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SYNTHESIS OF 1-ACYLOXYINDOLIZINES. CORRECTION OF A STRUCTURE MISASSIGNMENT

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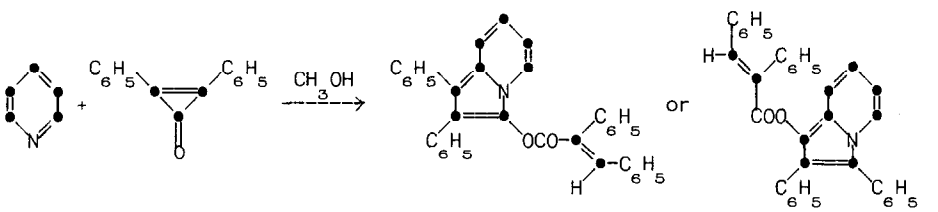
Abstract: The assignment by Lown of a 3-acyloxyindolizine structure to the product of the reaction of diphenylcyclopropenone and pyridine is shown to be in error. Both 1- and 3-acyloxyindolizines were prepared and their structures established by X-ray analysis.

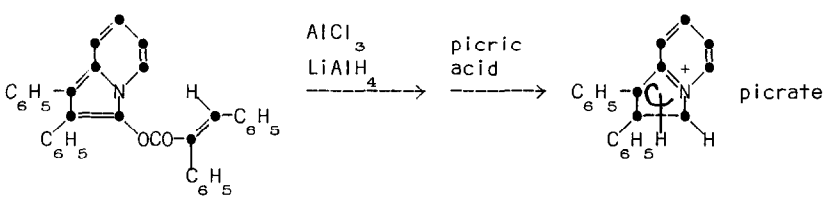
Breslow[1] reported that the reaction of diphenylcyclopropenone and pyridine forms the diphenylacrylate ester of an indolizinol of undetermined regiochemistry (eq 1).



(1)

1 2 3

Later, Lown and Matsumoto[2] assigned structure 2 to the compound, basing their assignments on the formation of the known 1,2-diphenylindolizine picrate[3] (4) by hydrogenolysis of the unknown ester (eq 2).

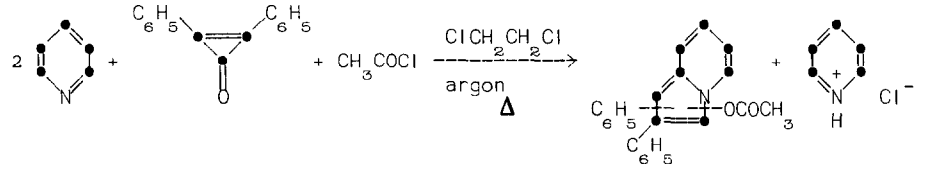


(2)

2 4

Lown has extended the reaction to include a variety of nitrogen heterocycles and diphenylcyclopropenethione.[4] In all products, he assigned structures

analogous to 2, with the oxygen- or sulfur-bearing carbon α to the nitrogen. During our studies of the reactions of cyclopropenium ions and cyclopropenones, we prepared an acetate ester of a diphenylindolizinol by a variation of Lown's procedure (eq 3).

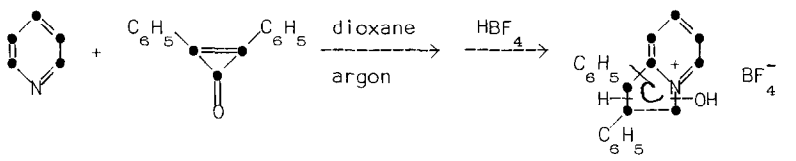


(3)

1 5

Refluxing equivalent amounts of the reactants in 1,2-dichloroethane for 4 h gave 5 in near quantitative yield.

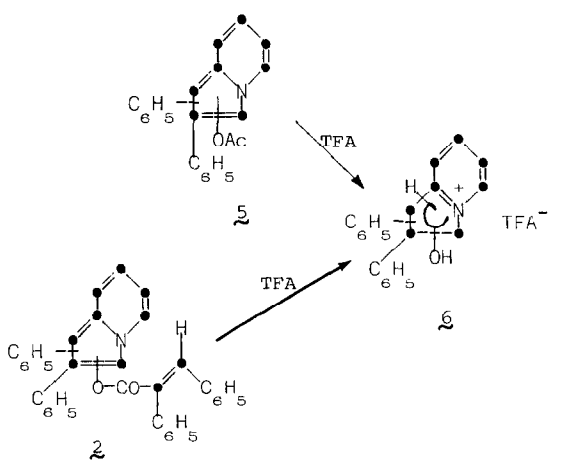
Although the free alcohol was very oxidatively unstable, a stable HBF_4 salt could be prepared in near quantitative yield by refluxing equivalent amounts of pyridine and 1 in dioxane in an inert atmosphere, acidifying the reaction mixture with 48% HBF_4, and evaporating to dryness (eq 4). Recrystallization from methanol-HBF_4(aq) gave pure 6.



