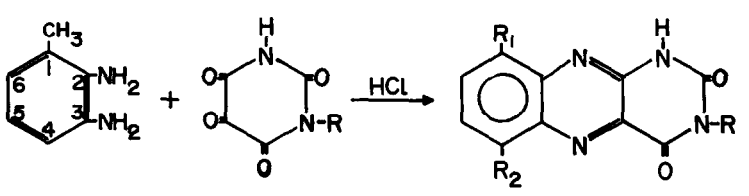
Tetrahedron Letters No. 42, pp 4117 - 4118.
0040-4039/79/1015-4117$01.00/0

SIMPLE SYNTHESIS OF 6-METHYL-, 3,9-DIMETHYL-, 3-METHYL-, AND 3,7,8-TRIMETHYLALLOXAZINE.

Danuta Panek-Janc and Jacek Kozioł*
Institute of Commodity Sciences, Academy of Economics, 60-967 Poznań, Poland

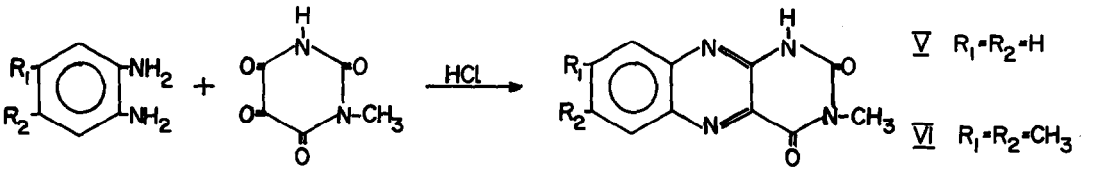
Our attempts to synthesize alloxazine derivatives methylated at different positions in the benzene ring by the methods of Goldner et al.[1] and Müller and Dudley[2] failed for 6-methylalloxazine. The observation that, in a particular case[3] the condensation of a mono-substituted o-phenylenediamine with alloxan in the presence of acid[4] can, under appropriate conditions, produce one of the two possible isomeric alloxazines prompted us to use this synthetic approach. The condensation of freshly prepared 1-methyl-2,3-phenylenediamine in methanolic solution with alloxan in the presence of aqueous HCl was performed at 50°C under chosen conditions. These conditions were a) substrates in equimolar concentrations of not less than 0.21×10^{-3}M, b) 70-160% of the stoichiometric amount of acid needed for the two amino groups, and c) less than 30% of water in the reaction mixture. This reaction yields equal amounts of compounds I and II; pure compound I precipitates out first, and can be filtered off after 10 minutes of reaction (ca.40% yield). After another 10 minutes compound II precipitates, also in ca.40% yield. At the end of the reaction (approx. 30 minutes) a small amount of a mixture of compounds I and II comes out of solution. Smaller amounts of acid result in the formation of a mixture of 2-hydroxy-(5- or 8-methyl-) quinoxaline-3-carboxyureids, whereas larger amounts of acid, or of water, lead to the precipitation of a mixture of compounds I and II. The reaction takes the same course in ethanol, propanol and butanol solutions, in which compound I precipitates first owing to its lower solubility in these alcohols (confirmed by TLC).



I R=R$_1$=H, R$_2$=CH$_3$
II R=R$_2$=H, R$_1$=CH$_3$
III R=R$_1$=CH$_3$, R$_2$=H
IV R=R$_2$=CH$_3$, R$_1$=H

With monomethylalloxan under the same reaction conditions, compounds III and IV are formed in solution (approx. ratio 3:1) from which, after about 10 minutes precipitates compound III and then a mixture of both compounds. Only traces of the isomeric alloxazines which have the methyl groups at the N-1 position are formed.

Condensation of o-phenylenediamine, or of 4,5-dimethyl-2,3-phenylenediamine, with methylalloxan under the chosen conditions leads to the exclusive formation of compounds V and VI, respectively. In both cases the other possible isomers with methyl groups at the N-1 position are present in the solution only in traces.



The pK_a values of the o-phenylenediamines were estimated potentiometrically to be about 2.95 and 4.3 in water, and about 1.6 and 4.5 in methanol, for the C-2 and C-3 amino groups, respectively. Thus, the first stage of the reaction most probably consists of the condensation of the C-2 amino group with the C-5 carbonyl group of alloxan, which appears to be the most reactive one. This is followed by condensation of the other amino group with the carbonyl at the C-4 or C-6 position of alloxan. When methylalloxan is employed, the second stage predominantly involves the C-6 carbonyl group in the case of 1-methyl-2,3-phenylenediamine, but exclusively the C-6 group when o-phenylenediamine or 4,5-dimethyl-2,3-phenylenediamine are used. Thus, depending on the structure of the reactants and/or properly chosen conditions, Kühling's reaction[4] results in specific products.

The synthesis of compounds I and III have not been previously reported; compounds II, V and VI are obtained in a much more convenient manner than they are by other methods[1,2]. 6-methylalloxazine (I) recrystallized from methanol, greenish-yellow crystals, UV (methanol): λ_{max} ($\log\varepsilon$) = 375(3.76), 335(3.98); IR (KBr): 1710(2-CO), 1750(4-CO)cm^{-1}; PMR($CDCl_3$+TFA, δ): 7.95(aromatic protons, 3H, unsymmetrical multiplet), 2.85(6-CH_3, 3H); mass(m/e): 228. 3,9-dimethylalloxazine(III) recrystallized from methanol, yellow crystals, UV(methanol): λ_{max} ($\log\varepsilon$) = 382(3.76), 336(3.81); IR(KBr): 1720(2-CO, 4-CO)cm^{-1}; PMR($CDCl_3$+TFA, δ): 8.1(aromatic protons, 2H, part of doublet), 7.92(6-CH, multiplet) 3.59(3-CH_3, 3H), 2.75(9-CH_3, 3H); mass(m/e): 242. On TLC(silica gel, benzene-methylethylketone-methanol, 14:1:1, vol./vol.) Rf 0.55 (I) and 0.7 (III). In the presence of acetic acid I showes unperturbed, III perturbed phototautomerism[5].

Acknowledgement. This work was supported, in part, by the Institute of Low Temperatures and Molecular Studies in Wrocław (PAN, project MR.I.9.).

References

1. H. Goldner, G.Dietz, E.Carstens, Liebiegs Ann.Chem., 694, 142 (1966)
2. F. Müller, K.H.Dudley, Helv. Chim. Acta, 54, 1487 (1971)
3. H. Pettering, G.J.Van Giessen, J.Am.Chem.Soc., 26, 2818 (1961)
4. O. Kühling, Ber., 24, 2363 (1891)
5. A. Koziołowa, Photochemistry and Photobiology, 29, 459 (1979)

(Received in UK 18 June 1979)