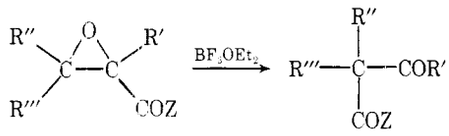
BF_3-induced rearrangement of glycidic esters is a concerted process proceeding with inversion of configuration at the migration terminus.[4c,6a]



Z = Ar, OR, SR, CHN_2

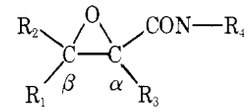
A study of the boron trifluoride induced rearrangement of glycidamides has not been reported, although examples of the reaction of glycidamides with aluminum chloride,[7] hydrochloric acid,[8,9] and sulfuric acid[9] are known. Thus *N*-methyl-*N*-phenyl-3,3-dimethylglycidamide is converted to 3-hydroxy-1,4,4-trimethyl-2(1*H*)-quinolinone in the presence of aluminum chloride.[7] Blicke and Faust[8] found that the 3,3-diphenylglycidamide is isomerized to diphenylpyruvamide when heated with HCl. Tung and Speziale[9] observed stereospecific conversion of (*E*)- and (*Z*)-*N*,*N*-diethyl-3-phenylglycidamides to the corresponding erythro and threo vicinal diols or chlorohydrins using aqueous sulfuric acid and hydrochloric acid in benzene or methanol solvents. In these cases the amide carbonyl function was not found to migrate. Indeed only one example of amide migration is known. This was observed in the base-induced benzilic acid rearrangement of α,β-diketo amides to α-hydroxymalonamides.[10]

We have thus undertaken a study of the boron trifluoride induced rearrangement of tertiary glycidamides with a view to evaluating the potential for amide migration in this system as well as to explore the synthetic utility of the process. At the outset it was recognized that the amide function is relatively basic and would thus compete effectively with the epoxide oxygen for the Lewis acid catalyst. Thus initially we examined the reaction of boron trifluoride etherate with relatively nonbasic amides, including *N*-phenyl- and *N*,*N*-diphenylglycidamides. α-Methyl- as well as β-methyl-substituted glycidamides were also studied in view of the observation by Kagan[3] that, whereas ethyl 3-phenylglycidate did not undergo rearrangement with ester migration, ethyl 2-methyl-3-phenylglycidate as well as ethyl 3-methyl-3-phenylglycidate did give ester migration products in high yield. In general we found a wide variety of products, including fluorohydrins, 2-hydroxy-3-butenamides and their BF_2 complexes, and both intra- and intermolecular Friedel–Crafts condensation products. In one instance a β-keto amide was obtained as a result of migration of the amide function. However, it appears that rearrangement with amide migration is not a pathway of major importance in the reaction of tertiary glycidamides with boron trifluoride etherate.

Results and Discussion

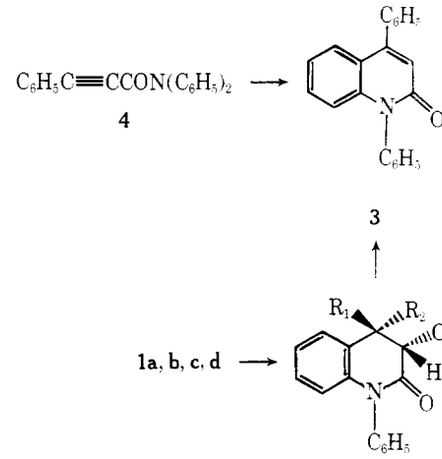
The required glycidamides were prepared by Darzens condensation of α-chloro tertiary amides with aldehydes and ketones using potassium *tert*-butoxide as the base.[9a,11] (*E*)-*N*,*N*-Diphenyl-3-phenylglycidamide (**1a**) was also obtained by *m*-chloroperbenzoic acid[12] epoxidation of (*E*)-*N*,*N*-diphenylcinnamamide.

The major process observed in the rearrangement of *N*,*N*-diphenyl tertiary glycidamides was intramolecular Friedel–Crafts cyclization, resulting in stereospecific formation of 3-hydroxy-4-phenyl-2(1*H*)-quinolinones. Of interest in this connection is the fact that formation of comparable intramolecular cyclization products was not found in the BF_3-induced rearrangement of *S*-phenyl thiolglycidates[4] or related phenyl oxygen glycidate esters,[3b] and such cyclization is probably not an important mode of reaction in these cases. Treatment of (*E*)-*N*,*N*-diphenyl-3-phenylglycidamide (**1a**)



1a, R_1, R_4, R_5 = C_6H_5; R_2, R_3 = H
b, R_2, R_4, R_5 = C_6H_5; R_1, R_3 = H
c, R_1, R_4, R_5 = C_6H_5; R_2 = CH_3; R_3 = H
d, R_2, R_4, R_5 = C_6H_5; R_1 = CH_3; R_3 = H
e, R_1 = C_6H_5; R_2 = CH_3; R_3 = H; R_4, R_5 = CH_2CH_3
f, R_1 = C_6H_5; R_2, R_4, R_5 = CH_3; R_3 = H
g, R_1, R_4 = C_6H_5; R_3, R_5 = CH_3; R_2 = H
h, R_1 = C_6H_5; R_3, R_4, R_5 = CH_3; R_2 = H
i, R_2 = C_6H_5; R_3, R_4, R_5 = CH_3; R_1 = H

with boron trifluoride etherate in refluxing benzene led to (*E*)-1,4-diphenyl-3-hydroxy-2(1*H*)-quinolinone (**2a**) in 87%



2a, R, R_2 = H; R_1 = C_6H_5
b, R = $COCH_3$; R_1 = C_6H_5; R_2 = H
c, R = tosyl; R_1 = C_6H_5; R_2 = H
d, R, R_1 = H; R_2 = C_6H_5
e, R = tosyl; R_1 = H; R_2 = C_6H_5
f, R = H; R_1 = C_6H_5; R_2 = CH_3
g, R = $COCH_3$; R_1 = C_6H_5; R_2 = CH_3
h, R = H; R_1 = CH_3; R_2 = C_6H_5
i, R = $COCH_3$; R_1 = CH_3; R_2 = C_6H_5

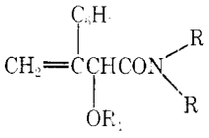
yield. Quinolinone **2a** was also obtained in high yield when the reaction was carried out in methylene chloride at room temperature for 30 min. The quinolinone assignment for **2a** was based on conversion to the corresponding fully aromatic quinolone **3** by pyrolysis of acetate **2b** or alternatively by heating tosylate **2c** with sodium hydroxide or sodium acetate in ethanol. The structure of **3** was established by independent synthesis involving treatment of *N*,*N*-diphenyl-3-phenylpropiolamide with boron trifluoride etherate in benzene.[13] The *E* configuration of **2a** was inferred from the fact that relatively low temperatures (250 °C) were sufficient in the acetate pyrolysis of **2b.** Furthermore, comparatively severe conditions were needed in the base-induced elimination of tosylate **2c** to give quinolone **3.** It was necessary to use excess sodium acetate in refluxing ethanol for 48 h to accomplish complete conversion of **2c** to **3.**

Using the same reaction conditions employed with (*E*)-glycidamide **1a** in benzene solvent, the *Z* isomer, **1b,** was converted to (*Z*)-1,4-diphenyl-3-hydroxy-2(1*H*)-quinolinone (**2d**) in 75% yield. Assignment of the *Z* configuration to **2d** is supported by the observation that the tosylate derivative **2e** underwent facile elimination to quinolone **3** by treatment with sodium acetate in refluxing ethanol. The (*Z*)-tosylate **2e** was completely converted to quinolone **3** within 1 h. Under the same conditions less than 20% of (*E*)-tosylate **2c** was converted to quinolone **3.** Vicinal coupling constants for **2a** (14 Hz), **2b** (13 Hz), and **2d** (7 Hz) are in agreement with the stereochemical assignments. The closeness found for the values

