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TABLE 1 Rate constants for the reaction of glycine with N-ethylmaleimide\*

| Hydrogen<br>ion activity<br>$a_{\rm H}^{+} \times 10^{7}$ | Glycine<br>(M) | $\mathrm{KCl}\left(M ight)$ | $k_1 \times 10^3$ (min <sup>-1</sup> ) | $k_2 \times 10^{10}$<br>(min <sup>-1</sup> ) |
|---|----------------|-----------------------------|--|--|
| 1.55  | 0.16           | 0.26                        | 3.76                                   | 35.2   |
| 1.59  | 0.32           | 0.13                        | 7.66                                   | 37.4   |
| 1.59  | 0.48           |                             | 10.86                                  | 35.5   |
| 4.47  | 0.40           |                             | 3.40                                   | 37.4   |
| 2.04  | 0.40           |                             | 7.71                                   | 38.8   |
| 1.12  | 0.40           |                             | 13.50                                  | 37.4   |

\*All measurements were made in 0.1 M phosphate. The initial N-ethylmaleimide concentration was about 7.5  $\times$  10<sup>-4</sup> M. Temperature 25  $\pm$  1°.

The observed rate law can be explained by a rate-controlling reaction of the unprotonated amino group with the N-ethylmaleimide. The dependency on the hydrogen ion activity is thus explained since this would determine the amount of the amino group present in the unprotonated form. The rate law is consistent with a mechanism in which there is a nucleophilic attack of the amino group on the N-ethylmaleimide (2). Analogous reactions would indicate that the product would be N-(1-ethyl-2,5-dioxopyrrolidine-3-yl)glycine (4), although in this work the product was not isolated and identified.

The rate constants were determined for glycine but it is unlikely that the amino groups of other amino acids would differ greatly from the value observed for glycine. This was not determined in the present work but it is indicated by the less quantitative studies of Riggs (8) which showed that histidine, valine, serine, and glycine reacted with N-ethylmaleimide at similar rates. However, constants cannot be calculated from his data as presented. At pH 7 and 0.1 M glycine one can calculate a rate constant of  $3.7 \times 10^{-3} \text{ min}^{-1}$  for the disappearance of *N*-ethylmaleimide, whereas it would be  $9.2 \times 10^5 \text{ min}^{-1}$  under similar conditions for the reaction with the sulfhydryl group of cysteine (9).

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# Photoreaction of nitroso compounds in solution.<sup>1</sup> XIII. Photo-oxidation of alkyl nitrites

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Photolysis of 1-pentyl and menthyl nitrites in the presence of oxygen were shown to give mainly the oxidized rearrangement products 4-nitratopentyl and 10-nitratomenthyl derivatives in disagreement with the published report (2). Under the photo-oxidation conditions, menthyl nitrite also gave 10-nitrosomenthyl derivatives which were also shown to be photo-oxidized to 10-nitratomenthyl derivatives. The photooxidation products were conveniently reduced to the corresponding diols and were, in turn, identified as bisbenzoate.

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It has been reported that photolysis of 1-octyl nitrite in the presence of oxygen gave 1-octyl nitrate as the major product but no rearranged product such as the dimer of 4-nitrosooctanol

or the oxidation product therefrom (2). The report implies that bimolecular oxidation processes leading to 1-octyl nitrate are far faster (by 100 times at minimum) than the intramolecular hydrogen-nitroso group exchange reaction (3) which is the major reaction in the absence of oxygen. In contrast we have demonstrated (1)

<sup>&</sup>lt;sup>1</sup>For the preceding paper (Part XII) in this series, see ref. 1.

that the intramolecular hydrogen-nitroso group exchange reaction is much faster than oxidation processes in the photo-oxidation of *N*-nitroso-*N*hexylacetamide yielding 4-nitratohexylacetamide in good yield. It has been well established that, in both photoreactions in the absence of oxygen, the formations of alkoxy and amido radicals are the primary step followed by an intramolecular hydrogen transfer (3, 4). As there was very little reason to believe that the hydrogen transfer to an alkoxy radical should be slower than that to an amido radical, photolyses of 1-pentyl and menthyl nitrites (1a, b) in the presence of oxygen were therefore investigated.

