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Studies on Diazepines. X.[1] The Sensitized Photo-oxygenation of 1H-1,2-Benzodiazepines

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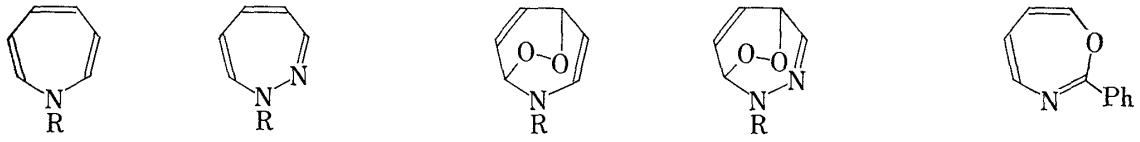
The photosensitized oxygenation of 1H-1,2-benzodiazepines (**6**) in methanol gave fragment products (**7**—**14**). Phenyl ketones (**7**) are assumed to originate from the 5-hydroperoxide (**5**), and cinnamic acids (**8** and **9**), 3-methoxy-3H-1,2-benzodiazepines (**10**), and indazoles (**11**—**14**) from the 3-hydroperoxide (**16**). Similar photooxygenation of 1-methyl-1H-1,2-benzodiazepines (**23**) gave 3-oxo-1,2-benzodiazepines (**25**), which may be formed *via* the zwitterionic 3-peroxide (**24**).

Keywords——1H-1,2-benzodiazepines; photo-oxygenation; sensitized photooxygenation hydroperoxide; mechanism

In view of the interesting photosensitized oxygenation behavior of seven-membered conjugated trienes such as cycloheptatrienes (tropilidenes)[3] and tropolones,[4] we have been examining similar reactions of aza-analogs, and we have already reported that the photooxygenation of the monocyclic azepines (**1**) and 1,2-diazepines (**2**) yields the relatively stable ($4\pi+2\pi$) cycloadducts (**3**) and (**4**) as the sole oxidized products.[5] On the other hand, 2-phenyl-1,3-oxazepine (**5**) was shown to undergo initial 1,2- (or 1,6-) and 1,4-addition of singlet oxygen, followed by decomposition to give several oxidized fragments.[6] In all cases of the aza-cycloheptatrienes (**1**, **2**, and **5**), 1,2- and 1,4-cycloadditions of oxygen did not occur in the aza-diene system. However, it has been shown that the oxygenation of imidazoles and xanthines involves 1,4-cycloaddition of singlet oxygen at the aza-diene function,[7] and the attack of oxygen occurs at both the double bond and benzene ring in the case of indenes.[8]



1 **2** **3** **4** **5**

Chart 1

In connection with the above-mentioned studies, we examined the photooxygenation of 1H-1,2-benzodiazepines (**6** and **23**), which were expected to produce different types of

1) Part IX: T. Tsuchiya and J. Kurita, *Chem. Pharm. Bull.* (Tokyo), **27**, 2528 (1979).
2) Location: *Kanagawa-machi, Kanazawa, 920-11, Japan.*
3) A.S. Kende and J.Y.-C. Chu, *Tetrahedron Lett.*, **1970**, 4837; A. Ritter, P. Bayer, J. Leitch, and G. Schomburg, *Ann. Chem.*, **1974**, 835; T. Asao, M. Yagihara, and Y. Kitahara, *Bull. Chem. Soc. Jpn.*, **51**, 2131 (1978).
4) E.J. Forbes and J.G. Griffiths, *J. Chem. Soc. (C)*, **1967**, 601; *idem, ibid.*, **1968**, 572; M. Oda and Y. Kitahara, *Tetrahedron Lett.*, **1969**, 3259.
5) T. Tsuchiya, H. Arai, H. Hasegawa, and H. Igeta, *Tetrahedron Lett.*, **1974**, 4013; *idem, Chem. Pharm. Bull.* (Tokyo), **25**, 2749 (1977).
6) O. Seshimoto, T. Tezuka, and T. Mukai, *Chem. Lett.*, **1976**, 793.
7) H.H. Wasserman, K. Stiller, and M.B. Floyd, *Tetrahedron Lett.*, **1968**, 3277; T. Matsuura and I. Saito, *Tetrahedron*, **24**, 6609 (1968); *idem, ibid.*, **25**, 541 (1969); and refs. cited therein.
8) P.A. Burns, C.S. Foote, and S. Mazur, *J. Org. Chem.*, **41**, 899 (1976); P.A. Burns and C.S. Foote, *ibid.*, **41**, 908 (1976).

