[Chem. Pharm. Bull. 22(10)2301—2305(1974)]

UDC 547.852.2.04 : 541.14

Photochemistry. XII.[1] Photochemical Behavior of 2-Methyl-3(2H)-pyridazinone 1-Oxides

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(Received March 20, 1974)

Irradiation of 6-unsubstituted-2-methyl-3(2H)-pyridazinone 1-oxide (**5**) in neutral alcohol resulted in the ring contraction to form N-methylamino-isomaleimide (**6**), γ-lactone of 4-hydroxy-2-pentenoic acid (**7**), 2-methyl-3,6-pyridazinedione (**8**), and the deoxygenated parent pyridazinone (**9**). The 6-substituted 1-oxide (**5**) afforded **7** and **9** alone.

On the other hand, in the case of irradiation in alcohol containing HCl, the 6-unsubstituted compound (**5**) afforded 6-chloro-2-methyl-3(2H)-pyridazinone (**14**), derived by chlorination at the α-position to the N-oxide group. The 6-substituted compound (**5**) gave 6-chloromethyl-3(2H)-pyridazinone (**15**), derived by chlorination at N–CH_3 group. The formation mechanism of these compounds is also discussed.

In prototropic tautomerism, it is well known that[3] among two possible tautomers of 3-hydroxypyridazine, the keto-structure, *i.e.*, 3(2H)-pyridazinone has a larger contribution. In photolysis, under the condition which could not cause any reaction of usual pyridazines, treatment of 3(2H)-pyridazinones resulted in the ring contraction to form N-amino-Δ^3-pyrrolin-2-ones[4] in alcohol. And irradiation of 3(2H)-pyridazinone in alcohol containing hydrogen chloride resulted in the elimination of molecular nitrogen. Namely, 3(2H)-pyridazinones having hydroxy group or halogen atom in the 6-position afforded paraconates and succinates, whereas 3(2H)-pyridazinones having methyl or phenyl group in the 6-position gave 3-acylpropanoates, on which we have already reported.[5]

Meanwhile, in both cases of 1- and 2-oxides of 3-hydroxypyridazine N-oxides, the hydroxy-structures were known to have a larger contribution from the spectral data.[6] The photolysis[7] of the 1-oxide (**1**) and the 2-oxide (**2**) gave Δ^3-γ-lactone (**3**) and isomeric Δ^2-γ-lactone (**4**), respectively. The reaction seemed to proceed through a similar mechanism to that of the pyridazine N-oxides.[8]

From this fact, the N-oxides (**1** and **2**) seemed to undergo the reaction not as the keto-forms but as the hydroxy-forms. Thus, we have examined the photochemical behavior

1) Part XI: T. Tsuchiya, M. Hasebe, H. Arai, and H. Igeta, *Chem. Pharm. Bull.* (Tokyo), **22**, 2276, (1974).
2) Location: *1-5-8, Hatanodai, Shinagawa-ku, Tokyo, 142, Japan.*
3) A.R. Katritzky and J.M. Logowski, "Advance in Heterocyclic Chemistry," Vol. 1 ed. by A.R. Katritzky, Academic Press, New York, 1963, p. 339.
4) T. Tsuchiya, H. Arai, M. Hasebe, and H. Igeta, Presented at the 6th Congress of Heterocyclic Chemistry, Nagoya, Japan, November, 1973.
5) T. Tsuchiya, H. Arai, and H. Igeta, *Tetrahedron Letters*, **1970**, 3839; *idem*, *Chem. Pharm. Bull.* (Tokyo), **19**, 1108 (1971); T. Tsuchiya, H. Arai, H. Kawamura, and H. Igeta, *Chem. Pharm. Bull.* (Tokyo), **20**, 269 (1972).
6) H. Igeta, T. Tsuchiya, M. Nakajima, and H. Yokogawa, *Chem. Pharm. Bull.* (Tokyo), **17**, 763 (1969).
7) T. Tsuchiya, H. Arai, M. Hasebe, and H. Igeta, Presented at the 93rd Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April, 1973.
8) Photolysis of pyridazine N-oxides generally afforded three kinds of the compounds, *i.e.*, pyrazoles, furans, and cyclopropenyl ketones. But, dependent on the substituents or the reaction conditions, they gave one or two kinds of the three. T. Tsuchiya, H. Arai, and H. Igeta, *Tetrahedron*, **29**, 2747 (1973); K.B. Tomer, N. Harrit, I. Rosenthal, O. Buchardt, P.L. Kumler, and D. Creed, *J. Am. Chem. Soc.*, **95**, 7402 (1973) and references cited therein.

