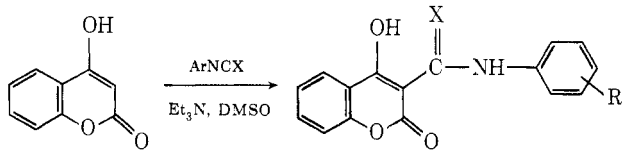
Scheme I



I

IIa, X = O; R = H
b, X = O; R = *p*-Cl
c, X = S; R = *p*-F

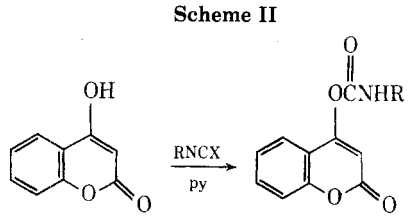
employ thermal activation in one form or another. The amides are formed by the thermal reaction of 4-hydroxycoumarin with isocyanates at 160°,[1-4] or by the reaction of 3-carbethoxy-4-hydroxycoumarin[5] in refluxing anilines.[2-4]

The room-temperature reaction of 4-hydroxycoumarin with aryl isocyanates or aryl isothiocyanates in DMSO containing triethylamine yields cleanly in one step the desired materials,[6] amides of 4-hydroxycoumarin-3-carboxylic acid. For example, 4-hydroxycoumarin and *p*-chlorophenyl isocyanate in DMSO (1 equiv of triethylamine) gave in 71% yield[7] 3-(*p*-chlorophenylcarbamoyl)-4-hydroxycoumarin (IIb, Scheme I), mp 218–220° (lit.[1,3] mp 219–221°). Similarly the reaction of 4-hydroxycoumarin with *p*-fluorophenyl isothiocyanate gave 3-(*p*-fluorophenylthiocarbamoyl)-4-hydroxycoumarin (IIc) in 82% yield[7] (Scheme I), mp 220–223°.[6]

This reaction is complete in 0.5–2 hr and is successful only with aryl isocyanates and isothiocyanates. Alkyl isocyanates and isothiocyanates yield some starting coumarin and polymeric materials. Those aryl isocyanates and isothiocyanates which have a limited solubility in DMSO (at room temperature) gave very poor yields.

The use of pyridine as a solvent yields urethanes. Thus 4-hydroxycoumarin and phenyl isocyanate in pyridine at room temperature gave 4-hydroxycoumarin, carbanilate (IIIa, Scheme II) in 60% yield, mp 210–213° (lit.[3] mp 206–209°).

Scheme II

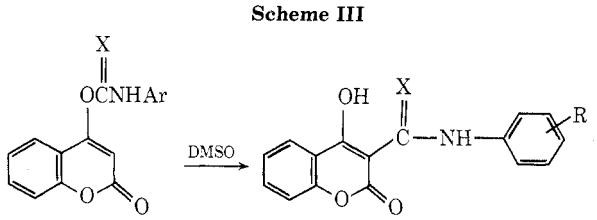


I

IIIa, R = Ph
b, R = *n*-Bu

This reaction was successful with both aryl and alkyl isocyanates and isothiocyanates. 4-Hydroxycoumarin and *n*-butyl isocyanate in pyridine gave 4-hydroxycoumarin *n*-butylcarbamate (IIIb), mp 168–171°. The aryl urethanes rearrange in DMSO (at room temperature) to the 3-carboxamides. Thus 4-hydroxycoumarin carbanilate is cleanly and quantitatively rearranged by overnight stirring in DMSO (containing several drops of triethylamine) to 3-phenylcarbamoyl-4-hydroxycoumarin (Scheme III, IIa),

Scheme III



III

IIa, X = O; R = H
d, X = O; R = *m*-Cl

yield 100%, mp 215–216° (lit.[1-4] mp 219–221°). Likewise 4-hydroxycoumarin *m*-chlorocarbanilate yields 3-*m*-chlorophenylcarbamoyl-4-hydroxycoumarin (IId), yield 95%, mp 191–193° (lit.[1] mp 190–192°). Alkyl urethanes fail to give amides, instead yielding polymer-like materials.

Experimental Section

All commercial reagents were used as received and all solvents were dried over molecular sieves. Melting points are uncorrected.

3-Phenylcarbamoyl-4-hydroxycoumarin (IIa). 4-Hydroxycoumarin (5 g, 0.031 mol), triethylamine (3.1 g, 0.031 mol), and phenyl isocyanate (1 equiv), added in the listed sequence to 50 ml of dry DMSO, were stirred at room temperature for 2 hr. The solution was poured into 100 ml of 3 *N* HCl, and the solid was filtered, air dried, and recrystallized from acetone, giving 6.1 g (70%) of a white powder, mp 215–216° (lit.[1,3] mp 219–221°).