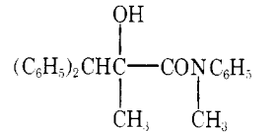
of **2c** (7 Hz) and **2e** (6 Hz) have precedent in earlier work on *E* and *Z* isomers of 3-methylamino-4-phenyl-2(1*H*)-quinolinone.[15]

NMR analysis of the crude reaction mixture obtained from the BF_3-induced rearrangement of (*Z*)-glycidamide **1b** did not indicate the presence of any (*E*)-quinolinone **2a.** Similarly, (*Z*)-quinolinone **2d** was not found in the rearrangement of (*E*)-glycidamide **1a.** Thus the formation of these quinolinones appears to be highly stereospecific. The generation of (*E*)-quinolinone **2a** from (*E*)-glycidamide **1a** and (*Z*)-quinolinone **2d** from (*Z*)-glycidamide **1b** suggests that the epoxide ring is opened with inversion of configuration at the β position.

The boron trifluoride induced rearrangement of (*E*)- and (*Z*)-*N,N*-diphenyl-3-methyl-3-phenylglycidamides (**1c,d**) proved to be somewhat less stereospecific. Both quinolinone isomers were isolated from the rearrangement of each of these glycidamides. However, one isomer, **2f,** which is presumably (*E*)-1,4-diphenyl-3-hydroxy-4-methyl-2(1*H*)-quinolinone, was the major product obtained from (*E*)-glycidamide **1c.** The (*Z*)-glycidamide **1d** gave predominantly the other isomer, presumably (*Z*)-quinolinone **2h.** The stereochemical assignments for **2f** and **2h** have not been rigorously established. In both rearrangements a lesser amount of *N,N*-diphenyl-2-hydroxy-3-phenyl-3-butenamide (**5a**) was also formed.



5a, R = C_6H_5; R_1 = H
b, R = C_6H_5; R_1 = $COCH_3$
c, R = C_2H_5; R_1 = BF_2
d, R = C_2H_5; R_1 = H
e, R = C_2H_5; R_1 = $COCH_3$
f, R = CH_3; R_1 = H



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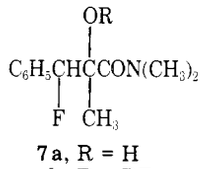
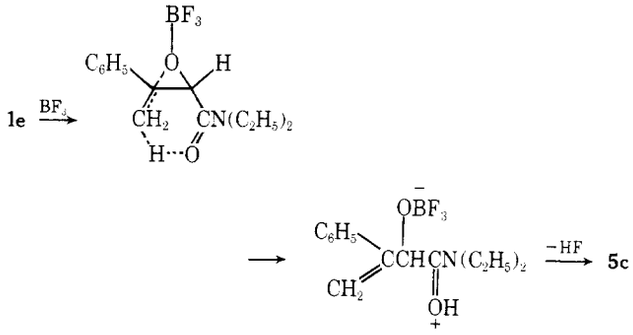


7a, R = H
b, R = BF_2
c, R = $COCH_3$

Analysis of the NMR spectrum of the crude reaction mixture from rearrangement of *E* isomer **1c** indicated an approximate ratio of 6:2.5:1.5 for compounds **2f, 2h,** and **5a,** respectively, while a ratio of 1:8:1 was found in the rearrangement of *Z* isomer **1d.**

Butenamide formation was also observed in the rearrangement of *N,N*-diethyl-3-methyl-3-phenylglycidamide (**1e**) in either benzene or methylene chloride solvent. When the reaction was carried out in benzene the BF_2 derivative **5c** was the major product isolated in 77% yield. **5c** was converted to the corresponding alcohol **5d** using sodium hydroxide in ethanol. Alcohol **5d** was obtained directly when the rearrangement was carried out in methylene chloride. Similarly, *N,N*-dimethyl-3-methyl-3-phenylglycidamide (**1f**) led primarily to hydroxybutenamide **5f** using boron trifluoride etherate in methylene chloride solvent. A rearrangement process of this type has been noted earlier in the reaction of BF_3 with 3-methyl-3-phenylglycidic esters,[3] although products arising from ester or alkyl group migration predominated in most of these cases. In contrast, this type of process was not observed for the BF_3-induced rearrangement of *S*-phenyl 3-methyl-3-phenylthiolglycidate[4] or in the corresponding β-methyl-β-phenyl α,β-epoxy ketone system.[2] In the amide case butenamide formation appears to be the major rearrangement process for *N,N*-dialkyl-3-methyl-3-phenylglycidamides. In the formation of butenamide **5c** the relatively basic *N,N*-dialkylamide function could assist in removal of a proton from the β-methyl group in formation of the product double bond (Scheme I). It is not clear in this case whether or not a carbonium ion intermediate is involved in the mechanism.

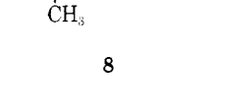
Scheme I



We have also examined the reaction of *N*-methyl-*N*-phenylglycidamide **1g** with boron trifluoride etherate in benzene solvent. As with the other BF_3-induced quinoline syntheses reported here, this reaction was also stereospecific. The presence of only one quinolinone isomer was indicated in the NMR spectrum of the crude reaction mixture. This compound is believed to be (*E*)-3,4-dihydro-1,3-dimethyl-3-hydroxy-4-phenyl-2(1*H*)-quinolinone. Also in the rearrangement of **1g,** a Friedel–Crafts reaction with benzene solvent was observed, resulting in formation of *N*-methyl-*N*-phenyl-3,3-diphenyl-2-hydroxy-2-methylpropionamide (**6**). A similar Friedel–Crafts reaction with solvent has been noted previously in the boron trifluoride induced rearrangement of ethyl 2-methyl-3-phenylglycidate in toluene solvent.[3b]

The rearrangement of (*Z*)-*N,N*-dimethyl-2-methyl-3-phenylglycidamide (**1i**) in methylene chloride led to formation of fluorohydrin (**7a**) along with its BF_2 derivative (**7b**). It is interesting that under the same conditions the *E* isomer **1h** gave rise to the same fluorohydrin diastereomer. A related result has been noted earlier by Tung and Speziale[9b] in the HCl-induced rearrangement of (*E*)- and (*Z*)-*N,N*-diethyl-3-phenylglycidamides in benzene solvent, leading in either case to the threo isomer of *N,N*-diethyl-3-chloro-3-phenyl-2-hydroxypropionamide. These workers suggest that neighboring group participation involving the amide function plays a role in the conversion of the *trans*-glycidamide to the *threo*-chlorohydrin, involving overall retention of configuration at the β position. It is likely that a similar neighboring group effect is involved in the BF_3-induced conversion of **1h** or **1i** to **7a.**

When under more severe conditions (*Z*)-glycidamide **1i** was warmed for 3.5 h in refluxing methylene chloride in the presence of excess boron trifluoride etherate, there was obtained a mixture of *erythro*- and *threo*-fluorohydrin stereoisomers **7a** along with smaller amounts of *N,N*-dimethyl-3-phenyl-3-methylpyruvamide (**8**) and *N,N*-dimethyl-2-phenylacetoacetamide (**9**). Formation of this same mixture



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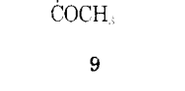

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of **8** and **9** along with the two fluorohydrin diastereomers was found when **7a** was warmed in refluxing methylene chloride for 3 h in the presence of excess boron trifluoride etherate. However, neither fluorohydrin diastereomer was found after **1i** was allowed to reflux for 6 h in chloroform in the presence of excess boron trifluoride etherate. Under these conditions pyruvamide **8** was isolated in 19% yield along with a smaller amount (~5%) of **9.** When **1i** was allowed to reflux for 6 h in chloroform in the presence of only 1 equiv of boron trifluoride

etherate there was obtained 15% pyruvamide **8**, 27% acetoacetamide **9**, and 10% of the mixture of fluorohydrin diastereomers. Acetoacetamide **9** is the product expected from amide migration. The structure of **9** was established by conversion to 3-methyl-4-phenyl-3-pyrazolin-5-one using hydrazine hydrate in ethanol.

