SYNTHESIS OF CYCLOHEPTADIIMIDAZOLE DERIVATIVES FROM A REACTIVE TROPONOID[1)]

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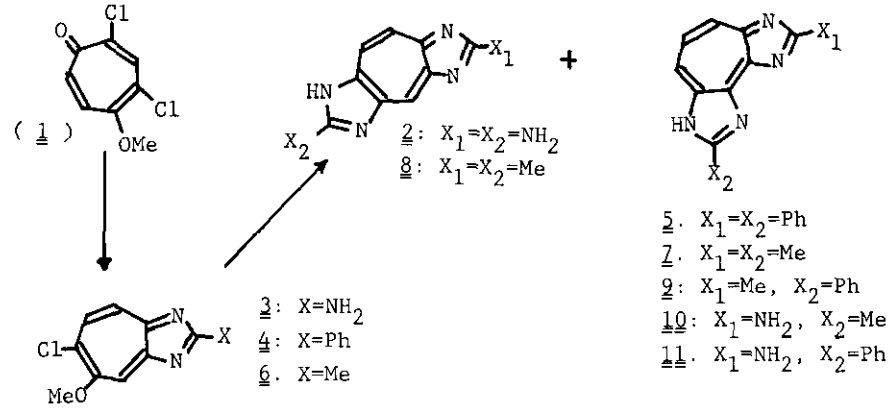
Abstract———The condensation of 2,4-dichloro-5-methoxytropone with guanidine or with amidines gave 1H-cyclohepta[1,2-d;3,4-d]-diimidazoles and 1H-cyclohepta[1,2-d;4,5-d]diimidazoles, which possess the same heterocyclic skeletons with unique metabolites isolated from marine organisms. According to the NMR analysis, the condensations proceeded in the exclusive cine reaction.

The isolations of cycloheptadiimidazoles, paragracines,[2)] zoanthoxanthins,[3)] and parazoanthoxanthins,[4)] from marine organisms are recent surprise of the natural product chemistry. A proposal on the biogenesis of these derivatives by Prota has been supported by the Büchi's total synthesis.[5)] In view of the basic skeletons of these natural products, we have undertaken the synthetic study of the ring systems. Normally, 1,3-diazazulenes are prepared by a condensation of 2-methoxytropone or 2-halotropones with guanidine, amidines, thiourea, or urea.[6–8)] Although there is a potential difficulty, i.e., no condensate has been obtained so far when tropones had an electron-releasing substituent,[7)] the two-fold condensation of amidines with an appropriate troponoid should produce the desired heterocycles. The condensation reaction of 2,4-dichloro-5-methoxytropone (1)[9)] indeed verified the prediction. When 1 and guanidine were allowed to react as benzene suspension with powdered KOH under vigorous stirring, a development of fluorescent spots was observed on thin-layer chromatograms. The high-pressure liquid chromatography of the mixture gave an intense fluorescent compound, 2 (yellow solid, mp >300°C, 2%), showing simple but characteristic NMR[δ[10)]: 8.93(2H, s), and 9.43(1H, s)] data, which resembled

those of parazoanthoxanthin A,[5] and a non-fluorescent product, 3 (yellow solid, mp 180-182°C, 84%). The NMR spectrum of 3[δ^{CDCl_3}: 4.09(3H, s), 7.62(1H, d, J=11 Hz), 7.80(1H, s), and 8.01(1H, d, J=11 Hz)] indicated to be a 1,3-diazazulene derivative, a 1:1-condensate, for which, depending on the mode of the reaction, two formulations must be considered. By the mutual NMDR experiments, a long-range spin-coupling between the methoxyl signal and the 1H signal at δ: 7.80(br. s) was confirmed to eliminate the normal condensation mode. Thus, the structure is depicted as shown. A further reaction of 3 with large excess of guanidine yielded 2 (8%) as expected.[11]