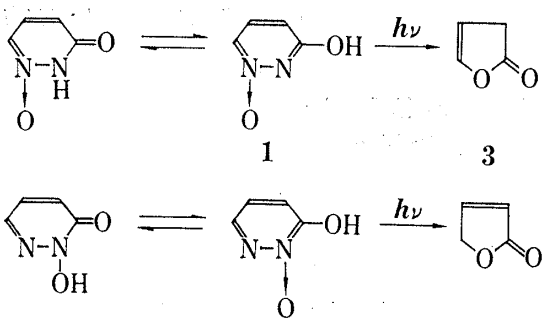
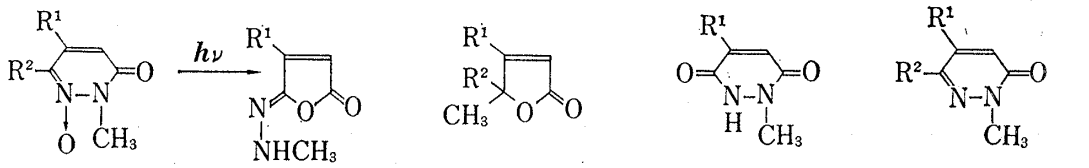


Chart 1

of 2-methyl-3(2H)-pyridazinone 1-oxide (**5**) having rigid keto-form in neutral and acidic alcohols and have obtained somewhat different results.

Photolysis in Neutral Alcohol

Irradiation of the N-oxides (**5a** and **5b**) having no substituent in the 6-position in MeOH or EtOH for *ca.* 2 hr under nitrogen atmosphere, gave N-methylaminoisomaleimide (**6a**: 20%, **6b**: 15%), 4-methyl-Δ^2-γ-lactone (**7a**: 18%, **7b**: 10%), and N-methyl-3,6-pyridazinedione (**8a**: 18%, **8b**: 23%), respectively. The N-oxide (**5c**) having methyl group in the 6-position did not afford the compound (**6** and **8**), but gave γ-lactone (**7c**: *ca.* 20%) and deoxygenated pyridazinone (**9c**: 13%). The compound (**9**) was also obtained in the case of **5** (**a** and **b**) in low yield.



5a: $R^1=R^2=H$
5b: $R^1=Me$, $R^2=H$
5c: $R^1=H$, $R^2=Me$

6a: $R^1=H$
6b: $R^1=Me$

7a: $R^1=R^2=H$
7b: $R^1=Me$, $R^2=H$
7c: $R^1=H$, $R^2=Me$

8a: $R^1=H$
8b: $R^1=Me$

9a: $R^1=R^2=H$
9b: $R^1=Me$, $R^2=H$
9c: $R^1=H$, $R^2=Me$

Chart 2

Isomaleimides (**6**) thus obtained were novel compounds and their structures were proposed by comparison with the data[9] of N-acyl- and N-phenyl-aminoisomaleimides. γ-Lactone (**7a**) was identical with the compound synthesized by alternative method described in the literature.[10] The structures of the compounds (**7b** and **7c**) were elucidated by comparison of their spectral data with those of **7a**.

