1,3-OXAZOLIDIN-5-ONES, NOT 1,3-DIAZETIDINONES, ARE FORMED IN THE REACTION OF TRYPTOPHAN WITH ALKYL ISOCYANATES IN THE PRESENCE OF ACETONE

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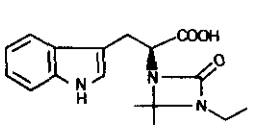
Abstract — A recent paper in This Journal by Braña et al. (Heterocycles 1987, 26, 95) reports isolation of 2-[(3-alkyl-4,4-dimethyl-2-oxo)-1,3-diazetidinyl]-3-(3-indolyl)propionic acids from reactions of tryptophan with alkyl isocyanates in acetone. It appears most likely that these products are instead 1,3-oxazolidin-5-ones.

During work on four-membered nitrogen heterocycles our attention was drawn to a paper by Braña et al. in This Journal[1] in which the synthesis of hydantoins from L-tryptophan and alkyl isocyanates was described. When acetone was used as a solvent another product could be isolated besides the expected hydantoin (45 % yield when ethyl isocyanate was used). Based on ir and proton and carbon nmr the authors suggested that the new products possessed the rare 1,3-diazetidinone structure (e.g. **1** from ethyl isocyanate). Since this simple reaction would allow the synthesis of a range of biologically interesting diazetidinones we tested it using phenylglycine and butyl isocyanate as reactants. Among the products, which were isolated by silica gel chromatography, the expected hydantoin together with N-benzyl-N'-butylurea were readily identified. A small amount (about 5 % yield) of a product having the expected spectroscopic properties for structure **2** was also isolated. This product, however, did not exhibit chromatographic behaviour expected



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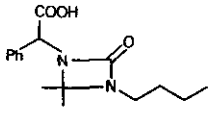

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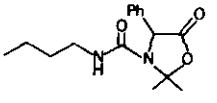


3

of a carboxylic acid, but was considerably less polar. This led me to consider instead the isomeric structure 3 and to suspect that the above-mentioned authors were in fact mistaken regarding the diazetidinone structures. Repetition of one of the reported reactions has reinforced this suspicion based on the following evidence.

L-Tryptophan was allowed to react with ethyl isocyanate in refluxing acetone as described.[1] After removal of unreacted tryptophan by filtration unsuccessful attempts were made to crystallize the product. Instead the residue was chromatographed (EtOAc-hexane, 2:1) affording a crystalline product (R_f= 0.5 in EtOAc) in 9 % yield which had the following spectroscopic and physical properties:

mp 153.5-154 °C (lit. 163-4 °C);

$[\alpha]_D^{20}$ +97.5° (c 2.0, MeOH), lit. +13.1° (c 2.2, MeOH);

ir (KBr): the reported absorption bands at 3400, 3280, 1780 and 1650 cm^{-1} are also found in our product;

^{13}C nmr (DMSO, run at 50.2 MHz and with DMSO-d_6 at 39.8 ppm as a reference): 172.0, 153.5, 136.0, 128.1, 124.8, 121.2, 118.8, 118.7, 111.5, 108.3, 96.9, 57.3, 34.8, 26.5, 26.2, 25.9, 15.8 ppm; all values are in agreement with lit. values within ±0.2 ppm;

^1H nmr (DMSO-d_6 , run at 200 MHz): very close agreement with the reported shifts (from recording in DMSO-d_6 at 60 MHz) except that an additional triplet (J 1.5 Hz) at 6.55 ppm is also observed;

ms (e.i.): the reported peaks at m/z 315 (M^+), 244 and 130 (base peak) are also the most prominent ones in the present spectrum.

There is a discrepancy of 10 °C regarding the melting point of the present product and the one isolated by the Spanish workers . This can, however, be readily accounted for by observing the very different optical rotations of the two samples which indicate different enantiomeric compositions that of course should be reflected in differing melting points. Regarding this point it is interesting to note the very different, yet uncommented, optical rotations of three homologues (methyl to propyl) that include compound 1.[1] An obvious explanation is that racemization occurs to a highly varying extent during these reactions.

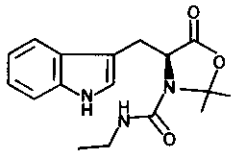
The triplet at 6.55 ppm in the present ^{1}H nmr spectrum (DMSO-d_6) is exchangeable with deuterium (MeOH-d_4), as is the singlet at 10.9 ppm, and is thus a typical amide proton as found in structure **4**. The failure of the Spanish workers to observe this peak could possibly be explained by the low resolution of their instrument combined with a downfield shift of the absorption into the aromatic region.

The peak at 10.9 ppm was assigned to a carboxylic acid proton.[1] This shift however, is also typical of an indole hydrogen[2] which indeed is present in structure **1** but for which no shift assignment was given. As shown by the following experiments, no carboxylic acid function is found in the present product:

- no acidic reaction upon dissolution in water (and no immediate decomposition)
- no shift change in ^{13}C nmr of the carbonyl carbon at 172 ppm in the presence of one equivalent of triethylamine.

Based on the above spectroscopic and chemical data it can be concluded that the product we have isolated from the reaction of L-tryptophan with ethyl

L-Tryptophan + ethyl isocyanate + acetone ⟶



4

isocyanate and acetone most likely has structure **4** and not **1**. This structural class of 1,3-oxazolidin-5-ones is well known from the literature,[3,4] where the unusually high frequency of the carbonyl absorption in the ir was also noted.[3] The frequency range is similar to that of 1,3-diazetidinones, which like beta-lactams absorb in the 1750-1800 cm^{-1} region.[5-7] The mode of preparation of 1,3-oxazolidin-5-ones is analogous to the above conditions in that amino acids have been treated with aldehydes or ketones followed by acylation in order to give more stabilized heterocycles. In contrast, 1,3-diazetidinones are rarely reported compounds.[5-7]

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