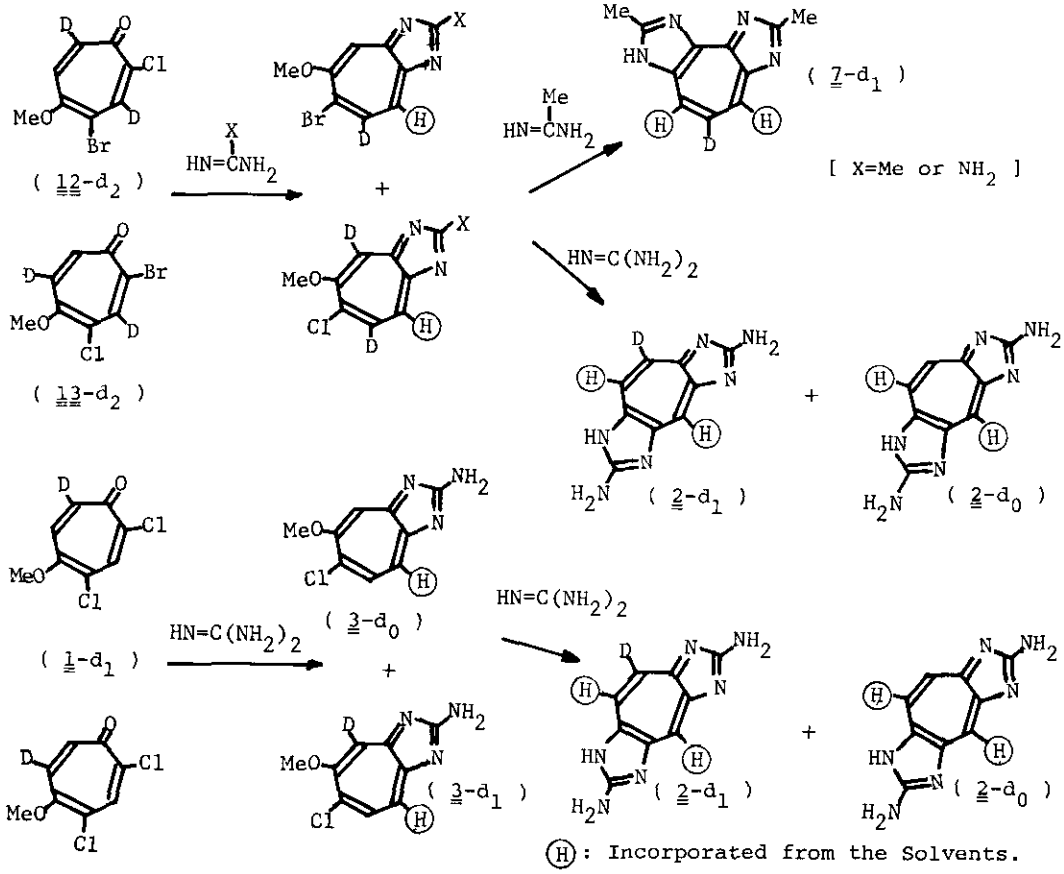
Similarly, the condensation of 1 with benzamidine gave a 1:1-condensate, 6-chloro-5-methoxy-2-phenyl-1,3-diazazulene (4, yellow needles, mp 170-171°C, 78%)[δ^{CDCl_3}: 4.13(3H, s), 7.3-7.7(3H, m), 8.13(1H, d, J=11 Hz), 8.26(1H, d, J=11 Hz), 8.33(1H, s), and 8.4-8.65(2H, m)] and 2,5-diphenyl-1H-cyclohepta[1,2-d;3,4-d]diimidazole (5, 180-183°C, 15%)[δ: 7.7-8.1(6H, m), 8.3-8.6(4H, m), 8.80(1H, t, J=10 Hz), and 9.36(2H, d, J=10 Hz)]. The highest yield, 31%, for 5 was obtained by the reaction of 4 with the amidine. With acetamidine, 1 produced 6-chloro-5-methoxy-2-methyl-1,3-diazazulene (6, yellow needles, mp >300°C, 71%)[δ^{CDCl_3}: 2.92(3H, s), 4.18 (3H, s), 8.18(1H, d, J=12 Hz), 8.25(1H, d, J=12 Hz), and 8.36(1H, s)], along with two 1:2-condensates, 2,5-dimethyl-1H-cyclohepta[1,2-d;3,4-d]diimidazole (7, yellow solid, 2%)[δ^{CD_3OD}: 2.84(6H, s), 8.00(1H, t, J=10 Hz), and 8.57(2H, d, J=10 Hz)] and 2,6-dimethyl-1H-cyclohepta[1,2-d;4,5-d]diimidazole (8, yellow solid, 1%) [δ^{CD_3OD}: 2.76(6H, s), 8.45(2H, s), and 8.99(1H, s)]. A further reaction of 6 with the amidine gave 7(15%) and 8(10%). However, the reaction of 1 with formamidine formed no isolable condensate.



