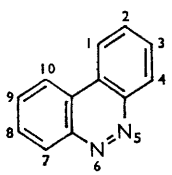
646. *Polycyclic Cinnoline Derivatives. Part III.* The Synthesis of the 4,5,9,10-Tetra-azapyrene Ring System and Some Non-planar Benzo[c]cinnolines.*

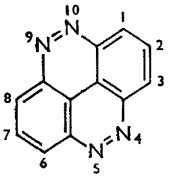
By P. F. Holt and A. N. Hughes.

A 4,5,9,10-tetrazapyrene di-*N*-oxide has been prepared but attempts to prepare 4,5-diazapyrene failed. Several new non-planar 1,10-disubstituted benzo[*c*]cinnolines are described.

Molecular models suggest that the benzo[*c*]cinnoline (I) molecule is planar but that it becomes non-planar when substituted in the 1- and the 10-position. The non-planarity of 4,7-diamino-1,10-dimethylbenzo[*c*]cinnoline has been established by its resolution into optical isomers.[1] It is probably because of the non-planarity of 1,10-disubstituted benzo[*c*]cinnoline intermediates that attempts to prepare the 4,5,9,10-tetra-azapyrene (II) ring system have previously failed. No attempts to prepare 4,5-diazapyrene (III) appear to have been reported.



(I)



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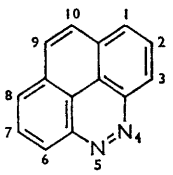

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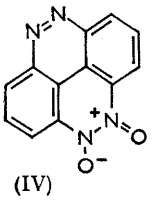
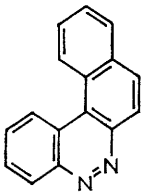


(IV)



(V)

The azo-group of the pyridazine ring in polycyclic cinnoline derivatives is usually formed by the reduction of suitably placed nitro-groups, but pyridazine rings are not formed when 2,6,2′,6′-tetranitrobiphenyl is reduced. Ruby,[2] as well as Braithwaite, Holt, and Hughes[3] who extensively investigated the reduction of 2,6,2′,6′-tetranitrobiphenyl and its 4,4′-dicarboxylic acid using twelve different reducing agents, produced only insoluble and unidentified substances or, in two cases, a diaminodinitrobiphenyl.

As the difficulty in forming the 4,5,9,10-tetra-azapyrene ring system appeared to be due to steric factors, we attempted a synthesis *via* 2,2′-diamino-6,6′-dinitrobiphenyl and 1,10-diaminobenzo[*c*]cinnoline which reduced steric effects to a minimum.

2,2′-Diamino-6,6′-dinitrobiphenyl was prepared by the reaction of 6,6′-dinitrobiphenyl-2,2′-dicarboxyamide with sodium hypobromite. It proved to be identical with a diaminodinitrobiphenyl obtained by the reduction of 2,6,2′,6′-tetranitrobiphenyl with aqueous alcoholic sodium polysulphide,[3] the constitution of which was in doubt.

2,2′-Diamino-6,6′-dinitrobiphenyl reacts abnormally with most reducing agents. Sodium sulphide in aqueous ethanol, which normally converts *oo*′-dinitrobiphenyls into the corresponding cinnoline *N*-oxides, is ineffective. Zinc dust and aqueous-alcoholic potassium hydroxide which normally give a benzo[*c*]cinnoline, or its oxide or dioxide, give a low yield of an unidentified compound, m. p. 86—92°. Sodium amalgam and methanol usually convert *oo*′-dinitrobiaryls into polycyclic cinnoline derivatives but in this case give 2,6,2′,6′-tetra-aminobiphenyl. Lithium aluminium hydride behaves normally, reducing 2,2′-diamino-6,6′-dinitrobiphenyl to 1,10-diaminobenzo[*c*]cinnoline.

The unusual behaviour of 2,2′-diamino-6,6′-dinitrobiphenyl towards reducing agents

* Part II, *J.*, 1959, 3025.