Possible mechanism of the formation of the products (**6**—**8**) is presented in Chart 3. It is well known in many cases[11] that irradiation of nitrones resulted in the rearrangement to give oxaziridines, and the deoxygenation to afford parent heterocycles. Thus, pyridazinedione (**8**) was considered to be formed directly from the intermediate (**10**). 3-Carboxyacryloylhydrazines carrying electron-withdrawing substituents such as acyl or phenyl group at their amino groups were enough stable to be isolated and gave three kinds of the compounds, *i.e.*, pyridazinones, maleimides, and isomaleimides by dehydration with acetic anhydride or thionyl chloride. Therefore, in the present work the mechanism *via* the hydrazine (**11**) as an intermediate is worth to be considered. But, the hydrazine (**11**) with electron-donating substituent such as alkyl group, which was formed by reaction of maleic anhydride with alkylhydrazine, was unstable to be isolated and gave pyridazinone directly in high yield but did not give isomaleimide.[12] Moreover, irradiation of maleic anhydride and methylhydrazine in alcohol afforded pyridazinone (**8**) alone, and did not give the compounds (**6** and **7**). And from **8**, the compounds (**6** and **7**) were not obtained by heating or irradiation in alcohol.

9) H. Rubinstein, J.E. Skarbek, and H. Feuer, *J. Org. Chem.*, **36**, 3372 (1971).
10) L.J. Haynes and E.R.H. Jones, *J. Chem. Soc.*, **1946**, 954.
11) C. Kaneko, *J. Syn. Org. Chem. Japan*, **26**, 735 (1968); E.C. Taylor, G.G. Spence, and O. Buchardt, *Chem. Rev.*, **70**, 231 (1970).
12) M. Tisler and B. Stanovnik, "Advance in Heterocyclic Chemistry," Vol. 9, edited by A.R. Katritzky and A.J. Boulton, Academic Press, 1968, p. 211.

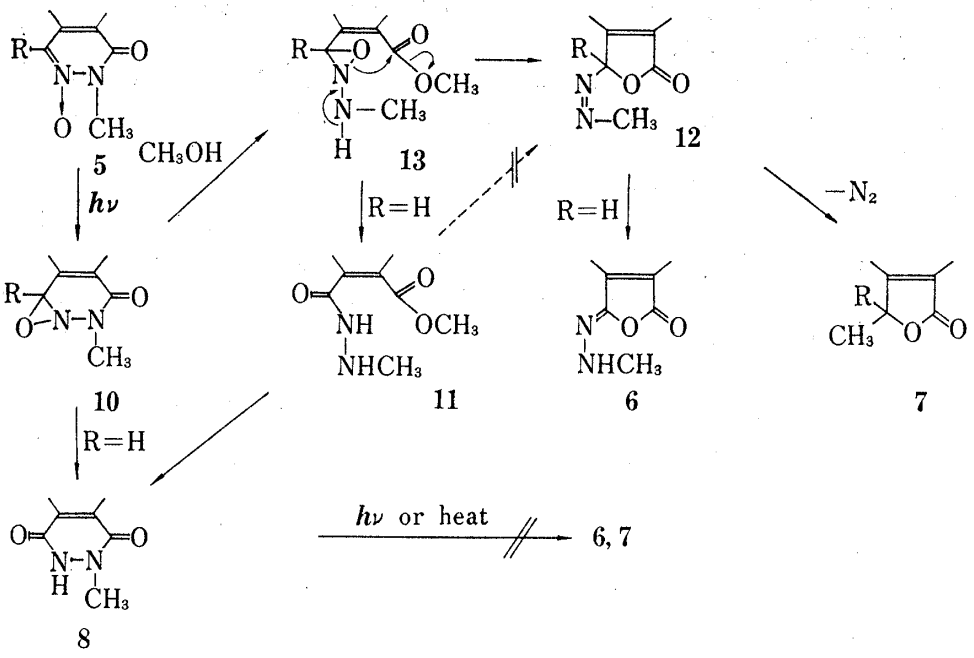


Chart 3

Therefore, it is reasonable to consider that the compounds (**6** and **7**) might be formed from the intermediate (**12**), derived by direct cyclization of oxaziridine (**13**). Presence of the methyl group in the 4-position of the γ-lactone (**7**) in case of irradiation in EtOH, suggests that the methyl group was apparently derived from the N-methyl group of the starting material (**5**) by rearrangement of the intermediate (**12**) during elimination of nitrogen molecule. Furthermore, irradiation of isomaleimide (**6**) did not give the γ-lactone (**7**).