oxidized products compared to those obtained in the oxygenation of **2** and **5** because of the presence of the benzene ring. We report here evidence that the main pathway may proceed through an ene reaction of singlet oxygen and not through cycloaddition.[9]

A methanol solution of 1H-1,2-benzodiazepine (**6a**)[10] was photooxygenated for 2 hr with a halogen lamp using Rose Bengal or Methylene Blue as a sensitizer while oxygen was slowly passed through the solution. After removal of the solvent, the photolysate was chromatographed on silica gel to give benzaldehyde (**7a**: *ca.* 20%), cinnamic acid (**8a**: 12%), methyl cinnamate (**9a**: 18%), 3-methoxy-3H-1,2-benzodiazepine[11] (**10a**: 6%), 3-formylindazole[12] (**11**: 3%), and 3-(*trans*-2′-methoxyvinyl)-1H-indazole[1] (**13**: 4%). In a similar manner, 5-methyl-1H-1,2-benzodiazepine[10] (**6b**) gave acetophenone (**7b**: 28%), β-methylcinnamic acid (**8b**: 20%), methyl β-methylcinnamate (**9b**: 11%), 3-methoxy-5-methyl-3H-1,2-benzodiazepine[11] (**10b**: 2%), 3-methylindazole[13] (**12**: 3%), and 3-methyl-3-(*trans*-2′-methoxyvinyl)-3H-indazole[1] (**14**: 5%), as shown in Chart 2.[14]