These results suggest that glycidamide **1i** is initially converted to fluorohydrin **7a** or its BF_2 derivative **7b**. Under more severe conditions the fluorohydrin undergoes rearrangement with either methyl or amide migration. A parallel for this is seen in the rearrangement of (*E*)-benzalacetophenone oxide with excess boron trifluoride etherate to give a mixture of *threo*-3-fluoro-2-hydroxy-1,3-diphenyl-1-propanone and α-formyldeoxybenzoin.[16] In the presence of excess boron trifluoride etherate the fluorohydrin is converted directly to α-formyldeoxybenzoin, the rearrangement product formed as a result of benzoyl migration. Kinetic examination[2e] of this process did not permit a distinction between direct conversion of the epoxy ketone to the rearrangement product as opposed to involvement of the fluorohydrin as an obligatory intermediate in the rearrangement.

In the rearrangement of **1i** in refluxing chloroform the percent of amide migration relative to α-methyl migration increases as the concentration of BF_3 is lowered. This result may be explained if we assume that coordination of BF_3 with the amide carbonyl group would lower its migratory aptitude. With excess BF_3 present it is conceivable that the amide function could be complexed with 1 molecule of BF_3 at the same time a second BF_3 molecule is involved in generating an electron-deficient site at the β position. This would give methyl migration an advantage, thus increasing the relative amount of the pyruvamide product when higher concentrations of catalyst are employed.

In summary, amide migration does not appear to be as general a phenomena as ketone, ester, or thiol ester migration, at least in the BF_3-induced rearrangement of α,β-epoxy carbonyl systems. For example, *N*-arylglycidamides tend to undergo intramolecular Friedel–Crafts cyclization in contrast to *S*-aryl thiol esters[4] or *O*-aryl oxygen esters,[3b] which give carbonyl or hydrogen migration products. β-Methylglycidamides give butenamides rather than products resulting from carbonyl migration, while glycidic esters[3] give both types of products and α,β-epoxy ketones[2] as well as glycidic thiol esters[4] give primarily the carbonyl migration product. With respect to a glycidamide system such as **1i** where butenamide formation or intramolecular Friedel–Crafts cyclization is not possible, the amide shift does occur but only after initial conversion to the fluorohydrin adduct. Relatively severe conditions are then required before this fluorohydrin will give rearrangement with amide migration. One explanation for this apparent reluctance of the amide group to migrate lies in its high relative basicity. This property may lead to serious competing reactions, including strong coordination of the amide function with the Lewis acid catalyst or amide carbonyl association with the electron-deficient β position to give a 2-amino-2-oxetanyl cation intermediate. It is of interest that, when these side reactions are reduced by the use of only 1 equiv of catalyst, the relative importance of amide migration increases to the point where the migratory aptitude of the amide function is greater than that of the α-methyl group.

In any case, the reaction of BF_3 with tertiary glycidamides appears to have considerable synthetic utility. The process offers an efficient stereospecific method for the preparation of 3-hydroxy-4-phenyl-2(1*H*)-quinolinones from the corresponding *N*-phenyl tertiary glycidamides. *N,N*-Dialkyl-3-phenyl-3-methylglycidamides are converted in high yield to the corresponding 2-hydroxy-3-butenamides, and fluorohydrins may be obtained stereospecifically in high yield from *N,N*-dialkyl-2-methyl-3-phenylglycidamides.

Experimental Section

General. Infrared spectra were recorded on a Perkin-Elmer Model 457 spectrometer. The ultraviolet spectra were recorded on a Cary Model 14 spectrometer. Nuclear magnetic resonance spectra were recorded on the Varian A-60A spectrometer using tetramethylsilane as an internal standard. Benzene was dried over sodium metal, and ether was dried over $LiAlH_4$. Both were distilled prior to use. The *tert*-butyl alcohol was dried over CaH_2 and distilled prior to use. Methylene chloride and chloroform were dried over phosphorus pentoxide and distilled prior to use. The petroleum ether had a boiling point range of 60–110 °C. The silica gel used for column chromatography was Baker reagent grade (60–200 mesh). Silica gel GF-254 (Merck) was used for the preparative thin-layer chromatography. Melting points and boiling points are uncorrected. Elemental analyses were performed by M. H. W. Laboratories, Garden City, Mich.

(*E*)-*N,N*-Diethyl-3-methyl-3-phenylglycidamide (1e) was prepared according to the method of Speziale and Frazier:[11] mp 94–95 °C (lit.[11] mp 94–95 °C); NMR ($CDCl_3$) δ 0.62 (t, 3 H, J = 7.5 Hz), 1.09 (t, 3 H, J = 7.5 Hz), 1.78 (s, 3 H), 2.70–3.50 (m, 4 H), 3.65 (s, 1 H), 7.05–7.50 (m, 5 H); IR (KBr) 1665 cm^{-1}.

The following glycidamides were prepared in a similar fashion: **(*E*)- and (*Z*)-*N,N*-diphenyl-3-phenylglycidamides (1a,b)** were obtained in the reaction of *N,N*-diphenyl-2-chloroacetamide[17] with benzaldehyde. The NMR spectrum of the crude reaction mixture indicated the presence of approximately 70% of the *E* isomer and 30% *Z*. Treatment of the mixture with 1:1 ether and hexane led to formation of crystals of **1a**, which were purified by fractional crystallization from ethanol. This afforded pure **1a** in 59% yield: mp 111–112 °C; NMR ($CDCl_3$) δ 3.39 (d, 1 H, J = 1.5 Hz), 4.27 (d, 1 H, J = 1.5 Hz), 7.32 (s) and 7.36 (s) (15 H); IR (KBr) 1675 cm^{-1}; UV λ_{max} (EtOH) 233 nm (ϵ 14 400). Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.51; N, 4.44. Found: C, 80.12; H, 5.59; N, 4.49.

The hexane–ether mother liquors obtained from the isolation of **1a** were concentrated to give a yellow oil which was dried under reduced pressure for 3 days. The resulting solid was purified by column chromatography on silica gel, eluting with 10% ethyl acetate in benzene. The purified material was recrystallized from benzene–hexane to give the pure *Z* isomer **1b** in 25% yield: mp 112–114 °C; NMR ($CDCl_3$) δ 3.75 and 3.85 (AB quartet, 2 H, J = 4.5 Hz), 6.88–7.50 (m, 15 H); IR (KBr) 1675 cm^{-1}. Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.51; N, 4.44. Found: C, 80.13; H, 5.64; N, 4.31.

(*E*)- and (*Z*)-*N,N*-diphenyl-3-methyl-3-phenylglycidamide (1c,d) were obtained in about equal amounts in the Darzens condensation of acetophenone with *N,N*-diphenyl-2-chloroacetamide. The mixture was separated by fractional crystallization from ethanol and water. For the *E* isomer **1c:** mp 143–144 °C; NMR ($CDCl_3$) δ 1.80 (s, 3 H), 3.24 (s, 1 H), 7.25 (singlet superimposed on a multiplet between δ 6.90 and 7.40, 15 H); IR (KBr) 1680 cm^{-1}; UV λ_{max} (EtOH) 238 nm (ϵ 16 300). Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 79.98; H, 5.96; N, 4.09.