Photolysis in Acidic Alcohol

The N-oxide (**5**) was irradiated in MeOH containing 5% HCl for 1.5—2 hr and the reaction mixture was neutralized with Na_2CO_3, followed by evaporation of the solvent. The products were separated by column chromatography on alumina.

From unsubstituted N-oxide (**5a**), 1-methyl-6-chloro-3(2H)-pyridazinone (**14**: *ca.* 8%), derived by chlorination in the α-position to the N-oxide group followed by deoxygenation, was obtained. From 6-methyl compound (**5c**), 1-chloromethyl-6-methyl-3(2H)-pyridazinone[13]

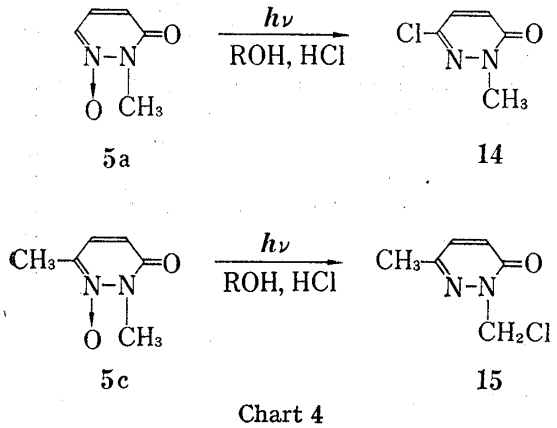


Chart 4

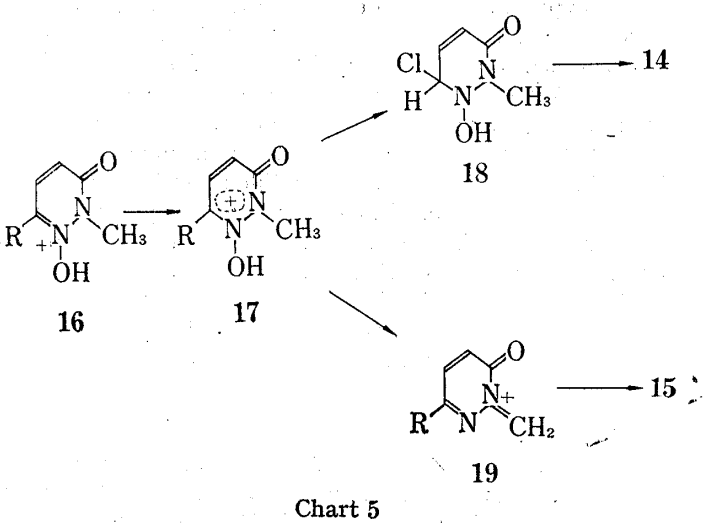


Chart 5

13) S.D. Breuil, U.S. Patent 2938902 (1960) [*Chem. Abstr.*, **54**, 21146 (1960)].

(**15**: *ca.* 15%) was obtained. In both cases, besides them, the deoxygenated compounds were obtained in 5—10% yields.

Since treatment of the N-oxide (**5**) with hydrochloric acid in alcohol and irradiation of 2-methyl-3(2H)-pyridazinones without N-oxide groups under similar condition did not give[14] any chloro compounds such as **14** and **15**, this photochemical chlorination might apparently concern the N-oxide functional group.