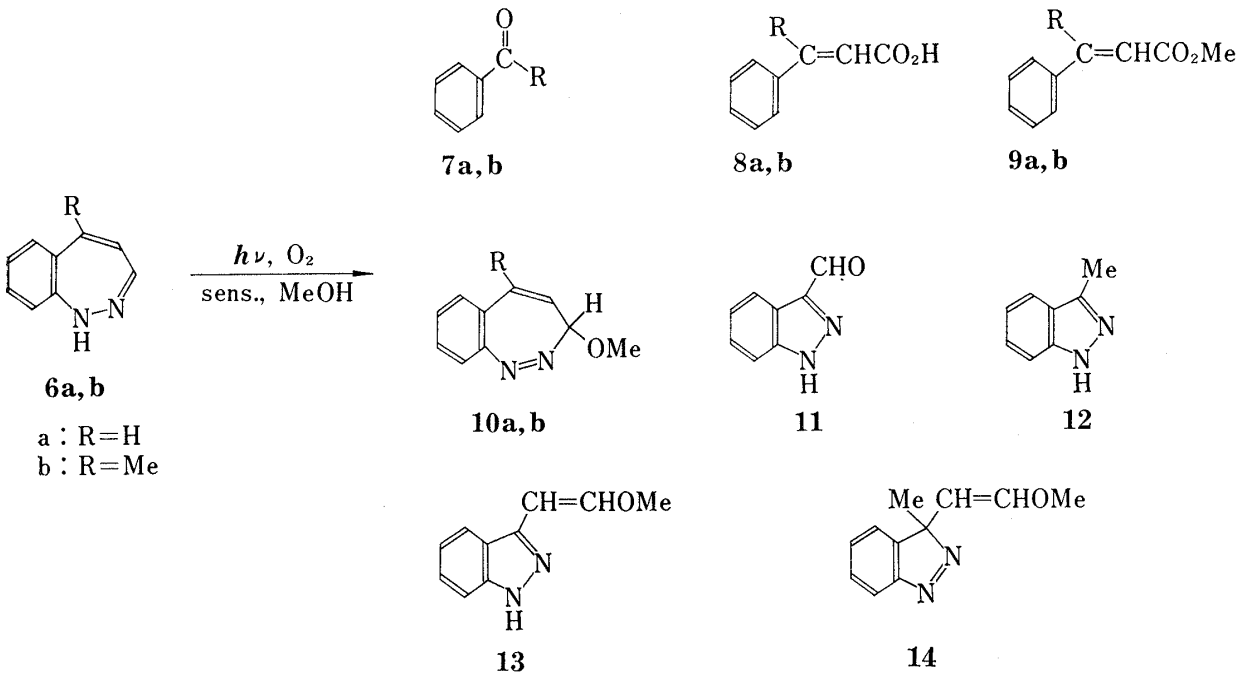


Chart 2

When methylene chloride was used as a solvent instead of methanol in the reaction, the photolysate decomposed with evolution of oxygen during concentration, and gave only the phenyl ketones (**7**: 15—20%) without any other characterizable products. Photooxygenation was negligible in the absence of a sensitizer.

In order to examine the relationships among these products, each of them was further photooxygenated under conditions similar to those used for their formation. The phenyl ketones (**7**) were not obtained by photooxygenation of the cinnamic acids (**8** and **9**) or any other products, suggesting that the ketones are not secondarily formed from the other isolated

9) A part of this work has been published in a preliminary communication: T. Tsuchiya, J. Kurita, and K. Takayama, *Heterocycles*, **9**, 1549 (1978).
10) T. Tsuchiya, J. Kurita, and V. Snieckus, *J. Org. Chem.*, **42**, 1856 (1977).
11) T. Tsuchiya and J. Kurita, *Chem. Pharm. Bull.* (Tokyo), **26**, 1890 (1978).
12) H.R. Hensel, *Chem. Ber.*, **99**, 868 (1966).
13) E.B. Dennler and A.R. Frasca, *Tetrahedron*, **22**, 3131 (1966).
14) All the products isolated are known and their identities were confirmed by comparison with authentic samples purchased or prepared according to the literature.

