Behaviour of an *N*-(*o*-Hydroxybenzyl)-β-amino-acid in the Presence of Dehydrating Agents. Synthesis of a 3,4-Dihydro-2*H*-1,3-benzoxazine

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Treatment of *N*-(2-hydroxy-3,5-dimethylbenzyl)-β-aminopropanoic acid with dehydrating agents gives 3,4-dihydro-3-(2-hydroxy-3,6-dimethylbenzyl)-6,8-dimethyl-2*H*-1,3-benzoxazine; a reaction pathway is proposed, involving loss of keten.

The Mannich reaction has been exploited extensively for synthesis of many types of compounds;[1] in particular, numerous amines have been utilized in this reaction. However one important class of compounds possessing an amino group, namely β-amino-acids, has been neglected as components in the Mannich reaction. We intended to determine if common β-amino-acids will participate in the Mannich reaction, and explore the reactivity of the new Mannich bases formed, particularly in the presence of dehydrating agents, which may induce lactamization; the most interesting derivatives of β-amino-acids are heterocycles containing the highly reactive β-lactam system, whose chief importance lies in its occurrence in the penicillin and cephalosporin group of antibiotics.[2]

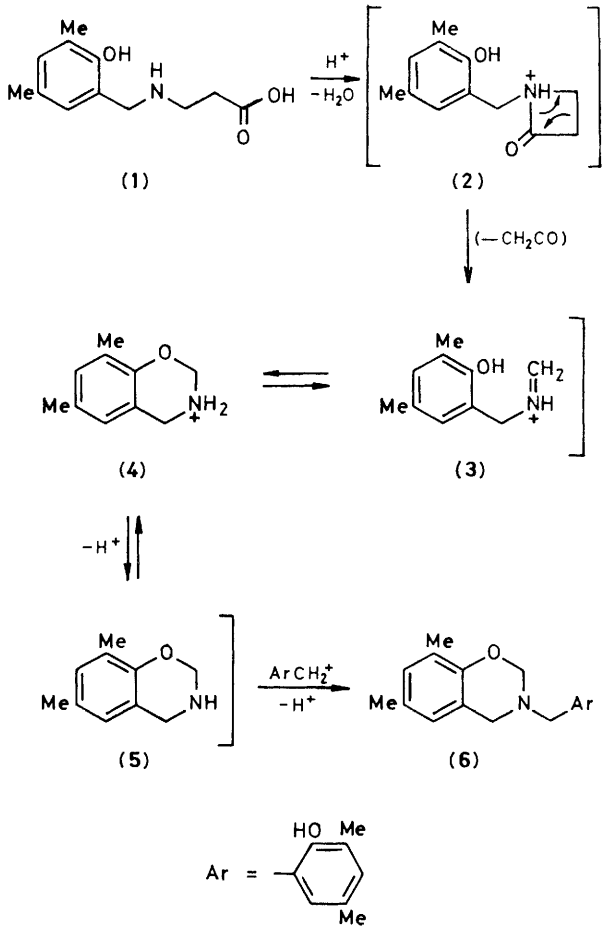
We report here the behaviour of the hitherto unknown *N*-(2-hydroxy-3,5-dimethylbenzyl)-β-aminopropanoic acid (**1**), on treatment with 96% H_2SO_4. The β-amino acid (**1**) (m.p. 179—181 °C, yield 73%) was synthesized *via* the Mannich reaction between 2,4-dimethylphenol (0.3 mol), aqueous formaldehyde (40 ml; 0.4 mol) and 3-aminopropanoic acid (0.3 mol) in EtOH under reflux for 22 h.

Compound (**1**) (13 mmol) in H_2SO_4 (15 ml) was allowed to react at room temperature for 3 h. The dark solution formed was poured into 50 ml of ice–water, the white precipitate was collected and dissolved in water, and the solution was neutralized with 30% NaOH and extracted with ether. The residue after evaporation of the dried solution was purified by t.l.c. to give the hitherto unknown benzoxazine (**6**) (m.p. 119—121 °C, yield 60%).†

The structure of (**6**) was assigned primarily on the basis of its spectral data: *m/z* 297 (9%, M^+), 163 (85), 148 (11), 134 (100), 106 (44), 91 (100), and 77 (19); ν_{max} (Nujol) 3400 cm^{-1} (OH); ^1H n.m.r. (C_6D_6, δ) 6.90 (1H, br s, ArH), 6.73 (1H, br s, ArH), 6.38 (1H, br s, ArH), 6.22 (1H, br s, ArH), 4.34 (2H, s, CH_2), 3.76 (2H, s, CH_2), 3.51 (2H, s, CH_2), 2.43 (3H, s, Me), 2.21 (3H, s, Me), and 2.07 (6H, s, 2 × Me).

Compound (**6**) was also synthesized from 2,4-dimethylphenol, formaldehyde, and 2-hydroxy-3,5-dimethylbenzylamine,[3] thus confirming the proposed structure. The hitherto unknown 2-hydroxy-3,5-dimethylbenzylamine (m.p. 59—61 °C) was itself prepared by Na(Hg) reduction of 2-hydroxy-3,5-dimethylbenzaldehyde oxime (m.p. 136—138 °C), the latter being prepared by a Reimer–Tiemann reaction with 2,4-dimethylphenol, and subsequent condensation with hydroxylamine. Satisfactory analyses were obtained for all compounds described, and their i.r., ^1H n.m.r., and mass spectra are consistent with the assigned structures.

A possible mode for the formation of (**6**) in the presence of 96% H_2SO_4 is shown in Scheme 1. This involves initial cyclisation of (**1**) to give the protonated azetidin-2-one (**2**); an acid-induced fragmentation of the β-lactam system then occurs, leading to keten and the iminium ion (**3**), a tautomer of protonated benzoxazine (**4**). Finally alkylation of the free benzoxazine (**5**) allows the isolation of (**6**). The tautomeric equilibrium (**3**) ⇌ (**4**) is in line with the reported ring–chain tautomerism of derivatives of *o*-hydroxybenzylamine with aldehydes and ketones.[4] The alkylating agent arises from acid-induced deamination of the phenolic Mannich base (**1**).[1]



Scheme 1

Evidence for the loss of keten during the transformation of (**1**) into (**6**) was obtained when the reaction was carried out in the presence of trifluoroacetic anhydride as dehydrating agent; keten was trapped as acetanilide.[5] In this experiment, (**1**) (0.45 mmol) and trifluoracetic anhydride (1.5 ml) were allowed to react at room temperature; the reaction was slightly exothermic, and the vapour produced was passed into aniline with dry nitrogen as carrier gas. Acetanilide, together with considerable amounts of trifluoroacetanilide were identified by g.l.c. Moreover, the mass spectrum of (**1**) showed an intense

† *N*,*N*′-Dicyclohexylcarbodi-imide, thionyl chloride, polyphosphoric acid, and trifluoroacetic anhydride have also been used in the conversion of (**1**) into benzoxazine (**6**), which occurs in each case in good yield.

peak (90%) at m/z 163 ($M^+ - 60$), which may correspond to the easy loss of water and keten from the molecular ion. In fact the formation of acetanilide proves that any activated acetic acid derivative, not specifically keten, is lost from (**1**); (**3**) may arise directly from (**1**) *via* a two-carbon-fragment elimination.

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