OXIDATION OF 2,5-DIHYDRO-1,2,3-TRIAZINES BY m-CHLOROPERBENZOIC ACID

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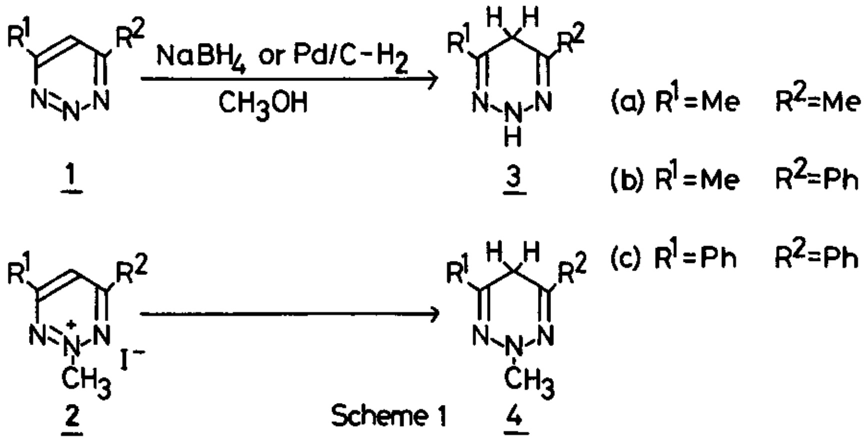
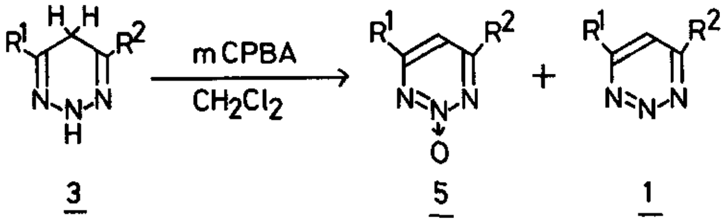
Abstract —— 2,5-Dihydro-1,2,3-triazines were oxidized by m-chloroperbenzoic acid to give only 1,2,3-triazine 2-oxides, while the oxidation of 1,2,3-triazines yielded the mixtures of 1- and 2-oxides.
In case of adopting 2-methyl-2,5-dihydro-1,2,3-triazines as starting materials, 2-methyltriazoles and 2,5-dihydro-5-oxo-1,2,3-triazines were obtained.

Monocyclic 1,2,3-triazines (1)[1] and their 2-methyl quaternary salts (2)[2] were readily reduced to corresponding 2,5-dihydro-1,2,3-triazines by catalytic hydrogenation or treatment with $NaBH_4$[2](Scheme 1).



Scheme 1

These dihydro compounds are of considerable interest as compared with 1,4-dihydropyridines, which are very important from the biological point of view. In this paper we wish to report that the oxidation of 2,5-dihydro-1,2,3-triazines by m-chloroperbenzoic acid (mCPBA) occurred in a peculiar manner. 1,2,3-Triazines (1) were oxidized by mCPBA to the mixtures of 1- and 2-oxides. For example, 1-(a) gave 20% of 1-oxide and 48% of 2-oxide when treated with 1.2 equivalent of mCPBA in CH_2Cl_2 solution.[3] Thus 2,5-dihydro-1,2,3-triazine (3)(1.0 mmol) was dissolved in CH_2Cl_2 (10 ml) under nitrogen atmosphere in order to avoid the air oxidation, and was stirred with various amounts of mCPBA for 12 h. After purification by alumina column chromatography, products were obtained as shown in Table 1.

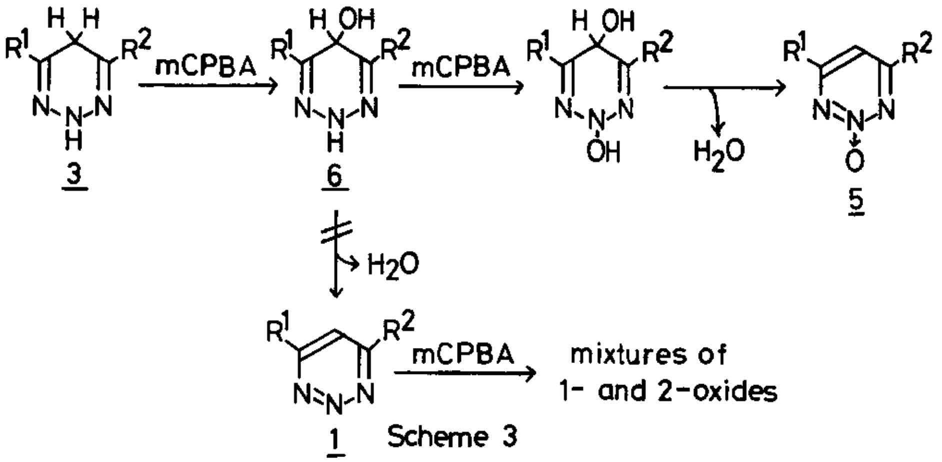


Scheme 2

Table 1 Oxidation of 2,5-Dihydro-1,2,3-triazines (3) by m-Chloroperbenzoic acid (mCPBA)