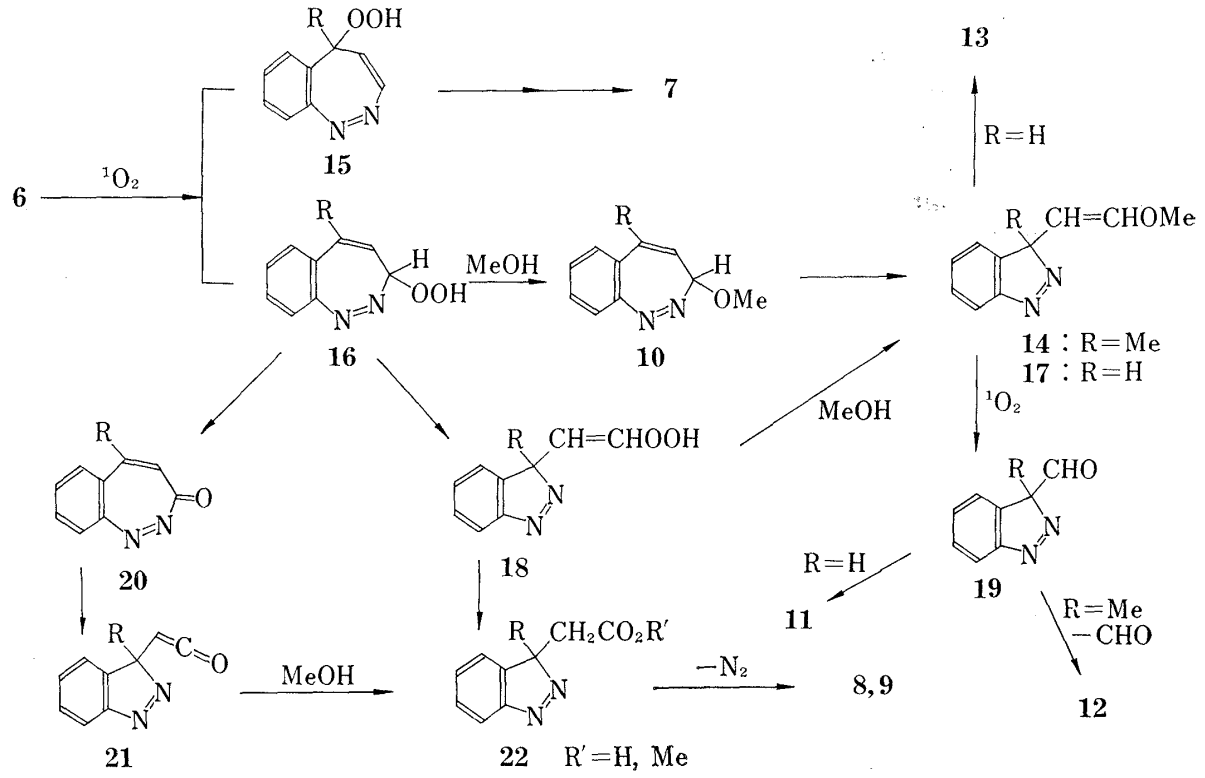


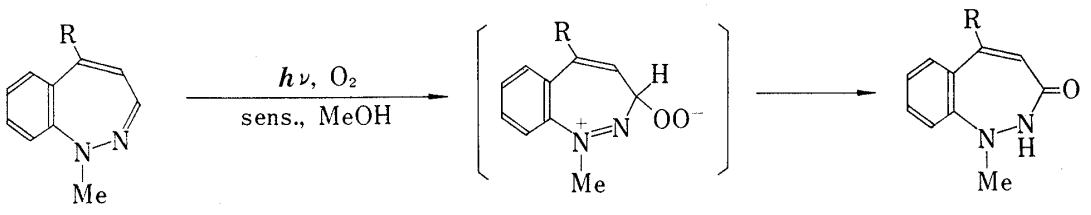
Chart 3

products. The 3H-indazole (**14**) was converted into 3-methyl-1H-indazole (**12**), whereas oxygenation of the 1H-indazole (**13**) did not give **11**. The reaction of the 3H-diazepines (**10**) resulted in the formation of indazoles **11** and **13** or **12** and **14**. These results suggest that the photooxygenation of the diazepines (**6**) may involve the initial formation of two different oxidized intermediates; one may be unstable and may readily decompose to give **7**, while the other is more stable and reacts with methanol followed by decomposition to give the products (**8**—**14**).

Based on these results and observations, the present photooxygenation can be accounted for by the scheme outlined in Chart 3. Although all attempts to isolate the key intermediates **15** and **16** failed, we believe that the reaction involves the initial formation of 5- (**15**) and 3- (**16**) hydroperoxides, followed by isomerization and/or decomposition to give the fragmental products. Since the 5H-1,2-benzodiazepines are known[15] to be unstable, the 5-hydroperoxides (**15**) may be decomposed to give the phenyl ketones (**7**) by C_4—C_5 bond cleavage and loss of nitrogen. On the other hand, 3H-1,2-benzodiazepines are known[11] to be relatively stable but to undergo both photochemical and thermal rearrangements to the corresponding 3-vinylindazoles in high yields. Therefore, the 3-peroxides (**16**) may rearrange into the 3H-indazoles (**14** and **17**) *via* **10** or **18**, followed by further oxygenation of the olefinic double bond to give the formylindazoles (**19**), which are then converted into either **11** or **12**. Cinnamic acids (**8**) and cinnamates (**9**) may also result from **16** *via* the 3H-indazoles (**22**), which are formed either *via* the 3-oxodiazepines (**20**) and the ketene intermediates (**21**), or *via* the peroxides (**18**).

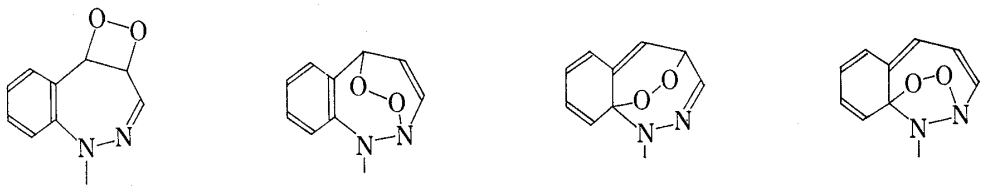
Next, methanol solutions of 1-methyl-1H-1,2-benzodiazepines (**23a**, **b**), prepared from **6** by treatment with *n*-butyl lithium followed by methyl iodide in tetrahydrofuran, were photooxygenated under similar conditions to give the 3-oxo-benzodiazepines (**25**) in 60—65% yields

15) T. Tsuchiya and J. Kurita, presented at the 47th Meeting of the Hokuriku Branch of the Pharmaceutical Society of Japan, Toyama, Nov., 1978.