In all the cases, the yields of the 1:1-condensates were sufficiently good, and some cross-condensations can be carried out: Thus, a condensation of benzamidine to

6 produced 2-methyl-5-phenyl-1H-cyclohepta[1,2-d;3,4-d]diimidazole (9, yellow needles, mp 220°C(dec), 79%)[δ: 3.32(3H, s), 7.7-8.1(3H, m), 8.4-8.6(2H, m), 8.88 (1H, t, J=10 Hz), 9.37(1H, dm, J=10 Hz), and 9.47(1H, dm, J=10 Hz)]. Guanidine and 6 also formed 2-amino-5-methyl-1H-cyclohepta[1,2-d;3,4-d]diimidazole (10, yellow solid, 11%)[δ: 3.20(3H, s), 8.54(1H, t, J=10 Hz), and 8.86(2H, d, J=10 Hz)]. In the same manner, the reaction of 4 with guanidine gave 2-amino-5-phenyl-1H-cyclohepta[1,2-d;3,4-d]diimidazole (11, yellow needles, mp 260-262°C, 41%)[δ: 7.6-8.05(3H, m), 8.35-8.6(2H, m), 8.55(1H, t, J=10 Hz), 8.85(1H, d, J=10 Hz), and 8.96(1H, d, J=10 Hz)].

Subsequently, we have carried out the experiments to determine the mode of the formation of cycloheptadiimidazole skeletons. As mentioned, the first step of the condensation with 1 was the cine-mode. Second step of the condensation to the 1H-cyclohepta[1,2-d;3,4-d]diimidazole derivatives must also be the cine-reaction, but that to the [1,2-d;4,5-d] derivatives may be either the cine- or the normal mode, which can be distinguished by means of the deuterium labelling experiments.



Accordingly, we have prepared[12] a deuterated mixture (ca. 1:1) of 12-d_2 (4-bromo-2-chloro-5-methoxytropone-3,7-d_2) and 13-d_2 (2-bromo-4-chloro-5-methoxytropone-3,6-d_2) [δ^{CDCl_3}: 4.01(3H, s) and 7.22(1H, br. s). $\delta(C)^{CDCl_3}$: 58.2, 113.1, 125.2*,[13] 133.6, 135.9, 137.5*, 159.5, and 177.8 (13-d_2); 58.1, 106.0, 124.8, 137.5*, 137.9*, 141.6, 158.5, and 177.5 (12-d_2)], and 1-d_1 (a 1:1-mixture of 2,4-dichloro-5-methoxytropone-6-d_1 and 2,4-dichloro-5-methoxytropone-7-d_1) [δ^{CDCl_3}: 4.01(3H, s), 7.25(1H, s), and 8.02(1H, s). $\delta(C)^{CDCl_3}$: 58.0, 123.2, 125.2*, 136.9*, 138.2, 140.3, 158.1, and 177.2], from 3,5,7-tropolone-d_3 and 4,6-tropolone-d_2, respectively.[14]

The condensation of the 1:1-mixture of 12-d_2 and 13-d_2 with acetamidine was carried out, until all the tropones reacted, to give the deuterated 6, 7 and 8, from which, the major product, 7-d_1 (10%), was isolated. The NMR spectrum of 7-d_1 [δ^{CD_3OD}: 2.84(6H, s), 8.57(2H, s), and 8.0(less than 0.05H, t)] showed the position of the deuterium to be C-8. Therefore, the second step in the formation of 7 is the typical cine-reaction as predicted, i.e., the codensation at C-4 and C-5. An absence of 7-d_0 on the basis of the NMR and mass spectroscopy ruled out the condensation at C-7 and C-8 positions. Such a possibility has to be considered since the Grignard reaction of 1,3-diazazulenes is known to cause a nucleophilic addition at C-4 (C-8) and C-6 positions.[15]

Similarly, the condensation of a mixture of 12-d_2 and 13-d_2 with guanidine led to the isolation of the major product, labelled 2 (10%). However, the NMR[δ: 9.00 (1H, s) and 9.50(1H, s)] and the mass[Found: m/e, 200 and 201(1:30)] spectra have indicated the absence of 2-d_2. It was rather an odd result; it should offer an explanation that a replacement of the halogen, chlorine to bromine, may diminish the reactivity, or alternatively, an exchange of deuterium of labelled 2 may occur during the work-up (reverse phase high-pressure liquid chromatography, Radial Pack A/MeOH-H_2O). The latter was, however, shown not to be the case; an attempted deuteration of 2-d_0 by D_2SO_4 or NaOD in methanol-d_4 resulted in the complete recovery. The condensation of another labelled compound (1-d_1) with guanidine was carried out in parallel; again it gave a mixture (10%) of 2-d_1 and 2-d_0 as indicated by the NMR[δ: 9.00(1.4H, s) and 9.50(1H, s). Ratio of two signals: Found=1.4. Calcd: 1.5 for the cine-mode; 4.0 for the normal mode] and the mass [Found: m/e, 200, 201(ca. 1:1)] spectra. Therefore, the cine-mode for the second-step has been established. In addition, the overwhelming formation of 2-d_1 from 12-d_2 and 13-d_2 is now explained by the difference of steric effect at the

reactive site; the bromine on the 1:1-condensates is sterically more hindered than the chlorine against an attack of amidines to give the results.[16)]