3-(*p*-Fluorophenylthiocarbamoyl)-4-hydroxycoumarin (IIc). The procedure described for IIa gave IIc in 82% yield, mp 220–223°.

Anal. Calcd for $C_{16}H_{10}FNO_3S$ (283.32): C, 60.94; H, 3.20; N, 4.44; S, 10.17; F, 6.03. Found: C, 60.69; H, 3.22; N, 4.50; S, 9.99; F, 5,80.

4-Hydroxycoumarin Carbanilate (IIIa). A solution of 5 g (0.031 mol) of 4-hydroxycoumarin in 50 ml of pyridine was treated in a dropwise fashion with 4 g (1 equiv) of phenyl isocyanate. After stirring for 3 hr at room temperature, the solution was poured into water, and the solid was collected, air dried, and recrystallized from chloroform–hexane, mp 210–212° (yield 5.6 g, 60%).

Rearrangement of Urethanes to Amides. A suspension of 250 mg of 4-hydroxycoumarin carbanilate in 5 ml of DMSO containing several drops of triethylamine was stirred overnight at room temperature. The solution was poured into 25 ml of 1 *N* HCl and the solid IIa was collected, mp 212–215° (250 mg, 100%). The spectral properties of the samples are identical with those of samples previously prepared.

Acknowledgment. We wish to acknowledge Mr. L. Brancone and staff for required microanalytical data, Mr. W. Fulmor, Mr. G. O. Morton, and coworkers for spectral information and interpretation, and Dr. G. Van Lear for his mass spectral considerations.

Registry No.—IIa, 14206-95-2; IIc, 50600-32-3; IIIa, 37982-58-4; 4-hydroxycoumarin, 1076-38-6; phenyl isocyanate, 103-71-9; *p*-fluorophenyl isothiocyanate, 1544-68-9.

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(5) D. S. Tarbell and J. A. Price, *J. Org. Chem.*, **22**, 245 (1957).
(6) All new materials had proper physical constants and correct elemental analyses.
(7) Isolated and recrystallized yields.

Product Evidence for an Enamine Mechanism in the Acid-Catalyzed Cleavage of β-Amino Alcohols. Independence of Mechanism on Nature of Acid[1]

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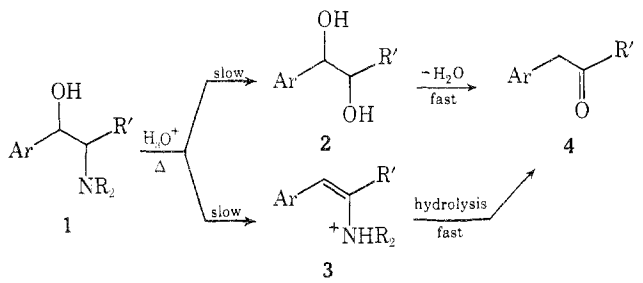
Two mechanisms have been suggested to explain the acid-catalyzed cleavage of α-aryl-β-amino alcohols to β-carbonyl compounds.[2-4] These mechanisms involve a gly-

Table I
Reaction of Compounds 1a, 1b, and 2a (= 2b) with Various Acids

Compd	Acid	Reflux period, hr	Products (yields, %)
1a	12 *M* HCl	7	**4a** (54)[a]
1b	12 *M* HCl	80	No reaction[b]
1b	48% HBr	25	**4b** (34)[a]
2a	12 *M* HCl	6	*p*-$CH_3C_6H_4(C_6H_5)CHCH{=}O$ (75), **4a** (~12), **4b** (<3)[c,d]
1a	6 *M* H_2SO_4	7	**4a** (68)[a]
1b	6 *M* H_2SO_4	27	**4b** (38)[a]
2a	6 *M* H_2SO_4	3	*p*-$CH_3C_6H_4(C_6H_5)CHCH{=}O$ (70),[c] **4a** (~11), **4b** (<2.5)
1a	85% H_3PO_4	2	**4a** (24)[a]
1b	85% H_3PO_4	4.5	**4b** (11)[b]
2a	85% H_3PO_4	4	*p*-$CH_3C_6H_4(C_6H_5)CHCH{=}O$ (47), **4a** (~33), **4b** (<6)[c]

