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REINVESTIGATION OF A RECENT 1,3,4-BENZOTRIAZEPINE SYNTHESIS, FORMATION OF 1,3,4-OXADIAZOLES

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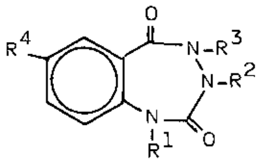
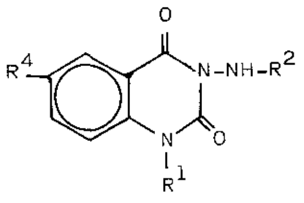
Abstract - It was shown by spectrosopic and synthetic methods that the reaction of anthranilic acid hydrazides with 1,1'-carbonylbisimidazole ($CO/Im/_2$) afforded, in contrast with earlier literature data, no 1,3,4-benzotriazepines or quinazolines but 1,3,4-oxadiazole derivatives.

Langis and Charest[1], later Hromatka et al[2]., further Bailey[3] reported methods for the preparation of the 3,4-dihydro-1H-1,3,4-benzotriazepine-2,5-diones 1. Peet and Sunder[4] reexamined these synthetic routes and proved, that Langis[1] and Bailey's[3] compounds were quinazoline-2,4-diones 2 instead of 1. The synthesis starting with anthranilic acid N,N'-dimethylhydrazides and phosgene described by Hromatka[2] was successful only for the desired benzotriazepines 3, by analogy to the known method for the preparation of this ring system[5]. Namely in this case the N-substitution of the hydrazide moiety hindered the formation of the six-membered ring, which was generally thermodynamically favored over the seven-membered triazepine ring.



1 $R^3 \rightarrow H$

3 $R^3 \rightarrow CH_3$



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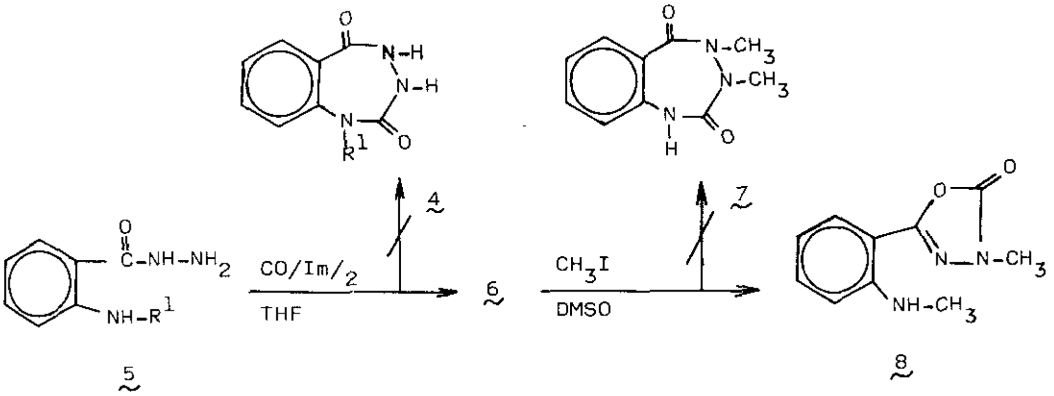
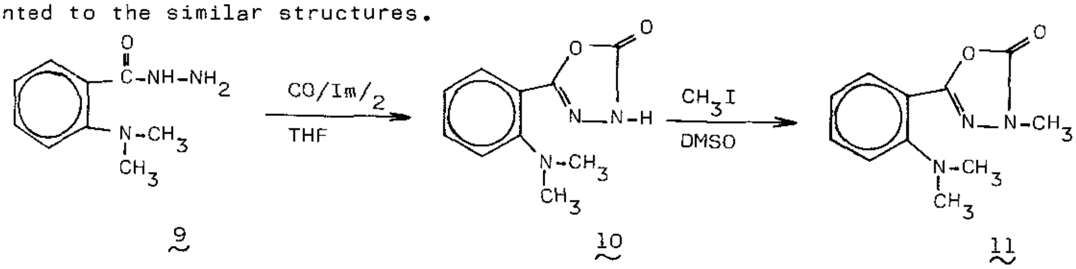
Since 1975, only a few authors have published new results in this field[6,7]. The last one was a simple synthesis from anthranilic acid hydrazides 5 and $CO/Im/_2$ reported by Davidson[8] to afford 1,3,4-benzotriazepines 4.

