result was found when the reaction was run with 2 equiv of benzoic acid.

Acetylation of Kojic Acid with H_3PO_4.—Woods' procedure[12] was followed exactly and gave **12** (20% yield after recrystallization from MeOH), mol wt 184 (mass spectrum), mp 135–137° (lit.[1] mp 136–137°), positive $FeCl_3$ test.

Hydrolysis of Acetylkojic Acid (12).—A solution of 200 mg of **12** in 20 ml of H_2O was refluxed for 24 hr. Nmr of the product showed it to be a mixture of **1** (43%) and **12** (57%).

Diacetylkojic Acid (7).—A solution of 2 g of **1** and 2.8 g of AcCl in 50 ml of $CHCl_3$ was refluxed for 8 hr. The product was recrystallized from MeOH to yield **7** in 88% yield, mp 101–102° (lit.[1] mp 102°), negative $FeCl_3$ test.

Acetylation of Kojic Acid with HCl.—Through a refluxing solution of 5 g of **1** in 25 ml of AcOH, HCl was bubbled for 4 hr. After concentration under vacuum, the product was recrystallized from EtOH to yield 4.7 g of **12**, mp 135–136°, identical with the sample prepared above.

Treatment of Kojic Acid with Diethyl Oxalate and CF_3COOH.—Woods' procedure[16] was followed exactly. After recrystallization from EtOH, the starting material was recovered in 26% yield, mp 155–157°.

Treatment of Kojic Acid with Zn and Ac_2O.—The above material (1.6 g) was treated with 2.6 g of Zn dust and 9 ml of Ac_2O.[16] After standing at room temperature for 48 hr and work-up, there was obtained 0.380 g of **7**, mp 102–103°.

Treatment of 5-*O*-Methylkojic Acid (13) with Diethyl Oxalate and Acetylation Reaction.—Woods' procedure[16] was followed using 0.935 g of **13**.[23] After recrystallization from EtOH, the starting material was recovered in 50% yield, mp 162–164°. A portion (0.366 g) was treated with 3 g of Zn dust and 10 ml of Ac_2O at room temperature for 18 hr. After work-up, there was obtained 0.193 g of **14**, mp 124–125°.

Formylation Reactions.—The published procedure[18] was applied to 5 g of **1**, 3 g of **13**, and 1 g of **15** to yield 1.62, 0.95, and 0.61 g of product, respectively. These were found to be unreacted starting materials by nmr and melting point determinations.

$NaBH_4$ Reduction of Kojic Acid.—The published procedure was repeated with 2 g of **1**, substituting $NaBH_4$ for KBH_4. The solid (0.8 g) obtained after work-up and recrystallization from EtOH was identical with the starting material (nmr and melting point).

Registry No.—**1**, 501-30-4; **2**, 33777-41-2; **3**, 33777-42-3; **4**, 25552-08-3; **5**, 644-46-2; **6**, 33777-43-4; **7**, 26209-93-8; **8**, 33777-44-5; **9**, 33886-26-9; **10**, 33777-45-6; **11**, 33777-46-7; **12**, 25552-08-3; **13**, 6269-25-6; **14**, 33777-49-0; **15**, 7559-81-1; **16**, 33777-51-4.

Acknowledgments.—We are grateful to the National Science Foundation for some financial support of this work and J. K. thanks the Department of Organic Chemistry, University of Geneva, for its hospitality (1971–1972).

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Synthesis of *cis*- and *trans*-3-Chloroazetidinones. II. Direct Acylation of Imines

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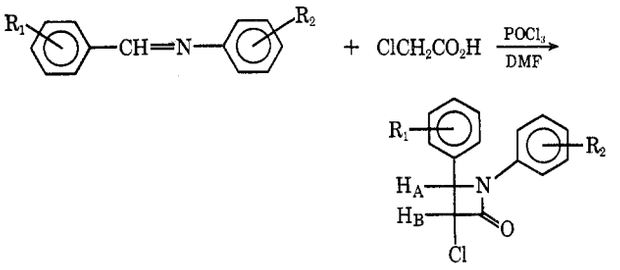
Diaryl-3-halo-2-azetidinones have been prepared by the addition of haloacetic acid and phosphoryl chloride, in dimethylformamide (DMF), to imines,[1] and the authors indicated that single isomers, not mixtures, were obtained. The similarity of the chloroketene reaction with this procedure prompted a more thorough investigation of the haloacetic acid–phosphoryl chloride method.

