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ACETYLATION OF N-ISOPROPYLIDENEANILINES. FORMATION OF A NOVEL 1,3-OXAZETIDINE DERIVATIVE[1)]

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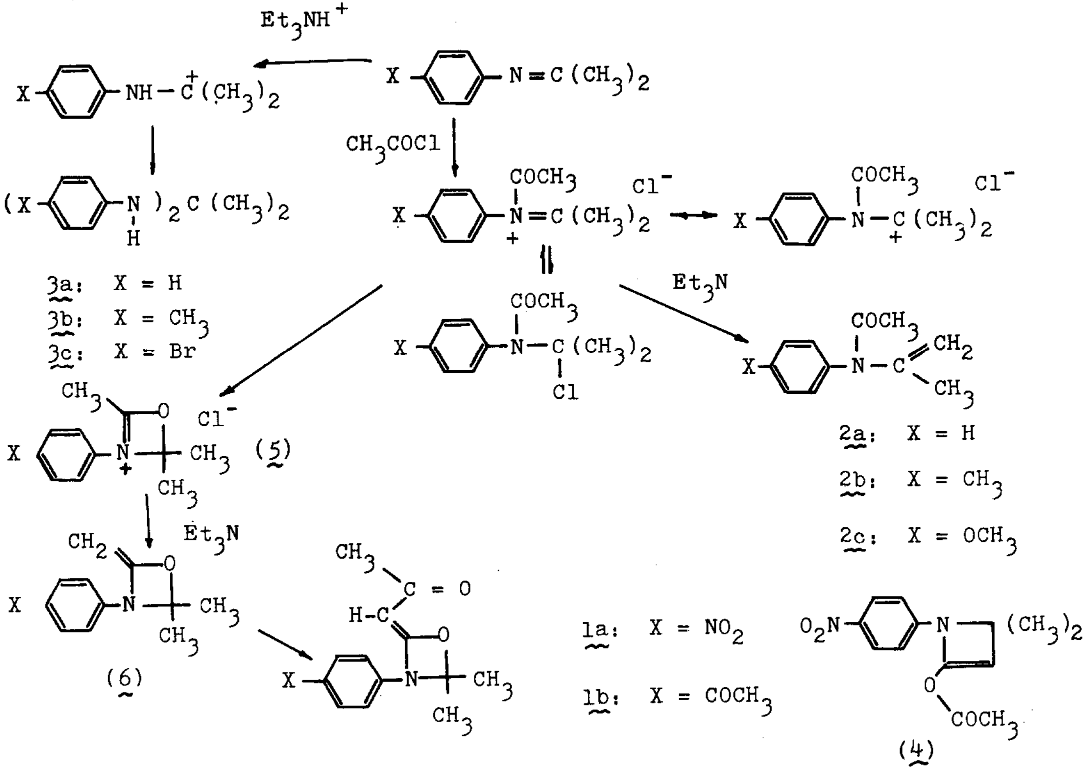
Acylation of imines often leads to β-lactams. The reactions are considered to be cycloaddition of imines with ketenes which may be formally generated in situ from an acid chloride and triethylamine.[2)] We have found that N-isopropylideneanilines give several products envisaged as derived from the N-acetyliminium salts. One of the products is a novel 1,3-oxazetidine derivative.

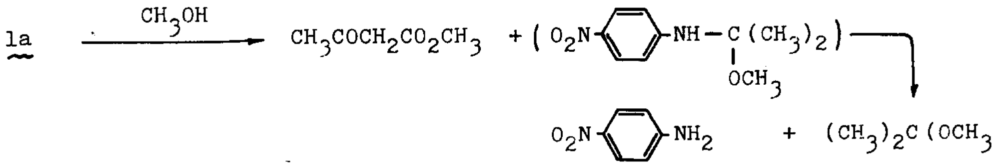
When 7.85 g (0.1 mole) of acetyl chloride is added to a solution of N-isopropylideneanilines (0.05 mole) and 10.1 g (0.1 mole) of triethylamine in 50 ml of anhydrous ether, the mixture is stirred under reflux for 30 min, and the precipitated triethylamine hydrochloride is removed by filtration, the residue gives a mixture of 1,3-oxazetidines (**1**), N-isopropenylacetanilides (**2**) and/or 2,2-dianilinopropanes (**3**). The composition of these products is found to be dependent on the substituents on the phenyl ring.

A) 1,3-Oxazetidines. A voluminous pale-yellow solid precipitates out of the ether solution of the reaction of N-isopropylidene-p-nitroaniline. After recrystallization from ether, the product obtained in 54% purified yield exhibits the following properties: mp 137°; Anal. (found) C, 59.60, H, 5.39 and N, 10.65; ir (KBr) 1660 and 1603 cm^{-1}; nmr ($CDCl_3$) δ 1.63 (s, 6H), 2.03 (s, 3H), 5.37 (s, 1H), 7.40 (d, 2H) and 8.28 (d, 2H). Out of a number of candidates which are

Scheme 1



consistent with the above data, only two structures, oxazetidine 1a and enol acetate 4 of β-lactam, are of importance when the possible mechanism of its formation is taken into account. Acetone and p-nitroaniline are obtained by mild acid hydrolysis of the acetylation product. When the compound is allowed to react with methanol at 50∼55° for 12 hr, p-nitroaniline (97%), methyl acetoacetate (93%) and acetone dimethylacetal (69%) are obtained.3) The results are depicted as Eq. 1 and are compatible only with oxazetidine structure 1a of



(Eq. 1)

the starting material.