In the presence of oxygen, 1-pentyl nitrite (1a)was slowly photolyzed to a mixture showing strong absorption for a nitrate group (1620, 1280, and  $870 \text{ cm}^{-1}$ ). The major part of the product consisted of highly polar compounds and could not be separated on a silicic acid column. Less polar fractions were, however, partially separated to give semi-pure 1,4-pentandiol dinitrate (2, 9.5%), 4-nitratopentanal (3, 5.5%), and 4-nitratopentanol (4, 12.5%). Due to the instability of these oily nitrates, attempted purification by various methods failed. The nuclear magnetic resonance (n.m.r.) spectra, however, show the terminal methyl signals as doublets indicating that the nitrate group is located at C-4 in 2, 3, and 4. The crude photolysate was therefore reduced with lithium aluminum hydride and benzoylated to give pentan-1,4-diol bisbenzoate (5).

Photolysis of menthyl nitrite (1b) under the same conditions turned out to be less amenable giving a complex mixture probably due to formation of stereoisomers. Only 10-nitratomenthone (6) could be obtained after extensive purification of less polar fractions. Reduction with lithium aluminum hydride of the crude product and subsequent benzoylation gave 10-benzoyloxymenthyl benzoate (7) and 10-benzamidomenthyl benzoate (8) in addition to two impure fractions. The last two impure fractions are assumed to be epimers of 7 since the infrared (i.r.), n.m.r., and mass spectra are very similar to those of 7. The isolation of 6-8 clearly demonstrated that the 10-methyl group had been functionalized as the nitrosomethyl (--CH<sub>2</sub>NO) and nitratomethyl  $(-CH_2ONO_2)$  group as the result of the photolysis. It should be pointed out that the 10-hydrogen atom nitroso (or nitrato) group exchange reaction in 1b could lead to two epimers, the preference of which is *a priori* not predictable since the nature of the transition state of hydrogen transfer is not precisely known (3, 5). The stereochemistry of **6**, **7**, and **8** is therefore unknown.

NOTES



$$R_1 = C_6H_5CO-; R_2 = C_6H_5CO_2-$$
  
8  $R_1 = C_6H_5CO-; R_2 = C_6H_5CONH-$ 

The results prove that alkoxy radicals, as generated in the photolysis, also readily undergo 1,5-hydrogen transfer to give a C-radical prior to oxidation processes. It is well known that nitric oxide is readily oxidized to nitrogen oxides of higher oxidation levels. Radical recombination of a C-radical with nitric oxide and  $\cdot$ NO<sub>3</sub> leads to a C-nitroso compound (such as 9) and a nitrate (such as 10). These results are in agreement with the results observed in the photolysis of nitrosamides. The formation of oxidation products 3 and 6 could be due to ozone generated during photolysis of nitrites (6).

Thus the photolyses produce not only the 4-nitrato compound 10 but also the 4-nitroso compound 9 as can be seen by the isolation of benzamido derivative 8, although the corresponding amide is not isolated in the photolysis of 1-pentyl nitrite. A C-nitroso compound is generally in equilibrium with the corresponding dimer (7) and photolabile when irradiated in Pyrex apparatus (8, 9). In analogy to the photooxidation of 4-nitrosohexylacetamide (1), 9 is expected to be transformed to 10 efficiently under the photolysis conditions. This is proven in the following manner. When 1b was photolyzed with



a light source of > 330 mµ under nitrogen, intense absorption at 295 mµ emerged rapidly as the nitrite absorption at 340 mµ faded away. The former peak corresponds to well established absorption of a nitroso dimer (7, 8). The crude product showed no nitrate i.r. absorption but did show a strong 1180 cm<sup>-1</sup> band typical of *trans*-dimer (6, 7) of *C*-nitroso compound 9. On further irradiation of the crude product with a light source of > 280 mµ under oxygen atmosphere, the ultraviolet (u.v.) absorption at 295 mµ disappeared. The crude product showed intense nitrate i.r. absorption and was worked up in the same way to afford **6** and **7**.

#### Experimental

Infrared spectra were determined as liquid films or nujol mulls. The n.m.r. spectra were determined with a Varian A-56/60 spectrometer in  $CCl_4$  with internal TMS reference. Mass spectra were determined at 80 eV on a heated inlet with Hitachi RMU-6E. The microanalyses were made by Dr. A. Bernhardt, West Germany.