[1] Theilacker and Baxmann, *Annalen*, 1953, **581**, 117.
[2] Ruby, University Microfilm, Ann Arbor, Michigan, 1853.
[3] Braithwaite, Holt, and Hughes, *J.*, 1958, 4073.

is difficult to explain since the steric effects are similar to those in 2,2'-dimethyl-6,6'-dinitrobiphenyl and the electronic effects are similar to those in 4,4'-diamino-2,2'-dinitrobiphenyl, both of which are reduced to the cinnoline or its oxide.[4]

1,10-Diaminobenzo[*c*]cinnoline is oxidised by peracetic acid to an orange compound having the empirical formula of a tetra-azapyrene dioxide, $C_{12}H_6O_2N_4$. This could be either a di-*N*-oxide of 4,5,9,10-tetra-azapyrene in which the oxygen atoms are on different aza-atoms, or 1,10-dinitrosobenzo[*c*]cinnoline which may also be regarded as 4,5,9,10-tetra-azapyrene 4,5-dioxide (IV) owing to the tendency of nitroso-compounds to dimerise (cf. Ross and Kuntz [5]). The new compound is almost certainly 4,5,9,10-tetra-azapyrene 4,9(?10)-dioxide for the following reasons.

(1) Peracetic acid normally oxidises primary aromatic amines to azo- or azoxy-compounds.[6,7] For example, aniline usually yields 85% of azoxy- and 15% of nitro-benzene [6] although mixtures of azoxy- and nitroso-benzene containing up to 57% of the nitroso-compound may be formed under some conditions.[7] In 1,10-diaminobenzo[*c*]cinnoline the mutual proximity of the amino-groups would favour the formation of an intramolecular azoxy-link. Badger and Walker [8] used a similar method to form a polycyclic cinnoline derivative. They oxidised 1-*o*-aminophenyl-2-naphthylamine to dibenzo-[*c*,*f*]cinnoline (V) with ammonium persulphate in sulphuric acid.

FIG. 1. *Absorption spectra of: A, pyrene in ethanol;*[14] *B, 4,5,9,10-tetra-azapyrene dioxide in* (210—260 mμ) *ethanol and* (260—440 mμ) *dioxan; C, reduction product of the tetra-azapyrene dioxide in acetic acid.*

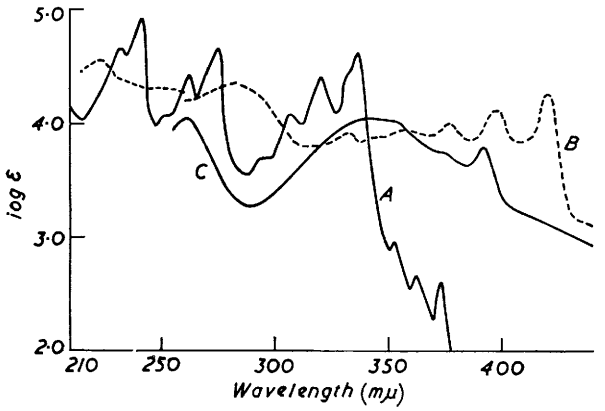
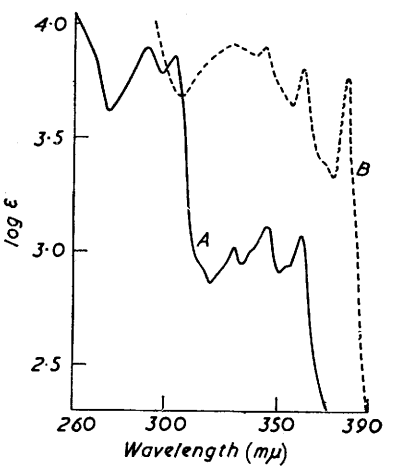


FIG. 2. *Absorption spectra of: A, benzo-[c]cinnoline; B, benzo[c]cinnoline 5-oxide in hexane.*



(2) Polycyclic cinnoline derivatives form *N*-oxides on oxidation with peracetic acid,[5,9] but no example of the further oxidation of an *N*-oxide of a polycyclic cinnoline derivative to an *NN'*-dioxide has been reported. Hence it is likely that, once oxidation of the amino-groups of 1,10-diaminobenzo[*c*]cinnoline has occurred, further oxidation will follow giving 4,5,9,10-tetra-azapyrene 4,9(?10)-dioxide. The 4,9-dioxide is the more likely since the induced charges on the nitrogen atoms are further apart.

