BENZOXAZINES AND RELATED COMPOUNDS

III.* INTERCONVERSION OF 2-ALKYL-4,4-DIETHYL-4H-1,3-BENZOXAZINES AND N-ACYL-α,α-DIETHYL-o-HYDROXYBENZYLAMINES

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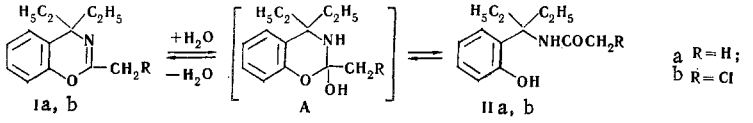
Interconversion of 2-alkyl-4,4-diethyl-4H-1,3-benzoxazines and N-acyl-α,α-diethyl-o-hydroxybenzylamines was accomplished, and it is shown that cupric ion catalyzes these reactions.

We have previously [1, 2] established that 2-substituted 4,4-dialkyl-4H-1,3-benzoxazines (I), rather than the expected products – the corresponding substituted N-benzylamides (II) – are chiefly formed by the reaction of α,α-dialkyl-o-hydroxybenzyl alcohols with nitriles under the influence of mineral acids ($HClO_4$, H_2SO_4); II were isolated in individual cases in low yields. Despite the fact that the reaction to form the benzoxazines is extremely interesting in itself, the desire to find a convenient route to II remained justified since these sorts of amides can be used for various syntheses, particularly for seeking new, biologically active substances.

The previously [1] described method for obtaining II by alkaline hydrolysis of I could not become preparative in view of the low yields of amides, while the acid hydrolysis of I turned out to be entirely unsuitable. As a result of a more detailed study of the hydrolytic cleavage of heterocycle I, we found that this reaction proceeds readily in the presence of cupric salts, e.g., cupric acetate or nitrate.



Thus, in 70% acetic acid in the presence of 1 mole of cupric acetate, 2-methyl-4,4-diethyl-4H-benzoxazine (Ia) is hydrolytically cleaved in 2 h to give 41% of N-acetyl-α,α-diethyl-o-hydroxybenzylamine (IIa). Cupric acetate can be used in catalytic amounts (10 mole %). Cleavage of I does not occur in the absence of cupric acetate. The same sort of picture is observed when aqueous alcohol solutions are used, during which the addition of sodium acetate apparently promotes hydrolysis.

In addition, we found that amide II can be cyclized to benzoxazine I under the influence of acetic anhydride or perchloric acid. But the most interesting fact is that cyclization proceeds in 70% acetic acid in the presence of cupric acetate. Compound I is not formed if a cupric salt is not added. We also opened and closed the benzoxazine ring in the case of Ib and IIb, respectively.

We have not yet established whether these reactions are reversible. The role of the cupric salt probably consists in reinforcing the electrophilicity of the 2 position in I and the carbonyl carbon atom in II as a result of coordination of the cupric ion with the nitrogen atom of benzoxazine I, with the amide oxygen atom of II, or with the amino group in an intermediate of the A type. In strongly acidic media, II can be

*See [1] for Communication II.

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cyclized to I without participation of cupric ion, since protonation of the amide oxygen activates it sufficiently. Hydrolysis of I is not observed in dilute hydrochloric acid with or without added cupric ion; this is probably associated with a simultaneous decrease in the hydroxide ion concentration in solution and disruption of the I-cupric-ion complex. The possibility of accomplishing cyclization of amides II also indicates that the formation of benzoxazines of the I type from o-hydroxy-α,α-dialkylbenzyl alcohols and nitriles in mineral acid media [1, 2] may also proceed through intermediate amides of the II type.