## Synthesis of Nitrites

1-Pentyl nitrite was prepared from 1-pentanol according to known procedures (10). The yellow oil was distilled at 18°/12 mm; i.r. 1640, 1460, 1050, 980, and 800 cm<sup>-1</sup>; n.m.r.  $\tau$  9.1 (3H, t, J = 6 Hz), 8.57 (6H), and 5.33 (2H, m). A solution of *l*-menthol (m.p. 40–43°) in pyridine was treated with nitrosyl chloride (11) to give an oil which was chromatographed on a silicic acid column to give oily menthyl nitrite; i.r. 1635, 1450, 800, and 765 cm<sup>-1</sup>; n.m.r.  $\tau$  4.90 (1H, m).

#### Photolysis of 1-Pentyl Nitrite

(A) A solution of 1-pentyl nitrite (2.2 g) in benzene (100 ml) was placed in a flat-bottom flask (Pyrex) and irradiated with a G. E. Par 38 lamp for 12 h. A slow stream of oxygen was introduced during the irradiation. The progress of the reaction was followed by monitoring the decrease of the nitrite absorption at 371, 357, 345, and 333 mµ. Evaporation of benzene gave an oil showing i.r. absorption at 1730 (m), 1620, 1280, and 870 cm<sup>-1</sup>. The oil was chromatographed on a silicic acid column to give the following fractions. With pure chloroform, the first fraction contains 1,4-pentanediol dinitrate (2, 350 mg) slightly contaminated with 4-nitratopentanal (3, 150 mg), and the second fraction contains nearly pure 3. Preparative thin-layer chromatography (t.l.c.) separation did not effect an analytically pure sample. The impure dinitrate 2 shows i.r. 1620, 1280, and 870 cm<sup>-1</sup>; n.m.r. τ 4.83 (1H, m), 5.55 (2H, m), 8.56 and 8.61 (3H, two sets of d, J = 6Hz); m/e (at 15 eV) 147, 132, 115, 101, 86, and 85. The pentanal 3 shows i.r. 2740, 1730, 1620, 1280, and 870  $cm^{-1}$ ; n.m.r.  $\tau$  8.64 (3H, d, J = 6 Hz), 7.97 (2H, m), 7.47 (2H, m), 4.91 (1H, m), and 0.33 (1H, t, J = 1.5 Hz).

A mixture of chloroform-methanol (95:5) elutes a fraction (1.14 g), a part of which (500 mg) was separated by preparative t.l.c. to give the major component, 4-

nitratopentanol, (4, 347 mg); i.r. 3400, 1620, 1275, 1060, 1010, and 865 cm<sup>-1</sup>; n.m.r.  $\tau$  8.7 (3H, d, J = 7 Hz), 6.50 (2H, m), 4.95 (1H, m); m/e, 132, 115, 101, and 85.

A 2,4-DNPH derivative of pentanal 3 was prepared but could not be purified by chromatography or recrystallization. The best 2,4-DNPH derivative has m.p.  $85-90^{\circ}$ ; n.m.r.  $\tau$  4.81 (1H, sextet, J = 6 Hz), 7.45 (2H), 7.90 (2H), 8.52 (3H, d, J = 6.5 Hz), 2.49 (1H, t, J = 4 Hz); m/e (direct insertion) 327, 281, 265, 167, and 182.

(B) The crude photolysate (500 mg) was stirred with lithium aluminum hydride (600 mg) in anhydrous ether overnight. A sodium hydroxide solution (10%) was added to decompose the reaction mixture. The crude product (150 mg) shows no nitrate absorption. This oil was treated with benzoyl chloride in pyridine. The benzoylation product was chromatographed on a basic alumina column twice to afford 1-pentyl benzoate (80 mg) and 1,4-pentandiol bisbenzoate (5, 80 mg). Bisbenzoate 5 was distilled to afford an analytical sample; i.r. 1720, 1280, and 1100 cm<sup>-1</sup>; n.m.r.  $\tau$  8.62 (3H, d, J = 6 Hz), 8.13 (4H), 5.65 (2H), and 4.81 (1H); m/e 312, 227, 207, 190, 149, 105, and 85.