1,3-Oxazetidine derivative **1b** from N-isopropylidene-p-acetylaniline has the following properties: mp 122°; Anal. (found) C, 69.53, H, 6.66 and N, 5.34; nmr ($CDCl_3$) δ 1.58 (s, 6H), 2.00 (s, 3H), 2.58 (s, 3H), 5.35 (s, 1H), 7.28 (d, 2H), and 8.02 (d, 2H). It is noted that 1,3-oxazetidines **1** are obtained only when ring substituents are strongly electron-withdrawing.

B) N-Isopropenylacetanilides (Table I). From N-isopropylideneaniline, -p-toluidine and -p-anisidine, the corresponding N-isopropenylacetanilides **2a**~**c** are obtained by distillation under reduced pressure and purified by preparative vpc.[3] Yields are quite good for the p-anisidine, but fall off to 10% (isolated yield after preparative vpc) for the aniline. N-Isopropenylacetanilides with electron-withdrawing ring substituents are not formed. Nmr spectra are practically first-order. The assignment of the isopropenyl methyl is made by the presence of long-range coupling with the olefinic protons. While most of the signals other than those of aromatic are relatively broad at ambient temperature, they are normal at 50°. The trends are characteristic of the presence of hindered rotation in amides.

C) 2,2-Dianilinopropanes. The residues obtained from distillation of the acetanilides solidifies on standing. The compound obtained in 25% yield from N-isopropylideneaniline has the following properties: mp 115.5°; Anal. (found) C, 79.55, H, 8.00 and N, 12.31; nmr ($CDCl_3$) δ 2.15 (s, 6H), 7.17~7.53 (broad, 10H) and 8.28 (broad s, 2H). Acetone and aniline are characterized by vpc of the acid (6N HCl) hydrolysate of the compound. The results are interpreted as the

Table I. N-Isopropenylacetanilides $p\text{-}X\text{-}C_6H_4\text{-}N(COCH_3)C(CH_3){=}CH_2$

X	bp °	Anal. (found)			nmr ($CDCl_3$) δ				
	(mm Hg)	C	H	N	CH_3	$COCH_3$	$=CH_2$	ring protons	other protons
H	93~95(7)	75.45	7.47	7.93	1.93	2.08	4.95, 5.05	7.30	
CH_3	112~115(7)	76.03	7.95	7.26	1.92	2.03	4.92, 5.02	7.13	2.35
OCH_3	129~133(8)	70.15	7.29	6.87	1.93	2.03	4.92, 4.99	6.87 7.12	3.78

2,2-dianilinopropane structure 3a for the crystalline product. Formation of this type of compounds are confirmed also for the p-toluidine; mp 148.5° and p-bromoaniline; mp 166°.

Formation of these products **1**~**3** on acetylation and the dependence of the product ratios on the ring substituents of N-isopropylideneanilines are uniformly interpreted interms of Scheme 1. It was suggested by Sheehan and Ryan that the formation of a ketene from the acid chloride and triethylamine and subsequent cycloaddition were probably not the pathway to the β-lactams.$^{4)}$ One alternative in which N-acetyliminium chlorides or the corresponding covalent intermediates are formed has been proposed on a spectroscopic ground.$^{5)}$ The N-acetyliminium chlorides can either ring-close to give **5** or deprotonate to give **2**. The nucleophilic ringclosure by the carbonyl oxygen atom is considered to be facilitated as the positive charge is induced at the isopropylidene carbon atom by electron-withdrawing ring substituents. Deprotonation to give enamine **6** followed by the second acetylation leads to **1**. Studies to examine the generality of this 1,3-oxazetidine formation are in progress.$^{6)}$

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References and Notes

(1) Part V of "N-Alkylideneanilines." For Part IV of the series, see: H. Iwamura, M. Tsuchimoto, and S. Nishimura, Bull. Chem. Soc. Japan, in press.

(2) H. Staudinger, Ber., **40**, 1145 (1907): **50**, 1035 (1917); H. Staudinger and R. Endle, Ber., **50**, 1042 (1917).

(3) Vpc was carried out on a column of 10% polyethylene glycol 20M.

(4) J. C. Sheehan and J. J. Ryan, J. Amer. Chem. Soc., **73**, 1204 (1951).

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

(6) Not much is known on the chemistry of 1,3-oxazetidines. 1,3-Oxazetidin-2-ones obtained by cycloaddition of isocyanates to carbonyl compounds are a few example.