Examination of the final products from ten reactions (Tables I and II), performed with the haloacetic acid–



phosphoryl chloride conditions,[1] indicated that both cis and trans β-lactams were formed. The coupling constants of vicinal protons in 3-chloro-2-azetidinones, $J(\text{cis}) > J(\text{trans})$, were used to distinguish the isomers.[2]

Since the isomer distribution differed from the original investigation,[1] the reaction was further examined in order to define the disparity. The nearly equal distribution of cis and trans isomers suggested that isomerization may have occurred. No isomerization occurred in refluxing DMF with either *cis*- or *trans*-**1**. However, in the presence of phosphoryl chloride and chloroacetic acid, isomerization was noted. An equilibrium mixture was established within 7 hr, starting from pure *cis*-**1**, and 22 hr from pure *trans*-**1**. This mixture contained 53% *cis*-**1** and 47% *trans*-**1** in both cases. When *cis*-**1** was subjected to these conditions for 2 hr, only 18% *trans*-**1** was formed; however, when *trans*-**1** was refluxed in the reagents for 2 hr, no *cis*-**1** was detected. This small amount of isomerization cannot fully account for the product distribution within the 2-hr reaction time.

Stereochemical evidence was obtained which favored direct acylation of the imine followed by ring closure. Since it is known that acyl chlorides can be formed from carboxylic acids with DMF–phosphoryl chloride,[3] chloroacetyl chloride was added to a solution of benzalaniline in DMF at 80°. The product was **1** (45% cis, 55% trans). No β-lactam was formed at 25°. A ketene mechanism was disfavored since chloroacetyl chloride addition to a DMF solution of benzalaniline and triethylamine at 25° gave only *trans*-**1**. Similar cycloadditions performed in benzene gave only *trans*-**1**.[4]

The proposed intermediate **11** was prepared by the direct acylation of benzalaniline with chloroacetyl chloride. No β-lactam was formed when **11** was stirred in DMF at 25°. However, mixed isomers of **1** (55% cis, 45% trans) were obtained when **11** was added to refluxing DMF. These results compare quite well with the results from the preparative reaction (see Table I). The treatment of **11** with triethylamine in either DMF or benzene at 25° yielded only *trans*-**1**. No β-lactam was observed when **11** was refluxed in benzene. Thus, the possibility of solvent participation, *i.e.*, DMF, cannot be neglected. The zwitterionic intermediate **12**, previously proposed for haloketene

(1) E. Ziegler, T. Wimmer, and H. Mittelbach, *Monatsh. Chem.*, **99**, 2128 (1968).

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(3) H. H. Bosshard and H. Zollinger, *Helv. Chim. Acta*, **42**, 1659 (1959).

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TABLE I

YIELD AND ISOMER DISTRIBUTION OF SOME 3-CHLORO-2-AZETIDINONES

Compd	R_1	R_2	Cis/trans	Mp, °C Cis	Mp, °C Trans	Yield, %
1	H	H	53/47	192[a]	86–87	59
2	*o*-Nitro	H	50/50	*b*	*b*	~1
3	*o*-Nitro	*p*-Methoxy	50/50	148–149	114–116	~1
4	*p*-Nitro	*p*-Methoxy	53/47	134–136	133–134	53
5	*p*-Nitro	H	50/50	170–171	*b*	40
6	*o*-Chloro	H	54/46	*b*	128–130[c]	38
7	*p*-Chloro	*p*-Methoxy	48/52	134–135	97–99	42
8	*p*-Chloro	H	50/50	187–189[a]	102–103	33
9	*o*-Metoxy	H	50/50	106–107	130–131	46
10	*p*-Methoxy	*p*-Methoxy	50/50	162–164	118–119	53

[a] See ref 1. [b] Values could not be obtained for these isomers due to their similar solubility characteristics; ref 5 gave 150–152° for *trans*-**5**. [c] Value obtained from chloroketene cycloaddition product.[2]

additions,[4] would account for the stereospecificity of the base-catalyzed route (pathway B). Recently, it was proposed that direct acylation (such as **11**), rather than *in situ* prepared ketene, is involved when acyl chloride and imine are present with triethylamine.[5] The lack of stereospecificity for pathway A is not completely understood at this time. See Scheme I.