Anal. Calcd. for C<sub>19</sub>H<sub>20</sub>O<sub>4</sub>: C, 73.06; H, 6.45. Found: C, 73.15; H, 6.22.

### Photolysis of Menthyl Nitrite (1b)

(A) The photolysis of 1b (1.5 g) was carried out in the same manner as above except that air was substituted for oxygen. The crude product showed i.r. absorption at 1710 (weak), 1630, 1280, and 870 cm<sup>-1</sup> and a long streak on a t.l.c. plate. Chromatography of the crude product on a silicic acid column did not afford any separation except the first fraction (150 mg) eluted with pure chloroform. This fraction was purified by preparative t.l.c. to give 10-nitratomenthone (6, 75 mg); i.r. 1710, 1625, 1280, and 870 cm<sup>-1</sup>; n.m.r.  $\tau$  5.20 (2H, m), 9.1 (6H, m); *m/e* 169, 153, 139, 127, 112, and 98.

The crude product (1.5 g) was reduced with lithium aluminum hydride followed by benzoylation. Alumina chromatography of the crude material gave fractions containing (*i*) menthyl benzoate (186 mg), (*ii*) bisbenzoate 7 (656 mg), and (*iii*) other (700 mg). The first fraction was shown to be identical by t.l.c., i.r., and n.m.r. spectra with an authentic menthyl benzoate. The second fraction was further purified by preparative t.l.c. to give 10-benzoyloxymenthyl benzoate 7 as a thick resin; i.r. 1730, 1600, 1270, and 1120 cm<sup>-1</sup>; n.m.r.  $\tau 2.07$  (4H), 2.65 (6H), 5.05 (1H), 5.84 (2H, AB part of ABX system), 9.03 (3H, J = 5 Hz) and 9.08 (3H, J = 7 Hz); *m/e* 275, 258, 244, 169, 153, 138, 124, 119, 105, and 95.

Anal. Calcd. for C<sub>24</sub>H<sub>28</sub>O<sub>4</sub>: C, 75.76; H, 7.42. Found: C, 75.48; H, 7.35.

The third fraction was rechromatographed (silicic acid) to afford more bisbenzoate 7 and two fractions (340 mg) both of which showed very similar i.r. and n.m.r. spectral patterns but different t.l.c. behaviors from those of 7. Both fractions were oil and decomposed on vacuum distillation. The fraction (230 mg) eluted with benzene-ethyl acetate (9:1) was further purified by preparative t.l.c. to give crystalline 10-benzamidomenthol benzoate 8; m.p. 162–163°; i.r. 3340, 1710, 1640, 1535, and 1275 cm<sup>-1</sup>; n.m.r.  $\tau$  2.1 (2H), 2.36 (2H), 2.65 (6H), 5.12 (1H, m), 6.70 (2H, broad d, J = 6.5); m/e 379, 274, 257, 186, 174, 162, 161 (100%), 134, 122.

(B) Menthyl nitrite (1.5 g) was photolyzed in the same manner except that purified nitrogen was substituted for oxygen and the light was filtered through a 0.01% solution of 2,7-dimethyl-3,6-diazacyclohepta-1,6-diene perchlorate. This filter solution cuts off the incident light below 330 mµ. After 6.5 h, the absorption in the 375 mµ region decreased to nil but very intense absorption appeared at 295 mµ which tailed to 330 mµ. The crude product shows 7 major spots on a t.l.c. plate. Small amounts of menthol (132 mg) and menthone (35 mg) were removed by alumina chromatography. Other components could not be separated by repeated chromatography.

The same photolysis was repeated as above. When the nitrite had disappeared, the photolysate was further irradiated under condition A until the u.v. absorption at 295 mµ had disappeared. The reaction mixture was worked up in a manner similar to that of A to afford menthyl benzoate (150 mg) and bisbenzoate 7 (980 mg).

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# Erratum: Structure of didehydrochelidonine

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On page 3703, in footnote 5, an  $R_f$  is given as 0.41. This line should read "... respectively 0.57 and 0.14 in methanol-benzene (5:95, v/v), ..."