(4)

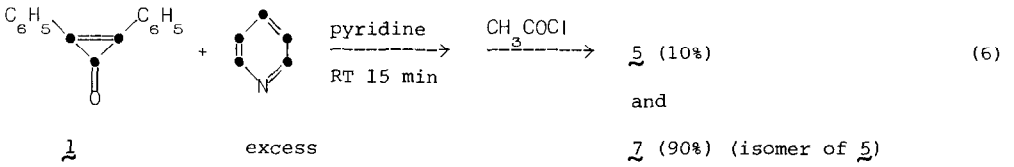
6

Indolizinol 6 (as the TFA salt) was also formed by hydrolysis of either 2 or 5 in moist trifluoroacetic acid, indicating 3-oxo configurations for 2, 5, and 6 (eq 5), based on Lown's assignment.

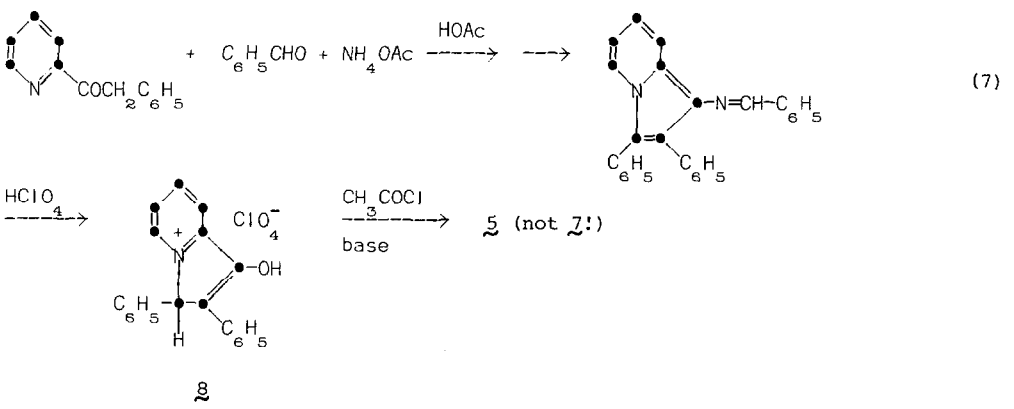


(5)

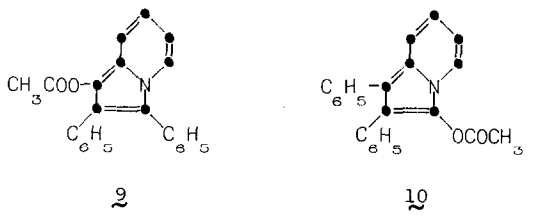
In what appeared to be merely a variation in procedure for the preparation of 5, namely the use of excess pyridine as solvent for the reaction, a mixed product was obtained consisting of 5 as the minor product and an isomer thereof in a ratio of 1:9 (by NMR) (eq 6).



Isomer 7, which was assumed to be the 1-acetoxyindolizene, could be separated from 5 by column chromatography (silica gel/methylene chloride eluent) and crystallized from methanol. For a structure proof of 7, an independent synthesis of 1-acetoxy-2,3-diphenylindolizine (9) by the method of Kröck and Kröhnke[5] was attempted (eq 7).



To our surprise, compounds 8 and 6 gave identical NMR spectra, indicating a mistaken assignment by either Lown or Kröhnke. To resolve the problem, we examined both 5 and 7 by X-ray crystallography and unequivocally assigned structures 9 (for 5) and 10 (for 7).



Detailed X-ray data will be presented in a subsequent publication.

Lown's mistaken structural assignment apparently resulted from confusion in comparing compounds with similar physical properties (4 and 2,3-diphenylindolizine picrate) and failure to carefully compare all compounds spectroscopically. Since his structural assignment of 2 is in error, his assignments in other systems which are based on analogy with the present case should be viewed cautiously.

Further elaboration of the preparation of 1- and 3-indolizinols and the structural elucidation of the corresponding thioindolizinols is in progress and will be reported in subsequent publications.

References

(1) Breslow, R.; Eicher, T.; Krebs, A.; Peterson, R. A.; Posner, J. J. Am. Chem. Soc. 1965, 87, 1320.

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(3) Kröhnke, F.; Weis, W. Ann. Chem. 1964, 679, 136.

(4) Lown, J. W.; Matsumoto, K. Can. J. Chem. 1971, 49, 3119.

(5) Kröck, F. W.; Kröhnke, F. Chem. Ber. 1971, 104, 1629.

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