For the *Z* isomer **1d:** mp 120–121 °C; NMR ($CDCl_3$) δ 1.40 (s, 3 H), 3.65 (s, 1 H), 6.70–7.60 (m, 15 H); IR (KBr) 1680 cm^{-1}; UV λ_{max} (EtOH) 233 nm (ϵ 12 300). Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.42; H, 5.72; N, 4.12.

(*E*)-*N*-Methyl-*N*-phenyl-2-methyl-3-phenylglycidamide (1g) was obtained from benzaldehyde and *N*-methyl-*N*-phenyl-2-chloropropionamide in 68% yield: mp 149–151 °C; NMR ($CDCl_3$) δ 1.15 (s, 3 H), 3.38 (s, 3 H), 4.10 (s, 1 H), 6.85–7.50 (m, 10 H); IR (KBr) 1650 cm^{-1}. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.19; H, 6.26; N, 5.18.

N-Methyl-*N*-phenyl-2-chloropropionamide was prepared from *N*-methylaniline and 2-chloropropionyl chloride (Aldrich Chemical Co.) in ether in the presence of pyridine: mp 49–51 °C (ethanol); NMR (CCl_4) δ 1.50 (d, 1 H, J = 6.5 Hz), 3.25 (s, 3 H), 4.25 (q, 1 H, J = 6.5 Hz), 7.38 (s, 5 H). Anal. Calcd for $C_{10}H_{12}NOCl$: C, 60.76; H, 6.12; N, 7.09; Cl, 17.94. Found: C, 60.69; H, 5.99; N, 7.03; Cl, 18.17.

(*E*)-*N,N*-Dimethyl-3-methyl-3-phenylglycidamide (1f) was obtained from acetophenone and *N,N*-dimethyl-2-chloroacetamide[18] in 60% yield: mp 57–58 °C; NMR ($CDCl_3$) δ 1.80 (s, 3 H), 2.66 (s, 3 H), 2.97 (s, 3 H), 3.71 (s, 1 H), 7.17–7.53 (m, 5 H); IR (KBr) 1650 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.07; H, 7.35; N, 6.83. Found: C, 70.07; H, 7.35; N, 6.75.

(*E*)- and (*Z*)-*N,N*-dimethyl-2-methyl-3-phenylglycidamides (1h,i) were obtained from benzaldehyde and *N,N*-dimethyl-2-chloropropionamide[19] in 49% yield (60% *E* and 40% *Z*). The two isomers were separated by preparative thin-layer chromatography on silica gel using 3:1 benzene–ethyl acetate as eluent. The *Z* isomer **1i** was recrystallized from benzene–hexane: mp 98–100 °C; NMR ($CDCl_3$) δ 1.69 (s, 3 H), 2.70 (s, 3 H), 2.85 (s, 3 H), 3.93 (s, 1 H), 7.26 (s, 5 H); IR

(KBr) 1645 cm^{-1}. Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.31; H, 7.45; N, 6.45.

The *E* isomer **1h** was obtained as an oil: NMR ($CDCl_3$) δ 1.30 (s, 3 H), 2.98 (s, 3 H), 3.17 (s, 3 H), 4.17 (s, 1 H), 7.36 (s, 5 H); IR (film) 1650 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.97; H, 7.35; N, 6.54.

Epoxidation of (*E*)-*N*,*N*-Diphenylcinnamamide. The following procedure was also used in the preparation of **1a:** 85% *m*-chloroperbenzoic acid (1.31 g, 6.5 mmol) in methylene chloride (30 mL) was added to (*E*)-*N*,*N*-diphenylcinnamamide[20] (5.0 mmol, 1.50 g) in methylene chloride (30 mL). The reaction was allowed to reflux for 56 h before workup by extraction with saturated sodium sulfite followed by repeated extractions with 5% sodium bicarbonate. Evaporation of the methylene chloride gave a residue which was subjected to column chromatography on silica gel eluting with benzene and chloroform, affording **1a** as a solid. Recrystallization from ethanol gave pure **1a,** mp 110–111 °C. The NMR spectrum of this material was identical with that of **1a** obtained in the Darzens condensation described above. The mixture melting point with the Darzens material was not depressed.

Reaction of 1a with Boron Trifluoride Etherate. An excess of boron trifluoride etherate (15 mL, 0.12 mol) was added to a solution of **1a** (1.40 g, 4.4 mmol) in anhydrous benzene (50 mL) under nitrogen, and the mixture was refluxed for 8 h. After cooling to room temperature the benzene solution was washed with 5% NaCl. The benzene layer was separated, dried (Na_2SO_4), and concentrated under reduced pressure to give the quinolinone product **2a** (1.21 g, 3.8 mmol, 87%), mp 225–228 °C. An analytical sample was obtained by recrystallization from 1:1 chloroform–petroleum ether: mp 230–231 °C; NMR ($CDCl_3$) δ 3.91 (d, 1 H, J = 1.5 Hz, exchangable with D_2O), 4.36 (d, 1 H, J = 14 Hz), 4.81 (doublet of doublets, 1 H, J = 14, 1.5 Hz), 6.50–7.85 (m, 14 H); IR (KBr) 3450, 1670 cm^{-1}; λ_{max} (EtOH) 252 nm (ϵ 10 000). Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.51; N, 4.44. Found: C, 80.07; H, 5.44; N, 4.44.

Acetate 2b was obtained by treating **2a** (0.12 g, 0.38 mmol) with acetic anhydride (3 mL) and pyridine (3 mL). The mixture was kept overnight at room temperature. The excess pyridine and acetic anhydride were evaporated under reduced pressure, and water (2 mL) was added to the residual oil. This resulted in the formation of a white solid (0.102 g, 75%), mp 151–153 °C. Recrystallization from ethanol gave an analytical sample: mp 156–157 °C; NMR ($CDCl_3$) δ 1.92 (s, 3 H), 4.59 (d, 1 H, J = 13 Hz), 5.93 (d, 1 H, J = 13 Hz), 6.30–7.60 (m, 14 H); IR (KBr) 1700, 1750 cm^{-1}. Anal. Calcd for $C_{23}H_{19}NO_3$: C, 77.37; H, 5.32; N, 3.93. Found: C, 77.60; H, 5.47; N, 3.85.

Tosylate 2c was prepared in the following manner. A solution of *p*-toluenesulfonyl chloride (1.81 g) in anhydrous benzene (20 mL) was added to a solution of **2a** (3.00 g) in benzene (120 mL). In a separate flask sodium hydride (2.28 g of a 57% dispersion in mineral oil) was washed with hexane (2 × 25 mL) and benzene (20 mL) was added. This NaH–benzene suspension was then added to the mixture of **2a** and *p*-toluenesulfonyl chloride. After stirring for 80 min at room temperature, the mixture was filtered through a scintered glass funnel and the benzene layer was concentrated to give a solid (4.02 g, 90%), mp 186–189 °C. This was recrystallized from ethanol to give an analytical sample: mp 190–192 °C; NMR ($CDCl_3$) δ 2.28 (s, 3 H), 4.54 (d, 1 H, J = 7 Hz), 5.33 (d, 1 H, J = 7 Hz), 6.20–6.50 (m, 1 H), 6.80–7.70 (m, 17 H); IR (KBr) 1705 cm^{-1}. Anal. Calcd for $C_{28}H_{23}NO_4S$: C, 71.62; H, 4.90; N, 2.98; S, 6.82. Found: C, 71.74; H, 4.95; N, 2.78; S, 6.60.