The extremely low yields of **2** and **3** may be due to reaction of the *o*-nitro groups of their corresponding imines or the intermediates (**13** and **14**). These reactions were very complex (tlc indicated at least 13 components).

SCHEME I

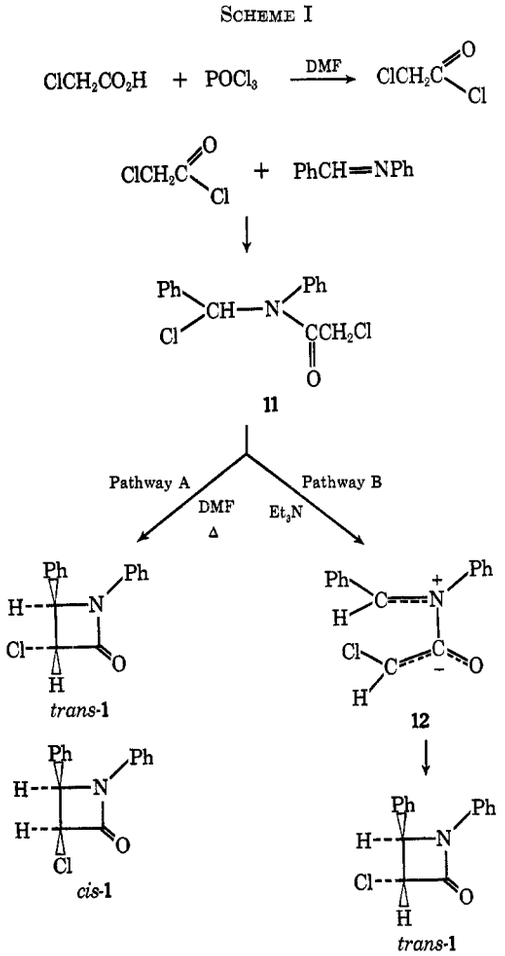
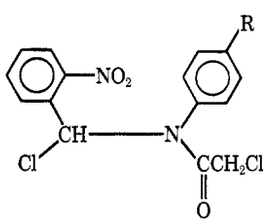


TABLE II

NMR SPECTRAL DATA OF SOME 3-CHLORO-2-AZETIDINONES[a]

	δ_{H_A}, ppm Cis/trans	δ_{H_B}, ppm Cis/trans	J_{AB}, Hz Cis/trans
1	5.42/4.98	5.24/4.58	5.3/2.0
4[b]	5.48/5.13	5.32/4.64	5.5/1.9
5	5.53/5.11	5.34/4.61	5.4/2.0
7[b]	5.35/4.95	5.22/4.57	5.3/1.9
8	5.39/4.99	5.26/4.57	5.4/2.0
9	5.71/5.32	5.25/4.71	5.4/2.0
10	5.32/4.92	5.19/4.57	5.3/1.9

[a] Values are reported relative to internal TMS in $CDCl_3$. [b] See ref 2 for values of **2**, **3**, and **6**.



13, R = OCH_3
14, R = H

When **13** was refluxed in DMF, a complex reaction mixture, containing a trace of **3**, was obtained. Previous investigations[6,7] have shown that cyclization occurred with *o*-nitrophenyl compounds to give substituted isoxazoles.

Experimental Section

Nuclear magnetic resonance (nmr) spectra were recorded on a Varian A-60 spectrometer. Chemical shifts are reported as parts per million (δ) relative to tetramethylsilane. Infrared spectra were recorded on a Beckman IR-5 spectrometer. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected.