EXPERIMENTAL

Hydrolysis of 2-Methyl-4,4-diethyl-4H-1,3-benzoxazine (Ia). A solution of 4 g (0.02 mole) of Ia [2] in 10 ml of 70% acetic acid was added to a solution of 3.9 g (0.02 mole) of cupric acetate monohydrate in 10 ml of 70% acetic acid. The mixture was stirred for 2 h, 50 ml of water was added, and the mixture was made alkaline with sodium carbonate and extracted with ether. The ether was removed, the residue was triturated with petroleum ether, and the resulting crystals were filtered to give 1.75 g (40.7%) of IIa with mp 131-132° (from benzene–petroleum ether). A mixture of this product with a sample previously [2] obtained, which had an identical IR spectrum [in $CHCl_3$, c 0.6%; 3360 cm^{-1} (associated OH and NH groups); 1650 cm^{-1} (amide I), 1540 cm^{-1} (amide II)] showed no melting-point depression. Compound Ia [1.5 g (37.5%)] with bp 85-88 (3 mm) and n_D^{20} 1.5160 was isolated from the petroleum ether solution.

Hydrolysis of 2-Chloromethyl-4,4-diethyl-4H-1,3-benzoxazine (Ib). A solution of 4.9 g (0.02 mole) of Ib [1] in 20 ml of 70% alcohol was added to a solution of 3.9 g (0.02 mole) of cupric acetate monohydrate and 1.6 g (0.01 mole) of sodium acetate in 50 ml of 70% alcohol. Treatment of this mixture, as in the previous experiment, yielded 2.6 g (50%) of IIb with mp 119-120° (from benzene–petroleum ether). Found %: C 60.7; H 7.1; N 5.5; Cl 13.8. $C_{13}H_{18}NO_2Cl$. Calculated %: C 61.0; H 7.1; N 5.5; Cl 13.9. Ib [1.3 g (26.5%)] with bp 106-107° (1 mm) and n_D^{20} 1.5320 was also isolated.

Conversion of N-Acetyl-α,α-diethyl-o-hydroxybenzylamine (IIa) to Ia. A. Perchloric acid (70%, 3 ml) was added with stirring and cooling to a solution of 2.2 g (0.01 mole) of IIa in 8 ml of acetonitrile at such a rate that the temperature of the reaction mixture was 25-30°. After 24 h the reaction mass was poured over ice, and the resulting mixture was made alkaline with ammonia and extracted with ether. The ether was removed, and the oily residue (which, from the IR spectrum, did not contain IIa) was distilled in vacuo to give 1.5 g (75%) of Ia with bp 88-89° (2 mm), $n_D^{18.5}$ 1.5155, and R_f 0.75 [activity IV Al_2O_3, benzene–ether (1:1)].

B. Cupric acetate monohydrate [1.9 g (0.01 mole)] was added to a solution of 2.2 g (0.01 mole) of IIa in 40 ml of 70% acetic acid and the mixture was stirred for 2 h at about 20°. The reaction mass was then poured over ice and the mixture was made alkaline with ammonia and extracted with ether. The ether solution was dried over magnesium sulfate, the ether was removed, and the residue was drenched with petroleum ether. The precipitate of IIa was removed (60%), and the residual oil was distilled in vacuo to give 0.6 g (30%) of Ia with bp 88-89° (2 mm). The IIa to Ia ratio was approximately 1:1 during analysis of the composition of the reaction products from the IR spectrum without prior removal of IIa and distillation of Ia.

Conversion of N-Chloroacetyl-α,α-diethyl-o-hydroxybenzylamine (IIb) to Ib. The reaction with 4 g (0.015 mole) of IIb and 5 ml of 70% $HClO_4$ was carried out in the same way as in the previous experiment. Petroleum ether was added to the residue after removal of the ether, and the mixture was allowed to stand overnight in a refrigerator. The precipitated crystals of unchanged IIb were removed by filtration, the filtrate was evaporated, and the residue was distilled to give 3.2 g (86.5%) of Ib with bp 106-107° (1 mm) and n_D^{20} 1.5320.

LITERATURE CITED

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