Conversion of Acetate 2b to 1,2-Dihydro-1,4-diphenyl-2-quinolone (3). 2b (1.20 g, 3.8 mmol) was placed in a short-path distillation flask and heated under nitrogen for 4 h at 240 °C. A liquid distilled out of the flask, leaving a residue that solidified on cooling. The resulting solid was washed with a 1:1 mixture of ether and petroleum ether (50 mL) to give impure crystals, mp 110–120 °C. Recrystallization from ether gave pure **3** (0.752 g, 2.5 mmol, 67%): mp 150–152 °C; NMR ($CDCl_3$) δ 6.85–7.70 (m, 13 H), 6.60–6.80 (m, 2 H); IR (KBr) 1655 cm^{-1}; UV λ_{max} (EtOH) 225 nm (ϵ 62 000), 280 (20 000), 330 (11 900). Anal. Calcd for $C_{21}H_{15}NO$: C, 84.84; H, 5.05; N, 4.71. Found: C, 84.89; H, 5.10; N, 4.84. This material was found to be identical (mixture melting point and IR spectra) with authentic **3** prepared as described below.

Conversion of Tosylate 2c to Quinolone 3. 2c (0.500 g, 1.1 mmol) in absolute ethanol (100 mL) was treated with a solution of sodium acetate (4.49 g, 54 mmol) in absolute ethanol (70 mL). This was refluxed for 48 h. The ethanol was evaporated under reduced pressure, and the residue was treated with water (25 mL) and benzene (50 mL). The benzene layer was separated, and the aqueous solution was extracted again with benzene (2 × 50 mL). The combined benzene extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give an oil. Addition of ether resulted in formation of a solid (0.320 g). Recrystallization from a 1:1 mixture of ether and petroleum ether gave pure **3:** mp 150–152 °C; NMR ($CDCl_3$) δ 6.85–7.70 (m, 13 H), 6.60–6.80 (m, 2 H); IR (KBr) 1655 cm^{-1}; UV λ_{max} (EtOH) 225 nm (ϵ 64 000), 280 (21 600), 330 (13 500). The mixture melting point with authentic **3,** prepared as described below, was not depressed. The IR spectra of both samples were identical.

***N*,*N*-Diphenyl-3-phenylpropiolamide (4) and Its Conversion to Quinolone 3.** To a mixture of *N*,*N*-diphenylamine (1.35 g, 8.0 mmol) and pyridine (0.63 g, 8.0 mmol) in anhydrous ether (70 mL) was added dropwise at 0 °C under nitrogen atmosphere phenylpropiolyl chloride[21] (1.29 g, 7.9 mmol) in ether (10 mL) over a period of 1.5 h. The reaction was maintained at 0 °C for an additional 2 h, followed by 1 h at room temperature. Water (10 mL) and ether (50 mL) were added. The ether layer was separated, and the aqueous layer was extracted again with ether (50 mL). The combined ether layers were dried (Na_2SO_4) and concentrated under reduced pressure to give a yellow solid (2.20 g, 93%), mp 136–138 °C. Recrystallization from ether and petroleum ether gave an analytical sample of **4** as colorless prisms: mp 141–142 °C; NMR ($CDCl_3$) δ 7.20 (s) and 7.35 (s) superimposed on a multiplet between δ 7.00 and 7.55; IR (KBr) 2220, 1640 cm^{-1}. Anal. Calcd for $C_{21}H_{15}NO$: C, 84.84; H, 5.05; N, 4.71. Found: C, 84.72; H, 5.25; N, 4.46.

An excess of boron trifluoride etherate (10 mL, 0.80 mmol) was added to a solution of **4** (0.500 g, 1.7 mmol) in anhydrous benzene (50 mL) under a nitrogen atmosphere, and the solution was refluxed for 36 h. It was then washed with a 5% NaCl solution, and the benzene layer was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting oil was purified by column chromatography on silica gel, eluting with petroleum ether followed by a mixture of petroleum ether and ether (1:1), to obtain the product. This was recrystallized from ether to give pure **3** (0.260 g, 52%), mp 150–152 °C.

Rearrangement of 1b. The same procedure used with **1a** was followed. NMR analysis of the crude reaction mixture indicated the presence of only the *Z* isomer of 1,4-diphenyl-3-hydroxy-2(1*H*)-quinolinone (**2d**). Recrystallization from benzene–hexane gave pure (*Z*)-quinolinone (75%): mp 134–136 °C; NMR ($CDCl_3$) δ 3.68 (s, 1 H), 4.50 (d, 1 H, J = 7 Hz), 4.82 (d, 1 H, J = 7 Hz), 6.50–7.70, (m, 14 H); IR (KBr) 3450, 1680 cm^{-1}. Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.51; N, 4.44. Found: C, 79.73; H, 5.54; N, 4.19.

Tosylate 2e was prepared using the same procedure described earlier for the preparation of tosylate **2c.** The product was purified by preparative thin-layer chromatography on silica gel, eluting with absolute ethanol in benzene. An analytical sample was obtained by recrystallization from benzene: mp 171–172 °C; NMR ($CDCl_3$) δ 2.38 (s, 3 H), 4.66 (d, 1 H, J = 6 Hz), 5.63 (d, 1 H, J = 6 Hz), 6.35–6.65 (m, 1 H), 6.90–7.55 (m, 15 H), 7.84 (d, 2 H, J = 9 Hz); IR (KBr) 1700 cm^{-1}. Anal. Calcd for $C_{28}H_{23}NO_4S$: C, 71.62; H, 4.90; N, 2.98; S, 6.82. Found: C, 71.88; H, 5.08; N, 2.80; S, 6.68.

Conversion of Tosylate 2e to Quinolone 3. Tosylate **2e** (50 mg) was dissolved in benzene (0.5 mL), and 4 mL of a solution of sodium acetate (4.1 g) in 95% ethanol (100 mL) was added. The mixture was allowed to reflux for 1 h, at which point TLC analysis indicated complete conversion to quinolone **3.** Workup in the usual way followed by recrystallization from ether and hexane gave pure **3,** mp 151–153 °C. The mixture melting point with authentic **3** was not depressed. The IR spectrum was identical with that of authentic **3.**

Using the same reaction conditions the conversion of tosylate **2c** to **3** was less than 20% complete after refluxing for a period of 1 h.

Rearrangement of 1c. The procedure used with **1a** was followed with the exception that the reaction was complete within 4 h at reflux in benzene. NMR analysis of the crude reaction mixture indicated that it contained **2f, 2h,** and **5a** in a ratio of 6:2.5:1.5. The crude oil was treated with ether to give a solid which was recrystallized from ethanol to give pure **2f** (50%): mp 179–180 °C; NMR ($CDCl_3$) δ 1.70 (s, 3 H), 3.75 (d, 1 H, J = 2 Hz, exchangeable with D_2O), 4.87 (d, 1 H, J = 2 Hz), 6.70–7.80 (m, 14 H); IR (KBr) 3450, 1675 cm^{-1}; UV λ_{max} (EtOH) 258 nm (ϵ 16 000). Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.20; H, 6.08; N, 4.22.

A second compound, **5a,** was isolated as a solid from the mother liquors obtained from recrystallization of **2f.** This material was recrystallized from ethanol to give pure **5a** (10%): mp 155–156 °C; NMR ($CDCl_3$) δ 4.10 (broad s, 1 H), 5.05 (s, 1 H), 5.15 (s, 1 H), 5.25 (s, 1 H), 7.10–7.30 (m, 15 H); IR (KBr) 3440, 1660, 920 cm^{-1}; UV λ_{max} (EtOH) 238 nm (ϵ 10 100). Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.47; H, 5.59; N, 4.24.