[a] Yield after recrystallization; glc analysis of crude product showed no evidence of *p*-tolylphenylacetaldehyde or of the other, *a priori*, possible ketone product. [b] As shown by recovery of unreacted starting material in high yield. [c] Yields determined by glc analysis of crude product mixture and comparison with known mixtures of authentic samples. [d] Treatment of the glycol with 20% sulfuric acid has previously been reported to afford *p*-tolylphenylacetaldehyde. See ref 8.

col intermediate[2,3] and an enamine intermediate,[2,4] respectively. The reader is referred to a recent paper[5] for details of the mechanisms. Recent work[6] provides strong kinetic evidence for an enamine mechanism in the reaction of 2-(*N,N*-diethylamino)-1-phenylethanol derivatives with hydrochloric acid. However it is claimed,[2] although experimental details are vague, that glycols have been isolated from the reaction of similar amino alcohols with concentrated phosphoric acid.



a, R = Et; Ar = *p*-tolyl; R′ = phenyl
b, R = Et; Ar = phenyl; R′ = *p*-tolyl

One difficulty in resolving the problem is that all previously synthesized α-aryl-β-amino alcohols (**1**) have had alkyl or hydrogen R′ groups[7] and these would be expected to yield the same ketonic products in the event of either a glycol or an enamine mechanism. We have examined the reactions of two amino alcohols (**1a** and **1b**) with various types and concentrations of acid. The amino alcohols were chosen so that they would afford different enamine intermediates but a common glycol intermediate (**2a** = **2b**) if, indeed, the reactions involved such intermediates. An authentic sample of the glycol was prepared independently and was subjected to reaction conditions similar to those of the amino alcohols. Authentic samples of the two possible ketone products (**4a** and **4b**) were also prepared independently for comparison purposes. The results of the acid-catalyzed reactions are summarized in Table I.

The glycol **2a** yielded, as the major product, *p*-tolylphenylacetaldehyde[8] *via* rearrangement along with ketones **4a** and **4b**. Ketone **4a** was always predominant, an expected result since the rate-determining step in the dehydration of the glycol involves formation of a more favorable *p*-methyl benzylic carbonium ion.

The amino alcohols **1a** and **1b** afforded ketones **4a** and **4b**, respectively, as the only products (see Table I, footnote *a*). These results are consistent with an enamine intermediate but not with a glycol intermediate, since both amino alcohols must furnish the same glycol, hence the same products.[17] An enamine mechanism likely involves, as the rate-determining step, development of a benzylic carbonium ion by removal of the protonated hydroxyl group of the amino alcohol.[5,6] A feature of such a mechanism is the observed result that **1a** was consistently more reactive than **1b**, in agreement with previous kinetic data.[6] The unknown stereochemistry of **1a**, **1b**, and **2a** does not alter the validity of these results, since benzylic alcohols racemize rapidly in acidic solution.[9]

The results fail to show any variation in mechanism with the type of acid used; even with concentrated phosphoric acid the outcome is inconsistent with a glycol intermediate, in opposition to the earlier conclusion.[2] We believe that the present data, along with previous kinetic results,[6] no longer justify the possibility of a glycol mechanism of amino alcohol cleavage.

Experimental Section[10]

2-(*p*-Tolyl)-1-phenyl-2-(*N,N*-diethylamino)ethanol (1b). α-Bromo-α-(*p*-tolyl)acetophenone[11] (17.9 g, 0.062 mol) was added in small portions, under nitrogen, to diethylamine (62 ml) at 0° with stirring. After addition was complete the mixture was stirred for 3 hr at 0° and then refrigerated overnight. The diethylamine hydrobromide was filtered off and excess diethylamine was removed from the filtrate by evaporation under reduced pressure. The crude product was dissolved in cold, dilute HCl and washed with ether. The aqueous layer was neutralized with dilute NaOH and extracted with ether and the ether extract was dried ($MgSO_4$). Evaporation of ether followed by vacuum distillation of the product afforded 13.3 g (77%) of the amino ketone as a viscous yellow liquid, bp 145–146° (0.4 mm).

A solution of the amino ketone (13.2 g, 0.047 mol) in dry ether (50 ml) was added dropwise to a stirred solution of $LiAlH_4$ (1.33 g, 0.035 mol) in dry ether (50 ml) at a rate such that gentle refluxing was maintained. The mixture was then refluxed over a steam bath for 30 min. Excess $LiAlH_4$ was destroyed by cautious, dropwise addition of water with stirring followed by removal of solid material by filtration. The ether layer was washed with water, dried, and evaporated under reduced pressure, leaving a yellow-white solid residue. Recrystallization from pentane afforded white crystals: 9.1 g (70%); mp 71–73°; ir (CCl_4) 3400 cm^{-1} (broad, OH), no C=O; nmr δ 7.1 (m, 10, aryl H), 5.2 (d, J = 5 Hz, 1, >CHOH), 3.7 (d, J = 5 Hz, 1 >CHNEt$_2$), 3.3 (s, 1, OH), 2.65 (dq, J = 7 Hz, 8, $-CH_2CH_3$), 2.3 (s, 3, $-C_6H_4CH_3$), 0.9 (t, J = 7 Hz, 6, $-CH_2CH_3$).