23 a : R=H
b : R=Me

24 25



26 27 28 29

Chart 4

as the sole products.[16] In these cases, other possible dioxides and their decomposition products could not be isolated. This reaction may involve the initial formation of the zwitterionic 3-peroxides (**24**) analogous to those observed for enamines[17] with no formation of 5-peroxides.

In conclusion, it should be noted that no product derived from the other possible dioxides such as the 4,5- (**26**), 2,5- (**27**), 4,7- (**28**), or 2,7-(**29**) dioxide has been detected.[18] Thus, in the present photooxygenation of the 1H-1,2-benzodiazepines (**6** and **23**), the formation of hydroperoxides occurs predominantly, and 1,4-, 1,6-, and 1,2- cycloadditions of singlet oxygen do not occur either in the aza-diene system or the diene involved in the benzene ring.

Experimental

Melting points were measured on a Yamato MP-21 apparatus and are uncorrected. Infra red (IR) spectra were determined with a JASCO IRA-2 spectrometer and Mass (MS) spectra were obtained on a JEOL JMS-D100 instrument. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-MH100 spectrometer in $CDCl_3$ solution using tetramethylsilane as an internal standard, and spectral assignments were confirmed by spin-decoupling experiments and, in the case of NH protons, by exchange with D_2O. Microanalyses were performed in the Microanalytical Laboratory of this school by Miss R. Hamano. Photolyses were carried out using an immersion apparatus equipped with a halogen lamp (Ushio JCV-200W-GS) which was cooled internally with running water.

Photooxygenation of 1H-1,2-Benzodiazepine (6a)——A solution of **6a** (3.0 g) in methanol (300 ml) containing Rose Bengal or Methylene Blue (50—100 mg) was irradiated with a halogen lamp for 2 hr while a steady stream of oxygen was bubbled through the solution. After removal of the solvent *in vacuo*, the residue was dissolved in CH_2Cl_2 and the solution was extracted with satd. $NaHCO_3$. The alkaline solution was acidified with 10% HCl and extracted with ether. The extract was washed with water, dried over $MgSO_4$, and evaporated to dryness. The resulting solid was recrystallized from AcOEt to give cinnamic acid (**8a**: 360 mg, 12%). The above CH_2Cl_2 solution was washed with satd. NaCl, dried, and evaporated to dryness *in vacuo*. The resulting residue was chromatographed on silica gel using *n*-hexane–CH_2Cl_2 as an eluent to give benzaldehyde (**7a**: 440 mg, 20%), methyl cinnamate (**9a**: 620 mg, 18%), 3-methoxy-3H-1,2-benzodiazepine (**10a**: 210 mg, 6%, mp 53—54°), 3-formyl-1H-indazole (**11**: 57 mg, 2%), and 3-(*trans*-2′-methoxyvinyl)-1H-indazole (**13**: 140 mg, 4%, mp 82—84°), successively. The compounds **10a**[11] and **13**[1] were identical

16) These products (**25**) are the first examples of 3-oxo-1,2-diazepines.
17) For a review, see I. Saito, T. Matsuura, M. Nakagawa, and T. Hino, *Acc. Chem. Res.*, **10**, 346 (1977).
18) Although other routes for the formation of **7** from **6** *via* **26** or **27** can be considered, these routes seem unlikely based on the results of oxygenation of **23**.

with the authentic samples reported in our previous papers. An authentic sample of **11** was prepared by the reported method[12] and authentic samples of the other products were obtained from Tokyo Kasei Kogyo Co., Ltd, Tokyo, Japan.