2h was isolated by subjecting some of the material obtained from the crude reaction mixture to preparative thin-layer chromatography on silica gel, eluting with 2% ethanol in benzene (**2h** ran just below the other quinolinone **2f**). The **2h** isolated in this way was identical with the major product obtained in the reaction of **1d** with boron trifluoride

etherate as described below.

Acetate 2g: mp 190–191 °C; NMR ($CDCl_3$) δ 1.81 (s, 3 H), 1.88 (s, 3 H), 6.17 (s, 1 H), 6.35–7.60 (m, 14 H); IR (KBr) 1750, 1700 cm^{-1}; UV λ_{max} (EtOH) 255 nm (ε 13 000). Anal. Calcd for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.69; N, 3.77. Found: C, 77.39; H, 5.49; N, 3.57.

Acetate 5b: mp 116–117 °C; NMR ($CDCl_3$) δ 2.08 (s, 3 H), 5.51 and 5.55 (s, 2 H), 6.01 (s, 1 H), 7.00–7.25 (m, 15 H); IR (KBr) 1740, 1685, 930 cm^{-1}; UV λ_{max} (EtOH) 238 nm (ε 22 000). Anal. Calcd for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.69; N, 3.77. Found: C, 77.61; H, 5.96; N, 3.57.

Rearrangement of 1d. This was carried out employing the same procedure used with **1c.** NMR analysis of the crude reaction mixture indicated the presence of **2f, 2h,** and **5a** in a ratio of 1:8:1. The major product, **2h,** was obtained by column chromatography on silica gel, eluting initially with benzene followed by 0.5% ethanol in benzene. Recrystallization from hexane and benzene gave an analytical sample: mp 150–151 °C; NMR ($CDCl_3$) δ 2.02 (s, 3 H), 3.98 (d, 1 H, J = 3.5 Hz, exchangeable with D_2O), 4.52 (d, 1 H, J = 3.5 Hz), 6.50–7.65 (m, 14 H); IR (KBr) 3470, 1685 cm^{-1}; UV λ_{max} (EtOH) 246 nm (ε 10 000). Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.50; H, 5.79; N, 4.22.

Acetate 2i: mp 146–147 °C; NMR ($CDCl_3$) δ 1.87 (s, 3 H), 2.35 (s, 3 H), 5.77 (s, 1 H), 6.45–7.65 (m, 14 H); IR (KBr) 1755, 1710 cm^{-1}; UV λ_{max} 246 nm (ε 10 000). Anal. Calcd for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.85; H, 5.78; N, 3.81.

Rearrangement of 1e. The same conditions were followed that were employed with **1a** with the exception that the reaction was refluxed for 5 h in benzene. Using the same workup procedure, crude **5c** was obtained in 77% yield, mp 120–122 °C. Recrystallization from ether and petroleum ether gave an analytical sample: mp 122–124 °C; NMR ($CDCl_3$) δ 0.85–1.30 (overlapping triplets, 6 H), 3.90 (m, 4 H), 5.30–5.65 (m, 3 H), 7.15–7.65 (m, 5 H); IR (KBr) 1665, 895 cm^{-1}; UV λ_{max} (EtOH) 240 nm (ε 11 200). Anal. Calcd for $C_{14}H_{18}NO_2BF_2$: C, 59.81; H, 6.40; N, 4.98; B, 3.85; F, 13.4. Found: C, 59.86; H, 6.54; N, 5.06; B, 3.8; F, 12.8.

The hydrolysis of **5c** (1.00 g, 3.5 mmol) was carried out in 95% ethanol (80 mL) using NaOH (0.30 g, 7.5 mmol). After standing overnight at room temperature, the base was neutralized with 10% HCl and the ethanol was removed under reduced pressure. The residue was treated with water and extracted with ether, and the combined ether extracts were dried (Na_2SO_4) and concentrated to give an oil (0.830 g) which was distilled under reduced pressure [bath temperature, 175 °C (0.25 mm)]. **5d** was obtained as a colorless oil that solidified in the receiver, mp 31–32 °C. Recrystallization from ether gave an analytical sample: mp 31–32 °C; NMR ($CDCl_3$) δ 1.03 (t, 6 H, J = 7.0 Hz), 2.80–3.70 (m, 4 H), 4.32 (d, 1 H, J = 6.0 Hz), 4.85 (d, 1 H, J = 6.0 Hz), 5.15 (s, 1 H), 5.34 (s, 1 H), 7.00–7.60 (m, 5 H); IR (KBr) 3400, 1640, 915 cm^{-1}; UV λ_{max} (EtOH) 236 nm (ε 10 700). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.10; H, 8.15; N, 6.00. Found: C, 72.27; H, 7.94; N, 5.87.

Acetate 5e: $n^{25}D$ 1.5233; NMR ($CDCl_3$) δ 0.90–1.30 (m, 6 H), 2.15 (s, 3 H), 3.95–3.75 (m, 4 H), 5.48 (s, 1 H), 5.63 (s, 1 H), 6.12 (s, 1 H), 7.20–7.50 (m, 5 H); IR (film) 1740, 1660, 915 cm^{-1}; UV λ_{max} (EtOH) 235 nm (ε 10 000). Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.81; H, 7.63; N, 5.09. Found: C, 69.69; H, 7.87; N, 4.87.

Rearrangement of 1f. The glycidamide **1f** (0.50 g, 2.4 mmol) was suspended in anhydrous methylene chloride (25 mL) at room temperature, and boron trifluoride etherate (0.35 mL, 2.8 mmol) was added with stirring over a period of 1 min. The reaction was stirred for 1 h at room temperature before it was poured into a mixture of ether (100 mL) and water (100 mL). The layers were separated, and the water was reextracted with ether (100 mL). The combined ether extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give a yellow oil (0.45 g). Examination of the NMR spectrum of this material indicated that it was essentially pure butenamide **5f.** An analytical sample was obtained by column chromatography on silica gel, eluting with 20% ethyl acetate in benzene, followed by short-path distillation under reduced pressure to give **5f** as a colorless oil: $n^{23}D$ 1.5417; NMR ($CDCl_3$) δ 2.78 (s, 3 H), 2.95 (s, 3 H), 4.41 (broad s, 1 H), 5.03 (broad s, 1 H), 5.20 (s, 1 H), 5.42 (s, 1 H), 7.15–7.65 (m, 5 H); IR (film) 3400, 1660, 1640, 910 cm^{-1}. Anal. Calcd for $C_{12}H_{15}O_2N$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.13; H, 7.56; N, 6.90.

Rearrangement of 1g was carried out in benzene solvent using the conditions described for **1c.** Analysis of the NMR spectrum of the crude reaction mixture indicated the presence of 1,3-dimethyl-4-phenyl-3-hydroxy-2(1*H*)-quinolinone and **6** in a ratio of 3:1. A small amount of unidentified material (~2%) was also obtained. The latter had low solubility in chloroform and melted with decomposition at 240–245 °C. The mixture was separated by column chromatography on silica gel, eluting with 1% ethanol in benzene. **6** was eluted first from the column. It was recrystallized from ethanol and hexane: mp 135–136 °C; NMR ($CDCl_3$) δ 1.24 (s, 3 H), 3.16 (s, 3 H), 3.80 (broad s, 1 H), 4.15 (s, 1 H), 6.75–7.50 (m, 15 H); IR (KBr) 3360, 1610 (broad) cm^{-1}. Anal. Calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.05. Found: C, 79.89; H, 6.80; N, 3.88.

Further elution of the silica gel column gave the quinolinone, which was also recrystallized from ethanol and hexane: mp 159–160 °C; NMR ($CDCl_3$) δ 1.41 (s, 3 H), 3.47 (s, 3 H), 3.60 (s, 1 H, exchangeable with D_2O), 4.11 (s, 1 H), 6.85–7.45 (m, 9 H); IR (KBr) 3420, 1670 cm^{-1}. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.31; H, 6.45; N, 5.32.