Anal. Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4,94. Found: C, 80.72; H, 8.93; N, 4.64.

1-(*p*-Tolyl)-2-phenyl-2-(*N,N*-diethylamino)ethanol (1a) was prepared from α-bromobenzyl *p*-tolyl ketone[12] by the same procedure as above. The intermediate amino ketone had bp 155–160° (0.9 mm). The crude amino alcohol was vacuum distilled, bp 150–153° (0.75 mm). The distillate solidified on standing and was recrystallized from petroleum ether (bp 30–60°): mp 61–63°; ir (CCl_4) 3400 cm^{-1} (broad, OH), no C=O; the nmr spectrum was nearly indistinguishable from the spectrum of **1b**, all δ values and multiplicities being identical.

Anal. Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94. Found: C, 80.43; H, 9.08; N, 4.82.

1-(*p*-Tolyl)-2-phenyl-1,2-ethanediol (2a = 2b). The method of Jenkins[13] was adapted to the synthesis of α-hydroxybenzyl *p*-tolyl ketone. A suspension of α-bromobenzyl *p*-tolyl ketone[12] (20 g, 0.069 mol) in absolute ethanol (400 ml) was added dropwise to a stirred solution of sodium ethoxide (0.21 mol) in absolute ethanol (200 ml). The reaction mixture was stirred overnight at room temperature and then added to a cold solution of 3 *M* HCl (400 ml). After cooling to induce crystallization the solid was collected and recrystallized from ethanol–water to yield 9.2 g (59%) of α-hydroxybenzyl *p*-tolyl ketone, mp 106–108° (lit.[14] mp 108–109°).

Sodium borohydride (0.80 g, 0.021 mol) was added in small portions to a suspension of the hydroxy ketone (9.2 g, 0.041 mol) in ethanol (200 ml). After addition was complete the mixture was stirred at room temperature for 15 min, then refluxed on a steam

bath for 15 min. The volume of the mixture was reduced by ½ by distillation. Water was added to the boiling solution to the point of saturation; on cooling the diol precipitated as a mixture of stereoisomers: 7.5 g (80%); mp 104–168° (lit. mp[8] 94°, 129° for each racemic pair of enantiomers, respectively); ir ($CHCl_3$) 3590 cm^{-1} (OH), no C=O.

Reaction of 1-(*p*-Tolyl)-2-phenyl-1,2-ethanediol with Acid. General Procedure. A stirred mixture of the diol (1.0 g) and acid (50 ml) was refluxed (see Table I for acids and reaction times). After cooling to room temperature and pouring into water, the reaction mixture was extracted with ether four times. The combined ether extracts were washed with water, dried ($MgSO_4$), evaporated under reduced pressure, and weighed. The crude product mixture was then subjected to glc analysis using authentic samples of *p*-tolylphenylacetaldehyde,[8] and ketones **1a** and **1b**[15] for comparison. The results of the reactions are shown in Table I.

Reaction of Amino Alcohols 1a and 1b with Acid. General Procedure. A stirred mixture of the amino alcohol (0.2–1.3 g) and acid (15–50 ml) was refluxed for the periods indicated in Table I. After cooling and dilution with water the reaction mixture was extracted with ether. The combined ether extracts were washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The crude products were subjected to glc analysis. In every reaction of **1a** only ketone **4a** could be detected; likewise **1b** furnished only **4b**. The crude solid products were purified[16] by recrystallization and their identities were further confirmed by melting point and mixture melting point and by their infrared spectra, which were identical with those of authentic samples of the ketones. In the reactions with 85% H_3PO_4 the crude products were reddish pastes from which the pure products were extracted by trituration with hot petroleum ether, followed by filtration and cooling.

In the reaction of **1b** with 12 *M* HCl, the reaction mixture contained solid material which was filtered off prior to extraction with ether. This material was then remixed with the aqueous layer and the mixture was neutralized with excess 3 *M* NaOH. Extraction of the alkaline mixture with $CHCl_3$ followed by work-up gave unreacted amino alcohol (80%).