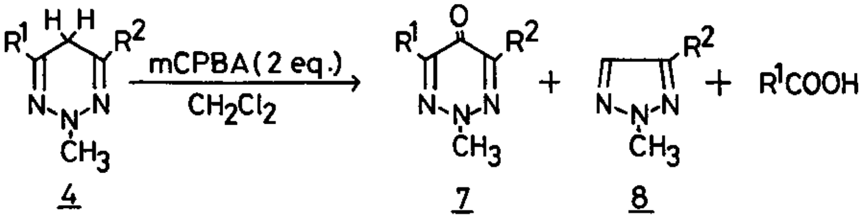
3	Amount of mCPBA (eq.)	Yield of 5 (%)	Yield of 1 (%)
(a)	0.5	21	2
(a)	1.0	46	2
(a)	2.0	94	trace
(b)	2.0	97	0
(c)	2.0	80	0

From 3, N-oxides (5) were also obtained, but the oxidation positions were selectively N-2. In addition, 1,2,3-triazines (1) which were postulated as oxidation intermediates were hardly obtained even by decreasing the amount of the oxidant (Scheme 2 and Table 1). These facts suggest that 1 is not the intermediate of the 2-oxide(5), that is, the intermediate 6 (Scheme 3) which is the compound formed by the first oxidation of 3 does not result in the formation of 1, but is oxidized immediately by the second mCPBA followed by H_2O elimination to give only 2-oxide (Scheme 3).



Scheme 3

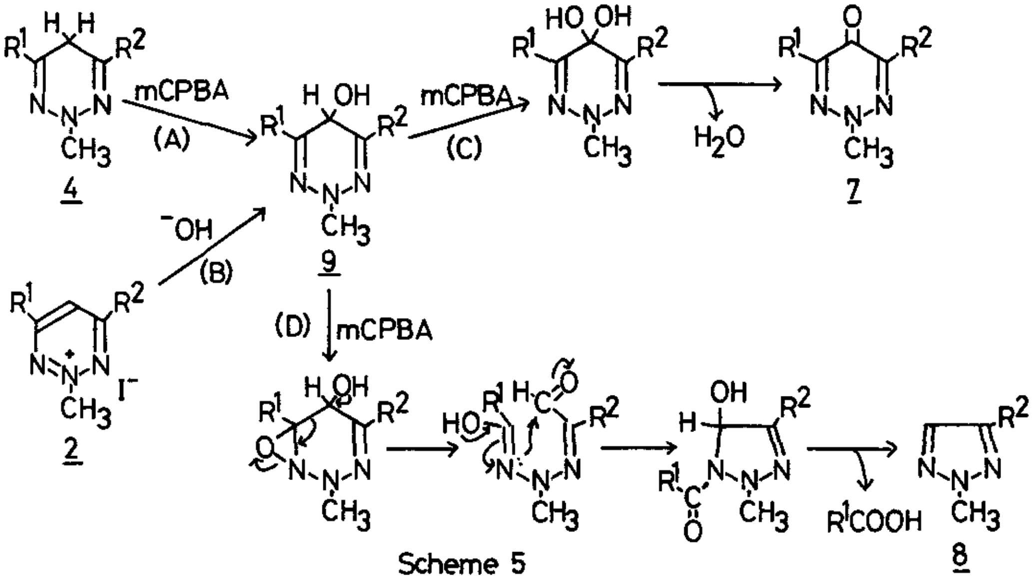
Next, 4 was allowed to react under the same conditions, 5-oxo-2,5-dihydrotriazines (7) and 2-methyltriazoles (8) were obtained as shown in Scheme 4 and Table 2. When R^1 and R^2 were phenyl group, benzoic acid was also produced in 23% yield.[4] On the other hand, 2 was treated with KOH in CH_2Cl_2/H_2O for 5 min under nitrogen atmosphere, succeeding separation of CH_2Cl_2 layer, and allowed to react with 1.2 equivalent of mCPBA, which resulted in the formation of 8. The above mentioned consequences suggest that the same intermediate 9 exists on both reactions (Scheme 5, A and B). When R^1 and R^2 are sterically small, path C has priority. First and second attacks of mCPBA to C-5 position occurred, and following H_2O elimination yielded 7. On the contrary, path D proceeds in case of R^1 or R^2 is phenyl group. Second attack of mCPBA to C-5 was inhibited because of steric hindrance, and N-2 was blocked in this case,



Scheme 4

Table 2 Oxidation of 2-Methyl-2,5-dihydro-1,2,3-triazines (4) by mCPBA

4	Yield of 7 (%)	Yield of 8 (%)	R^1COOH (%)
(a)	30	trace	-
(b)	9	68	-
(c)	0	69	23



Scheme 5

so the second oxidant reacted at N-1 and the following ring-opening and ring-closure afforded 8 accompanied by the elimination of carboxylic acid. In summary, C-5 positions of dihydrotriazines are most easily oxidized by mCPBA, and if N-2 is free, the second attack occurs at this position. In case of blocking at N-2, the second oxidation was also at C-5, but the presence of steric hindrance changes the reaction site to N-1 position.

REFERENCES AND NOTES

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2. A. Ohsawa, H. Arai, H. Ohnishi, T. Kaihoh, T. Itoh, K. Yamaguchi, H. Igeta, and Y. Iitaka, Yakugaku Zasshi, in press.
3. A. Ohsawa, H. Arai, H. Ohnishi, T. Kaihoh, K. Yamaguchi, H. Igeta, and Y. Iitaka, Chem. Pharm. Bull., in press.
4. Benzoic acid was estimated by being derived to its methyl ester.

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