Rearrangement of 1i and 1h. (*Z*)-Glycidamide **1i** (1.00 g, 4.86 mmol) was suspended in anhydrous methylene chloride (45 mL) under a nitrogen atmosphere, and boron trifluoride etherate (1.4 mL) was added with stirring over a period of 1 min. The reaction was allowed to stir at room temperature for 1.5 h before quenching by pouring into a mixture of water (200 mL) and ether (200 mL). The organic layer was separated, and the water layer was reextracted with ether (100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give a solid which by NMR analysis proved to be a mixture of fluorohydrin **7a** along with its BF_2 derivative **7b.** An identical result was obtained in the rearrangement of (*E*)-glycidamide **1h** carried out in a separate experiment using the same reaction conditions. This solid was washed with chloroform, and the remaining residue (0.50 g) was crystallized from acetone to give pure **7b:** mp 139–141 °C; NMR ($[CD_3]_2CO$) δ 1.55 (d, 3 H, J = 2 Hz), 3.35 (s, 3 H), 3.67 (s, 3 H), 5.95 (d, 1 H, J = 45 Hz), 7.30–7.80 (m, 5 H); IR (KBr) 1680 cm^{-1}. Anal. Calcd for $C_{12}H_{15}O_2NF_3B$: C, 52.78; H, 5.54; N, 5.13. Found: C, 52.37; H, 5.78; N, 4.92.

The chloroform washings were combined and evaporated to give a residue (0.40 g) which was purified by column chromatography on silica gel, eluting with 10% ethyl acetate in benzene, followed by crystallization from benzene–hexane to give **7a:** mp 87–89 °C; NMR ($CDCl_3$) δ 1.45 (d, 3 H, J = 2 Hz), 3.12 (s, 6 H), 4.50 (s, 1 H), 5.70 (d, 1 H, J = 45 Hz), 7.30 (s, 5 H); IR (KBr) 3410, 1620 cm^{-1}. Anal. Calcd for $C_{12}H_{16}NO_2F$: C, 64.00; H, 7.11; N, 6.22; F, 8.44. Found: C, 63.99; H, 7.23; N, 6.03; F, 8.22.

Acetate 7c was prepared by dissolving fluorohydrin **7a** (0.10 g) in acetyl chloride (3 mL) followed by stirring for 1.5 h at room temperature. The reaction was poured into ether (50 mL) and water (100 mL), and the water layer was separated and extracted with ether (50 mL). The combined ether layers were dried (Na_2SO_4) and concentrated to give a yellow oil (92 mg), which after standing at 5 °C for 4 days solidified. Crystallization from hexane gave an analytical sample: mp 61–63 °C; NMR ($CDCl_3$) δ 1.52 (d, 3 H, J = 1 Hz), 2.10 (s, 3 H), 3.03 (s, 6 H), 5.63 (d, 1 H, J = 45 Hz), 7.37 (s, 5 H); IR (KBr) 1745, 1640 cm^{-1}. Anal. Calcd for $C_{14}H_{18}NO_3F$: C, 62.92; H, 6.74; N, 5.24. Found: C, 62.68; H, 6.68; N, 5.43.

In a separate experiment boron trifluoride etherate (0.50 mL, 4 mmol) was added to **1i** (205 mg, 1.0 mmol) in anhydrous methylene chloride (10 mL), and the solution was allowed to reflux for 3.5 h before quenching by adding water (5 mL). This was refluxed an additional 15 min. The water layer was separated and extracted with methylene chloride (2 × 20 mL). The combined methylene chloride layers were dried (Na_2SO_4) and concentrated to give a mixture that was separated by preparative thin-layer chromatography, eluting with 5% ethanol in benzene. The products were extracted from the silica gel using 5% ethanol in chloroform. The first major band (R_f 0.7) proved to be *N,N*-dimethyl-3-phenyl-3-methylpyruvamide (**8,** 20 mg). An analytical sample was obtained by short-path distillation under reduced pressure: mp 36–38 °C; NMR ($CDCl_3$) δ 1.50 (d, 3 H, J = 7 Hz), 2.53 (s, 3 H), 2.80 (s, 3 H), 4.52 (q, 1 H, J = 7 Hz), 7.27 (s, 5 H); IR (film) 1710, 1645 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.48; H, 7.39; N, 6.82.

The next major band (R_f 0.5) was a 6:4 mixture of fluorohydrin **7a** and its diastereomer. The NMR spectrum in $CDCl_3$ suggested the following data for this diastereomer: δ 1.62 (d, 3 H, J = 1.5 Hz), 3.01 (s, 6 H), 4.0 (s, 1 H), 5.65 (d, 1 H, J = 45 Hz), 7.33 (s, 5 H).

In a third experiment boron trifluoride etherate (0.50 mL, 4 mmol) was added to **1i** (205 mg, 1.0 mmol) in anhydrous chloroform (10 mL), and the solution was allowed to reflux for 6 h. Water (5 mL) was added and refluxing was continued for 15 min. Workup in the usual way, including silica gel preparative thin-layer chromatography, eluting with 5% ethanol in benzene, gave in the first band pyruvamide **8** (40 mg, 19%) followed by a smaller band consisting primarily of *N,N*-dimethyl-2-phenylacetoacetamide (**9,** ~5%). This was converted to 3-methyl-4-phenyl-3-pyrazolin-5-one (mp 208–210 °C) using hydrazine hydrate in ethanol. The mixture melting point with an authentic sample[4a] was not depressed.

In a fourth experiment boron trifluoride etherate (0.25 mL, 2 mmol)

was added to **1i** (410 mg, 2.0 mmol) in $CHCl_3$ (5 mL), and the solution was allowed to reflux for 6 h. Workup in the usual way followed by preparative thin-layer chromatography gave pyruvamide **8** (15%) in the first band followed by the mixture of fluorohydrin diastereomers (10%) and finally acetoacetamide **9** (28%): NMR ($CDCl_3$) δ 2.17 (s, 3 H), 2.88 (s, 3 H), 2.97 (s, 3 H), 4.84 (s, 1 H), 7.30 (broad s, 5 H).

3-Methyl-4-phenyl-3-pyrazolin-5-one was prepared in the usual way.[4a,b] Preparative TLC, eluting with ethyl acetate, and finally recrystallization from ethanol–water gave the pure pyrazolone, mp 210–211 °C. The mixture melting point with authentic pyrazolone[4a] was not depressed, and the IR spectrum was identical with that of the authentic material.

Rearrangement of 7a. Boron trifluoride etherate (0.25 mL) was added to **7a** (113 mg) in anhydrous methylene chloride (5 mL), and the solution was allowed to reflux for 3 h before quenching with water (5 mL). This was then refluxed for 15 min and worked up in the usual way. Purification by preparative TLC followed by NMR analysis of the separated products indicated the presence of pyruvamide **8** (10% yield), acetoacetamide **9** (4%), and a 55:45 mixture (35%) of fluorohydrin **7a** together with its diastereomer.

Acknowledgment. This research was supported in part by a Research Corporation Frederick Gardner Cottrell Grant. We thank Professors Carl Johnson and Morton Raban of the Chemistry Department at Wayne State University for the use of their 60-MHz NMR facilities.