Registry No.—**1a**, 50600-27-6; **1b**, 50600-28-7; **2a**, 50600-29-8; **4a**, 2430-99-1; **4b**, 2001-28-7; *p*-$CH_3C_6H_4(C_6H_5)CHCH{=}O$, 50600-30-1; amino ketone, 50600-31-2.

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(7) An exception is an amino alcohol with Ar = R′ = phenyl (ref 2), but this compound would be expected to yield α-phenylacetophenone regardless of mechanism.
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(9) Reference 5 and references cited therein.
(10) Melting points were taken on a Fisher-Johns block and are uncorrected. Infrared spectra were taken on a Beckman IR-10 instrument and were calibrated against the 1601-cm^{-1} peak of polystyrene. Nmr spectra were recorded in $CDCl_3$ on a JEOL MH-60 spectrometer. Glc analyses were performed on a Carle Model 8000 gas chromatograph using a 6 ft × 0.125 in. 8% G.E. SF-96 on 90–100 mesh Anakrom ABS column. Elemental microanalyses were performed by Dr. G. I. Robertson, Jr., Florham Park, N. J.
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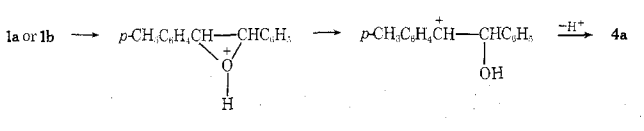
(16) Melting points of the crude products were only slightly lower than those of the pure ketones, except for the 85% H_3PO_4 reaction products.
(17) The results also rule out the possibility of an epoxide intermediate, since amino alcohols **1a** and **1b** would both furnish the same epoxide, hence the same product.



Conformational Preference of Cyclohexanespiroaziridine As Determined by Low Temperature Carbon-13 Magnetic Resonance

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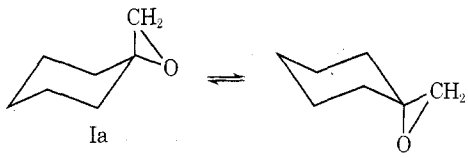
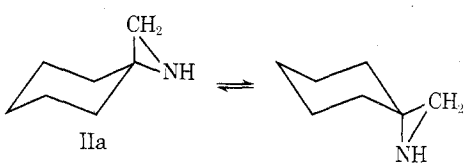
Received September 12, 1973

Considerable effort has been recently directed toward the elucidation of conformational preferences of spirocyclohexane derivatives. Cyclohexanespirooxirane (I) has been studied *via* kinetic,[1] low-temperature ^1H nmr,[2] and electric dipole moment[3] methods. The preference of *ca.* 0.27 kcal/mol for the conformation in which the oxygen is quasi-axial (Ib) is evident.



Ia Ib

By contrast, attempts to study the analogous spiroaziridine II by electric dipole moments have not permitted definitive conformational conclusions.[3]



IIa IIb

The low-temperature ^1H nmr peak area procedure cannot be applied to the problem owing to the accidental overlap of the aziridine methylene resonance (δ 1.45) with the cyclohexane ring methylene protons (δ 1.25–1.75). It is expected, however, that ^{13}C nmr should afford a solution, since it is now well established that carbon shieldings are an order of magnitude more sensitive to steric factors than proton shifts in favorable cases.[4,5] Furthermore, the likelihood of peak overlap in carbon spectra is considerably reduced. Accordingly, a sample of II 61% ^{13}C enriched at the aziridine methylene carbon was prepared and examined.

At room temperature under conditions of complete proton noise decoupling the aziridine methylene carbon of II appears as a sharp singlet at δ 31.84 downfield from internal TMS. When a 0.5 *M* solution of II in CD_2Cl_2 is cooled the absorption for this carbon gradually broadens and at $-80 \pm 2°$ the coalescence temperature is reached. Further cooling leads to the separation of the signal into completely resolved components separated by 6.4 Hz.

The resonance of higher integrated intensity appearing at lower field is assigned to conformer IIb. This is consistent with the observations for methylcyclohexane at low temperature,[6] where the equatorial methyl group is at considerably lower field than its axial counterpart. The peak areas were determined by a cutting and weighing procedure and the conformational energy of the spiroaziridine function was calculated from the equation $-\Delta G° = RT \ln K$. Results are shown in Table I, which indicate that conformer IIb is the more stable by 0.16 kcal/mol.

It is apparent that the preference for conformer IIb is much less than that predicted on the basis of the difference between the conformational free energy of the Me (1.7 kcal/mol) and the NHMe (1.0 kcal/mol) groups.[7] No doubt the small angle of the aziridine ring causes appre-