(3) The ultraviolet absorption spectrum of the new compound, compared with that of pyrene [10] in Fig. 1, is consistent with that to be expected from a 4,5,9,10-tetra-azapyrene

[4] Kenner and Stubbings, *J.*, 1921, 593; Sako, *Bull. Chem. Soc. Japan*, 1934, **9**, 393; Täuber, *Ber.*, 1891, **24**, 3081.
[5] Ross and Kuntz, *J. Amer. Chem. Soc.*, 1952, **74**, 1297.
[6] Greenspan, *Ind. Eng. Chem.*, 1947, **39**, 847.
[7] D'Ans and Kneip, *Ber.*, 1915, **48**, 1144.
[8] Badger and Walker, *J.*, 1956, 122.
[9] Braithwaite and Holt, *J.*, 1959, 3025; Corbett, personal communication; Hughes, unpublished work.
[10] Friedel and Orchin, " Ultraviolet Spectra of Aromatic Compounds," John Wiley, 1951, spectrum no. 472.

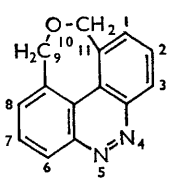
derivative. The spectra of aromatic aza-hydrocarbons are similar to those of their carbocyclic analogues except that there is some loss of fine structure and an increase in intensity of the longest-wavelength absorption band.[11] Where there are more than two nitrogen atoms in the ring system, a hypsochromic shift in the spectrum, particularly at the shorter wavelengths, may result.[12] The absorption curves for benzo[*c*]cinnoline and its 5-oxide in hexane (Fig. 2) show that *N*-oxidation further increases the intensity of the band of longest wavelength, leads to a partial merging of the two longest-wavelength bands, and produces a bathochromic shift.

All these effects are observed in the spectrum of the new compound which is similar is shape to that of pyrene: fine structure is almost absent, log ε of the longest wavelength band is increased from 2·6—2·9 to about 4·2, the shortest wavelength absorption peak is moved hypsochromically from 241 to 223 mμ, and the two longest-wavelength bands appear to have merged.

In view of this evidence it is reasonable to suppose that the new compound is 4,5,9,10-tetra-azapyrene 4,9(?10)-dioxide.

Reduction of the dioxide with stannous chloride and hydrochloric acid yielded a small quantity of a dark red powder, insufficient of which was obtained for analysis. The spectrum of this compound is recorded in Fig. 1. The compound was insoluble in the usual solvents and so slightly soluble in acetic acid that the concentration could not be accurately determined and the values for log ε are almost certainly low. Similarities and the expected variations between this curve and that of pyrene are apparent but it is impossible to say with certainty that the compound was 4,5,9,10-tetra-azapyrene.

No example has been found in the literature of the analogous ring system 4,5-diazapyrene (III) and our attempts to synthesise it were unsuccessful. However, several new 1,10-disubstituted benzo[*c*]cinnolines which are more distorted than 1,10-diaminobenzo[*c*]cinnoline occurred as intermediates in the attempted synthesis. An attempt to synthesise a dihydro-4,5-diazapyrene was made by a method similar to that used by Hall and Turner [13] for the preparation of 9,10-dihydrophenanthrene. This involved the reduction of dimethyl 6,6′-dinitrobiphenate to 1,10-bishydroxymethylbenzo[*c*]cinnoline with the object of converting this into 1,10-bisbromomethylbenzo[*c*]cinnoline and thence into 9,10-dihydro-4,5-diazapyrene. 1,10-Bishydroxymethylbenzo[*c*]cinnoline was prepared but with hydrobromic acid or phosphorus tribromide yielded, instead of the bromo-compound, a cyclic ether (VI). In this compound the ether group bridging the 1- and the 10-positions in the benzo[*c*]cinnoline is under strain and molecular models (Courtauld) indicate that the molecule can be either planar or non-planar.



(VI)

The strained nature of the compound suggested that it might be dehydrated to give 4,5-diazapyrene. It was unaffected, however, by hot concentrated sulphuric acid or by a hot solution of phosphorus pentoxide in phosphoric acid. Molten aluminium chloride converted the cyclic ether into a brown polymeric substance.

When heated at 200° for several hours with hydrobromic acid in an attempt to prevent the formation of an ether link, the bishydroxymethylbenzo[*c*]cinnoline gave a black, infusible polymer, similar to the polyazo-compounds described by Braithwaite, Holt, and Hughes.[3] With hydriodic acid, the cyclic ether (VI) gave a tar.