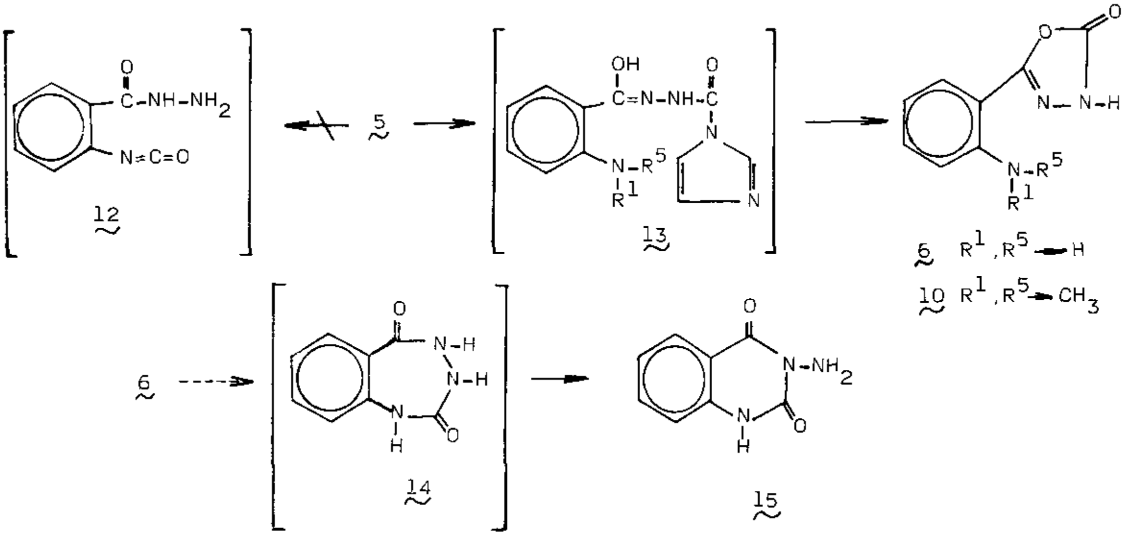
We reproduced his method ($R_1 \rightarrow H$) and established that the structure of the product (6) was not 4 as was claimed[8].



Though elementary analyses and mass spectra did not exclude the benzotriazepine or quinazoline structures, the IR spectrum contained no amide bands, but a very strong absorption band at 1780 cm^{-1}. The missing CO-NH band suggests that the hydrazide carbonyl may have taken part in the reaction. Dimethylation of 6 didn't give the known 7,[4,9] but a novel compound 8, which also has no CO-NH bands in the IR spectrum. In the ^1H NMR spectrum an N-CH_3 and an NH-CH_3 group were identified, so we assigned the structure of a 1,3,4-oxadiazol-5-one 8 to this product. Hence 6 must be the corresponding non-methylated oxadiazole. When N,N-dimethylanthranilic acid hydrazide 9 and CO/Im/$_2$ were reacted analogously, the same type of reaction was observed and 10 was isolated. This was methylated to give 11. The close similarity of the IR spectra of 6,8,10 and 11[10] have also pointed to the similar structures.



In light of the above results, in the reaction of 5 with CO/Im/$_2$, we do suppose an intermediate 13 rather than 12 which had earlier been suggested[8]. The rearrangement of 6 (erroneously proposed[8] to be the benzotriazepine 14) to quinazoline 15 observed by Davidson may be explained to proceed via 14.



Syntheses of 1,3,4-oxadiazoles from acid hydrazides are known[11], in which the one carbon fragment was from orthoesters, imidoesters, phosgene, thiophosgene, isocyanide dichlorides etc., but 1,1'-carbonylbisimidazole has not been applied for this purpose before.

ACKNOWLEDGEMENTS

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9. Methylation of both 3,4-dihydro-3-methyl- and 3,4-dihydro-4-methyl-1H-1,3,4-benzotriazepine-2,5-dione give **3**[4].

10. All compounds gave satisfactory microanalytical data.

6 mp 175-176 °C; 55 % yield; δ (DMSO-d_6) 6.2 b 2H, NH$_2$; 6.63-7.45 m 4H, Ar-H; ν 3470, 3370, 3140, 1770 cm^{-1}

8 mp 179-180 °C; 85 % yield; δ (DMSO-d_6) 2.88 d 3H, NH-CH$_3$; 3.25 s 3H, N-CH$_3$; 6.6 b 1H, NH; 6.6-7.7 m 4H, Ar-H; ν 3400, 1780 cm^{-1}

10 mp 108-110 °C; 72 % yield; δ (CDCl$_3$) 2.80 s 6H, N(CH$_3$)$_2$; 6.8-7.7 m 4H, Ar-H; 10.4 b 1H, NH; ν 3100 b, 1780 cm^{-1}

11 honey; 90 % yield; δ (CDCl$_3$) 2.80 s 6H, N(CH$_3$)$_2$; 3.50 s 3H, N-CH$_3$; 6.8-7.7 m 4H, Ar-H; ν 1780 cm^{-1}

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