Recently Kaneko, *et al.*[15] reported the photoalkoxylation and chlorination by irradiation of 2-cyanoquinoline 1-oxides in acidic alcohol. Thus, the chlorination in the present work might proceed through a similar mechanism. Namely, protonated N-oxide (**16**) gives **14** by adding chlorine anion to the diaziridine intermediate (**17**). After elimination of a proton from the N–CH_3 group, chlorination occurs to produce **15**. But, in this case, the alkoxylated product was not obtained. It is interesting that the photochlorination of the N-methyl group has not yet been known, and further investigations, including this findings, are now in progress.

Experimental

Photolyses were carried out in an immersion apparatus equipped with a 200 W high pressure mercury lamp (Nikko Sekiei Co., Japan) and cooled internally with running water. Infrared (IR) spectra were determined with a JASCO IR-1 spectrometer and Mass (MS) spectra were recorded on a Hitachi RMS-4 instrument. Nuclear magnetic resonance (NMR) spectra were recorded on a Hitachi R-20 and R-22 spectrometers in CCl_4 or $CDCl_3$ solution using tetramethylsilane as internal standard. Melting points were measured on a Yamato MP-1 apparatus and uncorrected. Microanalyses were performed in the analytical laboratory of this school by Miss T. Kihara and Mrs. K. Shiobara. Column and thin-layer chromatography were carried out with alumina and silica gel obtained from Merck Co., Ltd.

Preparation of 2-Methyl-3(2H)-pyridazinone 1-Oxides (5)——The N-oxides (**5**) were usually prepared by methylation of 3-hydroxypyridazine 1-oxides, but coventional method[16] such as Me_2SO_4–NaOH or MeI–Ag_2O resulted in the predominant formation of 3-methoxypyridazine 1-oxides and the yields of **5** were low. Thus, they were prepared by the following procedure using diazomethane.

General Procedure: To a suspension of 3-hydroxypyridazine 1-oxide in CH_2Cl_2 was added dropwise an ethereal solution of diazomethane at room temperature under stirring. Stirring was continued until the starting material was dissolved completely. The reaction mixture was evaporated *in vacuo* and the residue was chromatographed on silica gel, eluting with AcOEt, or on alumina, eluting with benzene. From initial parts of the eluates, N-methyl compound (**5**) and then 3-methoxy compound were obtained.

2-Methyl-3(2H)-pyridazinone 1-Oxide (**5a**): This compound was prepared from 3-hydroxypyridazine 1-oxide,[17] colorless needles, mp 124—125° (from benzene). Yield 70—75%, IR ν_{max}^{KBr}: 1660 cm^{-1}, NMR δ (DMSO-d_6): 3.57 (s, N–CH_3), 6.68 (d,d, 4-H), 7.54 (d,d, 5-H), 7.88 (d,d, 6-H), $J_{4,5}$=9.9 Hz, $J_{4,6}$=1.5 Hz, $J_{5,6}$=6.4 Hz. *Anal.* Calcd. for $C_5H_6O_2N_2$: C, 47.62; H, 4.80; N, 22.22. Found: C, 47.57; H, 4.95; N, 22.03.

2,5-Dimethyl-3(2H)-pyridazinone 1-Oxide (**5b**): This compound was prepared from 5-methyl-3-hydroxypyridazine 1-oxide,[18] colorless leaflets, mp 195—196° (from benzene). Yield 60—70%, IR ν_{max}^{KBr}: 1660 cm^{-1}, NMR δ (DMSO-d_6): 2.15 (b, 5-CH_3), 3.57 (s, N–CH_3), 6.58 (bd, 4-H), 7.89 (d, 6-H), $J_{4,6}$=1.5 Hz. *Anal.* Calcd. for $C_6H_8O_2N_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.60; H, 5.72; N, 19.86.

2,6-Dimethyl-3(2H)-pyridazinone 1-Oxide (**5c**): This compound was prepared from 6-methyl-3-hydroxypyridazine 1-oxide,[16] colorless needles, mp 110—111° (from benzene) (lit.[16] 111—112°).