All imines used in this study were prepared by direct condensation of the respective benzaldehyde and aniline in ethanol, and were recrystallized. The distilled solvents (Burdick and Jackson Laboratories) were dried: benzene over sodium metal and DMF over molecular sieves type 5A (Linde Co.) followed by elution through an alumina column.

General Preparation of 1,4-Diaryl-3-chloro-2-azetidinones.—To 50 ml of DMF was added 9.1 ml (0.1 mol) of phosphoryl chloride followed by 9.4 g (0.1 mol) of monochloroacetic acid. While this solution stirred, 0.1 mol of imine was added. The solution was heated to reflux for 2 hr (drying tube on condenser), then cooled. The reaction mixture was dissolved in 50 ml of dichloromethane and extracted with 100 ml of water. The

(5) A. K. Bose, G. Spiegelman, and M. S. Manhas, *Tetrahedron Lett.*, 3167 (1971).

(6) I. Tanasescu, C. Anghel, and A. Popescu, *Studia Universitatis Babes-Bolyai, Ser. Chem.*, **9**, 89 (1964).

(7) M. S. Gibson, *Tetrahedron*, **18**, 1377 (1962).

organic layer was dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*. The product mixture, oil or crystalline, was analyzed by nmr for isomer distribution. Purification was achieved on an alumina column eluted with dichloromethane or benzene–hexane (2:3 v/v). This solvent was removed, and the isomers were fractionally crystallized with ethanol. In general, the cis isomers were more insoluble in ethanol. Elemental analyses were consistent with the assigned structures. Yields were reported for the combined isolated isomers.

Isomerization of *cis*- and *trans*-1,4-Diphenyl-3-chloro-2-azetidinone (1).—The *cis*- or *trans*-**1** (5.0 g, 1.9×10^{-2} mol) was dissolved in 50 ml of DMF. To this was added 1.8 ml (1.9×10^{-2} mol) of phosphoryl chloride and 1.8 g (1.9×10^{-2} mol) of monochloroacetic acid. The solution was stirred at reflux and sampled every 2 hr. The 5-ml samples were dissolved in 10 ml of dichloromethane and extracted with 10 ml of water. The organic layer was evaporated and dissolved in chloroform-d_1 for nmr determination of the isomer distribution. The equilibrium isomer mixture was established within 7 hr from the cis isomer, but 22 hr were required for the trans isomer to reach the 53% cis–47% trans relationship.

2-Chloro-*N*-(α-chlorobenzyl)acetanilide (11).—A benzene solution of 30 g (0.16 mol) of benzalaniline was cooled to 0° with an ice bath. To this was added, dropwise, 18.7 g (0.16 mol) of chloroacetyl chloride over 2 hr while maintaining 0°. Moisture will cause hydrolysis of **11**, and chloroacetanilide may precipitate if the reaction is not performed under a dry atmosphere. Recent evidence indicated that adducts such as **11** may be in equilibrium with acyl chloride and imine.[5] The solvent was removed under reduced pressure and a white solid (46.5 g, 96%) was obtained, mp 50–52°. Since the product hydrolyzed readily, it was stored under dry nitrogen. Two characteristic nmr signals (chloroform-d_1) were obtained: nmr δ 3.76 (2 H, s, CH_2Cl), and 7.85 (1 H, s, ClCHN); ir ($CHCl_3$) 1661 cm^{-1} (carbonyl). For comparison, the carbonyl absorbance for chloroacetanilide ($CHCl_3$) was 1681 cm^{-1}.

Anal. Calcd for $C_{15}H_{13}Cl_2NO$: C, 61.2; H, 4.42; N, 4.7. Found: C, 60.7; H, 4.56; N, 5.06.

2-Chloro-*N*-(α-chloro-*o*-nitrobenzyl)-*p*-acetanisidide (13).—The adduct was prepared in a similar manner as **11**. Hydrolysis of **13** did not occur as readily as **11**. A light yellow solid (92%) was recovered: mp 115–117° dec; nmr (chloroform-d_1) δ 3.81 (2 H, s, CH_2Cl), 3.77 (3 H, s, OCH_3), 8.27 (1 H, s, ClCHN); ir ($CHCl_3$) 1686 (carbonyl), 1533 (asymmetrical nitro), and 1352 cm^{-1} (symmetrical nitro).