Registry No.—**1a,** 64754-77-4; **1b,** 64754-78-5; **1c,** 64754-79-6; **1d,** 64754-80-9; **1e,** 64754-81-0; **1f,** 64754-82-1; **1g,** 64754-83-2; **1h,** 64754-84-3; **1i,** 64754-85-4; **2a,** 64754-86-5; **2b,** 64754-87-6; **2c,** 64754-88-7; **2d,** 64761-01-9; **2e,** 64761-02-0; **2f,** 64761-03-1; **2g,** 64761-04-2; **2h,** 64761-05-3; **2i,** 64761-96-4; **3,** 32870-22-7; **4,** 64761-0705; **5a,** 64761-08-6; **5b,** 64761-09-7; **5c,** 64761-10-0; **5d,** 64761-11-1; **5e,** 64761-12-2; **5f,** 64754-59-2; **6,** 64754-60-5; **7a,** 64754-62-7; **7a** isomer, 64754-61-6; **7b,** 64754-64-8; **7c,** 64771-36-4; **8,** 64754-64-9; **9,** 64771-37-5; *N,N*-diphenyl-2-chloroacetamide, 5428-43-3; benzaldehyde, 100-52-7; acetophenone, 98-86-2; *N*-methyl-*N*-phenyl-2-chloropropionamide, 64754-68-3; *N,N*-dimethyl-2-chloroacetamide, 2675-89-0; *N,N*-dimethyl-2-chloropropionamide, 10397-68-9; (*E*)-*N,N*-diphenylcinnamamide, 64754-65-0; boron trifluoride etherate, 109-63-7; *p*-toluenesulfonyl chloride, 98-59-9; *N,N*-diphenylamine, 122-39-4; phenylpropiolyl chloride, 7299-58-3; (*E*)-3,4-dihydro-1,3-dimethyl-3-hydroxy-4-phenyl-2(1*H*)-quinolinone, 64754-66-1; 3-methyl-4-phenyl-3-pyrazolin-5-one, 64754-67-2; *n*-methylaniline, 100-61-8; 2-chloropropionyl chloride, 7623-09-8; hydrazine, 302-01-2.

References and Notes

(1) Taken in part from the M. S. Thesis of F. Jimenez, University of Detroit, 1975.
(2) (a, H. O. House, *J. Am. Chem. Soc.*, **76,** 1235 (1954); see also (b) H. O. House and D. J. Reif, *ibid.*, **77,** 6525 (1955), (c) *ibid.*, **79,** 649 (1957), (d) H. O. House, D. J. Reif, and R. L. Wasson, *ibid.*, **79,** 2490 (1957), and (e) H. O. House and G. D. Ryerson, *ibid.*, **83,** 979 (1961).
(3) (a) S. P. Singh and J. Kagan, *J. Am. Chem. Soc.*, **91,** 6198 (1969); (b) J. Kagan, D. A. Agdeppa, Jr., S. P. Singh, D. A. Mayers, C. Boyajian, C. Poorker, and B. E. Firth, *ibid.*, **98,** 4581 (1976).
(4) (a) J. Wemple, *J. Am. Chem. Soc.*, **92,** 6694 (1970); (b) D. J. Dagli, R. A. Gorski, and J. Wemple, *J. Org. Chem.*, **40,** 1741 (1975); (c) R. A. Gorski, D. J. Dagli, and J. Wemple, *J. Am. Chem. Soc.*, **98,** 4588 (1976).
(5) A. C. Brouwer, L. Thijs, and B. Zwanenburg, *Tetrahedron Lett.*, 807 (1975).
(6) (a) J. M. Domagala, R. D. Bach, and J. Wemple, *J. Am. Chem. Soc.*, **98,** 1975 (1976); (b) R. D. Bach and J. M. Domagala, *Tetrahedron Lett.*, 4025 (1976).
(7) K. Pfoertner and K. Bernauer, *Helv. Chim. Acta*, **51,** 1787 (1968).
(8) F. F. Blicke and J. A. Faust, *J. Am. Chem. Soc.*, **76,** 3156 (1954).
(9) (a) C. C. Tung, A. J. Speziale, and H. W. Frazier, *J. Org. Chem.*, **28,** 1514 (1963); (b) C. C. Tung and A. J. Speziale, *ibid.*, **28,** 2009 (1963); see also (c) S. O. Chan and E. J. Wells, *Can. J. Chem.*, **45,** 2123 (1967) and (d) C. C. Tung and A. J. Speziale, *Chem. Ind. (London)*, 1985 (1963).
(10) H. Dahn, M. Ballenegger, and H. P. Schlunke, *Chimia*, **18,** 59 (1964).
(11) A. Speziale and H. W. Frazier, *J. Org. Chem.*, **26,** 3176 (1961).
(12) Monoperphthalic acid has also been used in the synthesis of glycidamides: K. W. Wheeler, M. G. VanCampen, Jr., and R. S. Shelton, *J. Org. Chem.*, **25,** 1021 (1960).
(13) The use of sulfuric acid[14] in this reaction proved less satisfactory.
(14) Y. S. Abradushkin and I. V. Aleksandrov, USSR Patent 287 020; *Chem. Abstr.*, **75,** 35800 (1971).
(15) H. W. Smith and H. Rapoport, *J. Am. Chem. Soc.*, **91,** 6083 (1969).
(16) (a) H. O. House, *J. Am. Chem. Soc.*, **78,** 2298 (1956); (b) *J. Org. Chem.*, **21,** 1306 (1956).
(17) E. B. Kelsey, *J. Am. Chem. Soc.*, **46,** 1694 (1924).
(18) W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, **21,** 148 (1915).
(19) M. Saunders and R. W. Murray, *Tetrahedron*, **11,** 1 (1960).
(20) A. Bernthsen, *Chem. Ber.*, **20,** 1554 (1887).
(21) G. I. Poos, J. Kleis, R. R. Wittekind, and J. D. Rosenau, *J. Org. Chem.*, **26,** 4898 (1961).

New Synthesis of a 9-Substituted Adenine

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Received May 19, 1977

A new sequence of reactions, utilizing as the key intermediate 7-amino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine, has been employed to allow the preparation of a 9-substituted adenine from 4,5,6-triaminopyrimidine. Specifically, 9-(2-chloro-6-fluorobenzyl)adenine was readily prepared, uncontaminated with other positional isomers in a series of mild transformations. The method holds promise as a route to a wide variety of specifically substituted adenine derivatives.

The biological activity of adenine nucleosides and nucleotides[1,2] has prompted vigorous chemical activity directed toward the synthesis of specifically substituted adenine derivatives.[3,4] Specifically, adenine derivatives substituted at position 9 have received considerable attention.[5–8] We describe in this paper a new approach to the synthesis of 9-substituted adenine derivatives which allows the unambiguous introduction of the 9 substituent through a sequence of mild, efficient reactions.

Taylor et al.[8] have reported that 9-substituted adenines (**2**) may be prepared via reductive cleavage and subsequent cyclization of 7-amidofurazano[3,4-*d*]pyrimidines (**1**). Although a wide variety of adenine derivatives was prepared, the authors were unable to effect the conversion of 5-unsubstituted 7-amidofurazano[3,4-*d*]pyrimidines (**1**, R = H) to 2-unsubstituted adenines (**2**, R = H) due to the hydrolytic instability of the former compounds. We wish to report that the highly active coccidiostat 9-(2-chloro-6-fluorobenzyl)adenine[9] (**9**), a derivative possessing a hydrogen in the 2 position, may be readily prepared without isomer contamination (see Scheme I).

Treatment of 4,5,6-triaminopyrimidine (**3**) with thionyl chloride afforded 7-amino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (**4**)[10] in 79% yield. Nucleophilic displacement of the 7-amino group[11] of **4** was effected by reaction at 100 °C with 2-chloro-6-fluorobenzylamine (**5**) to provide **6** in 93% yield. Alternatively, **6** could be prepared from **4** in 25% yield by treatment of **4** with ammonia and 2-chloro-6-fluorobenzyl

0022-3263/78/1943-0960$01.00/0