Photolysis of 2-Methyl-3(2H)-pyridazinone 1-Oxide (5a—c) in Neutral Alcohol——A solution of the N-oxide (**5**, 2—3 g) in freshly distilled MeOH or EtOH (250—300 ml) was irradiated for 1.5—2.5 hr under nitrogen atmosphere. The solvent was evaporated *in vacuo* and the residue was extracted with benzene. The insoluble solid was recrystallized from AcOEt to give pyridazinedione (**8**). The benzene solution was chromatographed on silica gel. From the eluate with benzene, isomaleimide (**6**) was obtained and was purified by recrystallization from pet. ether. From the eluate with benzene containing 5% AcOEt, γ-lactone was obtained as an oil, which was distilled *in vacuo*. Then, from the eluate with AcOEt–benzene (1: 1), the deoxygenated pyridazinone (**9**) was obtained.

14) H. Arai, unpublished results.
15) C. Kaneko, H. Hasegawa, S. Tanaka, K. Sunayashiki, and S. Yamada, *Chem. Letters*, **1974**, 133.
16) T. Nakagome, *Yakugaku Zasshi*, **82**, 249, 1206 (1962).
17) H. Igeta, *Chem. Pharm. Bull.* (Tokyo), **7**, 938 (1959).
18) H. Igeta, T. Tsuchiya, M. Nakajima, T. Sekiya, Y. Kumaki, T. Nakai, and T. Nojima, *Chem. Pharm. Bull.* (Tokyo), **17**, 756 (1969).

N-Methylaminoisomaleimide (**6a**): Yield 18—20%, pale yellow needles, mp 82—83°, Mass Spectrum *m/e*: 126 (M^+), IR ν_{max}^{KBr}: 3310 and 1750 cm^{-1}, NMR δ ($CDCl_3$): 3.15 (s, N–CH_3), 5.5 (b, NH), 6.18 (d, 3-H), 7.20 (d, 4-H), $J_{4,5}$=5.0 Hz. *Anal.* Calcd. for $C_5H_6O_2N_2$: C, 47.62; H, 4.80; N, 22.22. Found: C, 47.81; H, 4.77; N, 22.05.

4-Methyl-N-methylaminoisomaleimide (**6b**): Yield *ca.* 15%, pale yellow needles, mp 103—104°, Mass Spectrum *m/e*: 140 (M^+), IR ν_{max}^{KBr}: 3300 and 1750 cm^{-1}, NMR δ ($CDCl_3$): 2.12 (d, J=1.5, 4-CH_3), 3.10 (s, N–CH_3), 5.7 (b, NH), 5.95 (m, 3-H). *Anal.* Calcd. for $C_6H_8O_2N_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.39; H, 5.85; N, 19.87.

4-Methyl-2-butenoic Acid γ-Lactone (β-Angelica Lactone) (**7a**): Yield 8%, bp_{20} 80° (bath temp.) (lit.[10] bp_{10} 84°), IR $\nu_{max}^{liq.}$: 1760 cm^{-1}, NMR δ ($CDCl_3$): 1.42 (d, J=7.0, 4-CH_3), 4.68 (m, 4-H), 5.99 (d,d, J= 6.5 and 1.8, 2-H), 7.39 (d,d, J=6.5 and 1.5, 3-H). This compound was confirmed in comparison with authentic sample synthesized by the method described in the literature.[10]

3,4-Dimethyl-2-butenoic Acid γ-Lactone (**7b**): Yield *ca.* 10%, bp_5 100° (bath temp.) (lit.[19] bp_{13} 111—112°), IR $\nu_{max}^{liq.}$: 1760 cm^{-1}, NMR δ ($CDCl_3$): 1.45 (d, J=7.0, 4-CH_3), 2.07 (d, J=0.6, 3-CH_3), 4.95 (bd, J= 7.0, 4-H), 5.84 (m, 2-H).