Anal. Calcd for $C_{16}H_{14}Cl_2N_2O_4$: C, 52.0; H, 3.79; N, 7.6. Found: C, 52.2; H, 3.97; N, 7.7.

Registry No.—**1b**, 27348-77-2; **3a**, 33281-33-3; **3b**, 33281-34-4; **4a**, 33949-24-5; **4b**, 33276-88-9; **5a**, 33949-26-7; **6b**, 33276-92-5; **7a**, 33949-28-9; **7b**, 33276-93-6; **8b**, 33949-30-3; **9a**, 33949-31-4; **9b**, 33276-96-9; **10a**, 33949-33-6; **10b**, 33276-97-0; **11**, 33949-35-8; **13**, 33949-36-9.

The *A* Value of the Deuterioamino Group Determined by the Nuclear Magnetic Resonance Peak Area Method at −93°

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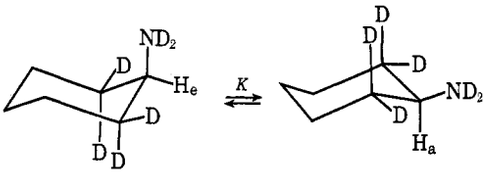
Although there have been many reports concerning the measurement of the axial *vs.* equatorial conformational preference of the hydroxyl group in cyclohexanol,[3] similar data concerning the amino group is relatively scarce, having been derived from indirect kinetic, pK_a, and nuclear magnetic resonance (nmr) techniques which necessarily involve the use of model compounds.[4] There have been no reports concerning the direct measurement of the conformational preference of the amino group in cyclohexylamine itself free from the constraints and possible distortions of locking substituents.[4]

This report concerns the direct measurement of the *A* value[5] (eq 1–2) of the deuterioamino group (ND_2)



(1)

$$A \text{ value} = -\Delta G^\circ = \frac{RT \ln K}{1000} \qquad (2)$$

in cyclohexylamine-*N*,*N*,2,2,6,6-d_6 (**1**) using the low-temperature nmr method. **1** was prepared from cyclohexanol-2,2,6,6-d_4 by the method of Streitwieser and Coverdale[6] and was purified by preparative glpc.

Examination of the ^1H nmr spectrum (60 or 100 MHz) of **1** in CD_3OD revealed broadening or coalescence of the various complex $(CH_2)_3$ resonances from about −40 to −70° and subsequent sharpening of the complex $(CH_2)_3$ spectrum at lower temperatures. Likewise, the HCN resonance broadened and sharpened as the temperature was lowered, separating into a large singlet resonance at δ 2.49 (H_a, eq 1) and a much smaller singlet at δ 3.02 (H_e, eq 1). Such spectral behavior is completely consistent with a slowing of the axial ⇄ equatorial equilibration in **1** (eq 1) on the nmr time scale and the direct observation of axial and equatorial conformers. The observed chemical shifts for axial and equatorial HCN protons in **1** are in good agreement with axial (δ 2.50) and equatorial (δ 3.09) HCN chemical shifts in *trans*- and *cis*-4-*tert*-butylcyclohexylamine, respectively (95% ethanol at room temperature).[4a]

Thus, we examined the ^1H nmr spectrum of **1** at −93° in three solvent systems at different concentrations obtaining the axial:equatorial conformer ratio (eq 1) by weighing cut-outs of the HCN proton resonances and by hand planimeter integration. The various equilibrium constants (*K*, eq 1) and associated free energy differences are compiled in Table I. It should be noted that the large equilibrium constants (Table I) at least by nmr standards necessitated the use of relatively high radiofrequency power levels, introducing the possibility of differential saturation effects.[5]

The various *A* values compiled in Table I are in remarkably good agreement with those obtained by more indirect methods.[4] Although the *A* value of ND_2 does

(1) Alfred P. Sloan Research Fellow, 1971–1973.

(2) Supported by Worcester Polytechnic Institute Undergraduate Work-Study Program, Summer 1971.

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