Finally, we like to make a comment on the ^{13}C-NMR spectra of new 1,3-diazazulenes, 3, 4, and 6. Since we have their parent derivatives, 2-amino-, 2-phenyl-, and 2-methyl-1,3-diazazulenes, a consideration of the substituent effects of chlorine and methoxy group evaluated in the benzene series[17)] should give an estimation. As shown in Table 1, they revealed a good agreement with the experimental, except C-6, where chlorine is located vicinally to the methoxy group. This constitutes another support for the revised assignment of the ^{13}C-NMR spectra of the 1,3-diazazulene derivatives.[18, 19)]

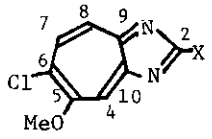


Table 1: The ^{13}C-NMR Spectra of 1,3-diazazulenes.

		2	4	5	6	7	8	9	10	[Solvents]
X=NH_2	Found:	175.8	106.8	162.8*	125.6	134.2	116.0	158.8	163.0*	[$(CD_3)_2SO$]
	Calcd:	175.5	109.2	164.8	120.6	134.6	115.8	154.1	163.0	
X=Ph	Found:	177.1	115.6	161.6*	136.0	134.4	126.6	159.3	161.1*	[$CDCl_3$]
	Calcd:	176.7	119.7	164.6	128.3	134.4	126.3	153.0	161.9	
X=Me	Found:	180.7	115.6	160.3*	136.1	134.3	126.0	159.3*	161.3*	[$CDCl_3$]
	Calcd:	179.8	119.0	164.5	128.5	134.3	125.6	152.5	161.2	

Asterisked assignments (*) may be reversed.

Acknowledgement: We are grateful to Mr. H. Mametsuka, This Institute, for the deuteration experiment of 2-d_0.

References and Notes

1) This paper was read in the 12th Symposium on the Chemistry of Non-Benzenoid Aromatic Compounds (September, 1979, Matsumoto), Abstract Papers, p. 85. We wished to publish the results simultaneously with Dr. M. Yasunami, Tohoku University, who informed us that his work was in progress. Recently, a paper on the synthesis of 2 (M. Yasunami, Y. Sasagawa, and K. Takase, Chem. Lett., 205 (1980)) appeared.

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10) Since these compounds are only slightly soluble in $CDCl_3$, the NMR spectra were obtained in CF_3COOD unless otherwise specified. The chemical shifts were expressed in the δ values from the internal standard, Me_4Si. The chemical shifts of these derivatives were concentration dependent.

11) We have obtained an intense fluorescent compound as crystalline by-product. Apparently, Yasunami et al. also obtained this material [δ: 8.20(s)], which was tentatively assigned as a [1,2-d;3,4-d] derivative.[1] However, on the basis of an independent mass spectral evidence, this may be a 1:3-condensate of the troponoid and guanidine. Its structure will be described in another paper.

12) An employment of 12-d_2 and 13-d_2 rather than 1-d_2 was due to the method of derivations: 1 was conveniently prepared from 2-bromo-4-chloro-5-hydroxytropone by ān HCl treatment. However, this might cause an unlabelling of deuterium from the dihalotropone. Later stage of this work, we have found conditions to get the isotopically pure 1-d_1.

13) Asterisked signals revealed dimished intensities due to the deuterations.

14) S. Itô, J. Tsunetsugu, T. Kanno, H. Sugiyama, and H. Takeshita, Tetrahedron Lett., 3659 (1965).

15) T. Mukai, H. Tsuruta, and Y. Momotari, Bull. Chem. Soc. Jpn., 40, 1967 (1967).

16) The 1,3-diazazulenes obtained from a mixture of 12-d_0 and 13-d_0 with guanidine were 3 and its bromo analog (in a ratio of 1:1).

17) G. L. Nelson, G. C. Levy, and J. D. Cargioli, J. Am. Chem. Soc., 94, 3089 (1972).

18) H. Takeshita and H. Mametsuka, Heterocycles, 12, 653 (1979).

19) The ^{13}C-NMR of cycloheptadiimidazoles will be reported elsewhere.

Received, 29th March, 1980