4,4-Dimethyl-2-butenoic Acid γ-Lactone (**7c**): Yield *ca.* 20%, bp_{20} 90° (bath temp.) (lit.[10] bp_{10} 80°), IR $\nu_{max}^{liq.}$: 1765 cm^{-1}, NMR δ ($CDCl_3$): 1.49 [6H, s, 4-$(CH_3)_2$], 5.95 (d, J=6.0, 2-H), 7.43 (d, J=6.0, 3-H).

1-Methyl-3,6-pyridazinedione (**8a**): Yield 18%, mp 213—214° (lit.[20] mp 210—211°). This compound was identical with authentic sample prepared by the method described in the literature.

1,4-Dimethyl-3,6-pyridazinedione (**8b**): Yield 23%, mp 262—263°, IR ν_{max}^{KBr}: 1660 cm^{-1}, NMR δ (DMSO-d_6): 2.0 (d, J=1.0, 4-CH_3), 3.40 (s, N–CH_3), 6.65 (m, 5-H), 10.8 (b, NH). *Anal.* Calcd. for $C_6H_8O_2N_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.43; H, 5.91; N, 19.88. Deoxygenated compounds, 2-methyl-3(2H)-pyridazinone[21] (**9a**: *ca.* 5%), 2,5-dimethyl-3(2H)-pyridazinone[22] (**9b**: 5—6%), and 2,6-dimethyl-3(2H)-pyridazinone[23] (**9c**: 13%) were identical with authentic samples.

Photolysis of 2-Methyl-3(2H)-pyridazinone 1-Oxide (5) in Acidic Alcohol——A solution of the N-oxide (**5**, 3 g) in MeOH or EtOH containing 5% HCl, was irradiated for 2 hr. The reaction mixture was neutralized with Na_2CO_3, followed by removal of the solvent *in vacuo*. The residue was extracted with CH_2Cl_2 and dried on $MgSO_4$, followed by evaporation. The residue was then dissolved in benzene and chromatographed on silica gel, eluting with a mixture of benzene and AcOEt (9: 1).

Photolysis of 2-Methyl-3(2H)-pyridazinone 1-Oxide (**5a**): Photolysis of **5a** was carried out. From the initial eluate, the mixture, presumably to be subsequent reaction products, was obtained as an oil. From the second eluate, 2-methyl-6-chloro-3(2H)-pyridazinone[20] (**14**) was obtained, yield 8%, mp 91—92° (from *n*-hexane). The subsequent eluate afforded the deoxygenated compound, *i.e.*, 2-methyl-3(2H)-pyridazinone,[21] yield 5—7%. These compounds were confirmed in comparison with the samples prepared by the method described in the literature.

Photolysis of 2,6-Dimethyl-3(2H)-pyridazinone 1-Oxide (**5c**): Photolysis of **5c** was carried out, affording an oil similar to the case of **5a**. The second eluate gave 1-chloromethyl-6-methyl-3(2H)-pyridazinone (**15**), yield *ca.* 15%, mp 94—95° (lit.[13] 96—97°) (from *n*-hexane), Mass Spectrum *m/e*: 158 (M^+), 123 (M–Cl), IR ν_{max}^{KBr}: 1675 cm^{-1}, NMR δ ($CDCl_3$): 2.35 (s, 6-CH_3), 5.80 (s, N–CH_2Cl), 6.88 (d, 4-H), 7.18 (d, 5-H), $J_{4,5}$=10.0 Hz. *Anal.* Calcd. for $C_6H_7ON_2Cl$: C, 45.43; H, 4.45; N, 17.66. Found: C, 45.21; H, 4.43; N, 17.37. The subsequent eluate gave the deoxygenated compound, *i.e.*, 2,6-dimethyl-3(2H)-pyridazinone,[23] yield 8—10%.

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21) G. Duffin and J. Kendall, *J. Chem. Soc.*, **1959**, 3789.
22) S. Linholter, A.B. Kristensen, R. Rosenoern, S.E. Nelsen, and H. Kaaber, *Acta Chem. Scand.*, **15**, 1660 (1961).
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