Photooxygenation of 5-Methyl-1H-1,2-benzodiazepine (6b)——A solution of **6b** (3.0 g) in methanol (300 ml) containing Rose Bengal (100 mg) was photooxygenated for 4.5 hr and worked up as described for **6a** to give β-methylcinnamic acid (**8b**: 75 mg, 2%), acetophenone (**7b**: 640 mg, 28%), methyl β-methylcinnamate (**9b**: 360 mg, 11%), 3-methoxy-5-methyl-3H-1,2-benzodiazepine[11] (**10b**: 80 mg, 2%, yellow viscous oil), 5-methyl-3-(*trans*-2′-methoxyvinyl)-3H-indazole[1] (**14**: 180 mg, 5%, colorless viscous oil), and 3-methyl-1H-indazole (**12**: 70 mg, 3%). Authentic samples of the products **7b**, **8b**, and **9b** were obtained from Tokyo Kasei Kogyo Co., Ltd. and authentic samples of the other products (**10b**, **12**, and **14**) were prepared by the reported methods.

Preparation of 1-Methyl-1H-1,2-benzodiazepines (23a, b)——A solution of *n*-butyl lithium (15% w/w in *n*-hexane, $d=0.68$, 24 ml) was added dropwise to a solution of **23** (5.0 g) in anhydrous tetrahydrofuran cooled in a dry ice–acetone bath with stirring under a nitrogen atmosphere, then a solution of methyl iodide (5.4 g) in tetrahydrofuran (10 ml) was further added dropwise to the reaction solution. After stirring for an additional 30 min at −50——−60°, the reaction mixture was warmed to room temperature and water (50 ml) was added. The mixture was extracted with CH_2Cl_2 and the extract was washed with water, dried, and evaporated to dryness *in vacuo*. The resulting residue was chromatographed on silica gel, eluting with *n*-hexane–CH_2Cl_2, to give **23**.

23a: 3.59 g, 68% yield, mp 61—62°, red prisms (from *n*-hexane). MS *m/e*: 158 (M^+). NMR δ: 3.24 (3H, s, N–Me), 6.12 (1H, dd, $J=11$ and 4 Hz, 4-H), 6.9—7.5 (6H, unassigned m, 3-, 5-, and Ar–H). *Anal.* Calcd. for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.78; H, 6.33; N, 17.60.

23b: 4.47 g, 86% yield, yellow oil, bp (bath temp.) 109° (3 mmHg). MS *m/e*: 172 (M^+). NMR δ: 2.23 (3H, br, 5-Me), 6.12 (1H, m, 4-H), 3.22 (3H, s, N–Me), 6.9—7.5 (5H, unassigned m, 3- and Ar–H). *Anal.* Calcd. for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.61; H, 7.13; N, 16.07.

Photooxygenation of 23a——A solution of **23a** (1.0 g) in methanol (300 ml) containing Methylene Blue (100 mg) was irradiated with a halogen lamp for 5 hr while a steady stream of oxygen was bubbled through the solution. After removal of the solvent *in vacuo*, the resulting residue was chromatographed on silica gel using acetone–CH_2Cl_2 as an eluent to give 1-methoxy-3-oxo-1,2-dihydro-1,2-benzodiazepine (**25a**): 640 mg, 60% yield, mp 170—172°, colorless prisms (from AcOEt). MS *m/e*: 174 (M^+). IR ν_{max}^{KBr} cm^{-1}: 2850—3200 (NH), 1660 (C=O). NMR δ: 3.12 (3H, s, N–Me), 6.23 (1H, d, 4-H), 6.99 (1H, d, 5-H), 6.9—7.4 (4H, m, Ar-H), 8.4 (1H, br NH), $J_{4,5}=11$ Hz. *Anal.* Calcd. for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.94; H, 5.78; N, 16.05.

Photooxygenation of 23b——A solution of **23b** (1.0 g) in methanol (300 ml) containing Methylene Blue (200 mg) was irradiated for 40 hr and worked up as described for **23a** to give 1,5-dimethyl-3-oxo-1,2-dihydro-1,2-benzodiazepine (**25b**): 706 mg, 65% yield, mp 201—203°, colorless needles (from AcOEt). MS *m/e*: 188 (M^+). IR ν_{max}^{KBr} cm^{-1}: 2850—3200 (NH), 1670 (C=O). NMR δ: 2.25 (3H, br, 5-Me), 3.09 (3H, s, N–Me), 6.25 (1H, m, 4-H), 7.0—7.5 (4H, m, Ar–H), 9.0 (1H, br, NH). *Anal.* Calcd. for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.11; H, 6.44; N, 14.88.