Although 1,10-bishydroxymethylbenzo[*c*]cinnoline could not be converted into the bisbromomethyl compound, it was converted by thionyl chloride into 1-chloromethyl-10-hydroxymethyl- and then into 1,10-bischloromethyl-benzo[*c*]cinnoline. Treatment of the latter product in boiling toluene with molten sodium gave, not the expected 9,10-dihydro-4,5-diazapyrene, but a mixture of coloured polymers which was slightly soluble

[11] Badger, Pearce, and Pettit, *J.*, 1951, 3199.
[12] Leese and Rydon, *J.*, 1955, 303.
[13] Hall and Turner, *Nature*, 1949, **163**, 537.

in alcohol. It is likely that in this reaction the sodium adds across the azo-group, the resulting disodio-derivative reacting with the chlorine atoms in other molecules to give a polymer.

Experimental

Methyl 2-Iodo-3-nitrobenzoate.—2-Iodo-3-nitrobenzoic acid (50 g.) was heated under reflux (14 hr.) in dry methanol (1 l.) saturated with hydrogen chloride. The solution was left for crystallisation. *Methyl 2-iodo-3-nitrobenzoate* (51 g.; m. p. 62—64°) was obtained as bright yellow needles (Found: C, 31·3; H, 2·2; N, 4·9; I, 41·4. $C_8H_6INO_2$ requires C, 31·3; H, 2·0; N, 4·6; I, 41·4%).

Dimethyl 6,6′-Dinitrobiphenate.—Methyl 2-iodo-3-nitrobenzoate (20 g.) was treated at 160—170° during 25 min. with activated copper bronze (17 g.). The temperature was then slowly raised over 15 min. and kept at 210—220° for a further 30 min. with constant stirring. After cooling, the mixture was extracted with benzene (3 × 250 ml.). The resulting dark brown solution was boiled with charcoal, filtered, and evaporated. Pale yellow crystals of dimethyl 6,6′-dinitrobiphenate (m. p. 125—128°; lit.,[14] m. p. 129°) were obtained. This product was pure enough for the next stage.

2,2′-Diamido-6,6′-dinitrobiphenyl.—Dimethyl 6,6′-dinitrobiphenate was hydrolysed to 6,6′-dinitrobiphenic acid by the method of Ingersol and Little.[14] A 94% yield of the acid was obtained (m. p. 255—258°; lit.,[14] m. p. 259°).

6,6′-Dinitrobiphenic acid (10 g.) was heated under reflux with thionyl chloride (60 ml.) until all the acid had dissolved (*ca.* 3½ hr.). The excess of thionyl chloride was removed by distillation and the remainder of the mixture was slowly added to aqueous ammonia (*d* 0·880). The flocculent cream-coloured precipitate was collected, washed with water, and dried at 100°. The diamide was obtained as a cream-coloured powder (9·0 g.), m. p. 268—272° (lit.,[4] m. p. 276°).

2,2′-Diamino-6,6′-dinitrobiphenyl.—The preceding diamide (10·8 g.) was slowly added to an ice-cold solution of sodium hypobromite prepared by dissolving bromine (4 ml.) in aqueous sodium hydroxide (13 g. in 136 ml.). The ice-cold solution was stirred for 10 min., then filtered, and the temperature was raised to 80—90° for 10 min. The solution was then filtered and poured into concentrated aqueous ammonium chloride. The resulting brown precipitate recrystallised from alcohol to give orange *2,2′-diamino-6,6′-dinitrobiphenyl* (4·26 g.), m. p. 242—244° (Found: C, 52·6; H, 3·8; N, 20·2. $C_{12}H_{10}N_4O_4$ requires C, 52·7; H, 3·8; N, 20·4%). Deviation from these conditions seriously reduces the yield.

Reduction of 2,2′-Diamino-6,6′-dinitrobiphenyl.—(a) *With zinc and aqueous-alcoholic potassium hydroxide.* 2,2′-Diamino-6,6′-dinitrobiphenyl (0·4 g.) in boiling 90% alcohol was treated with aqueous potassium hydroxide (5 g.) and zinc dust (10 g.). The solution was boiled for 25 min., filtered, evaporated, and poured into concentrated aqueous sodium hydroxide (200 ml.). The resulting tar was dissolved in ethanol and filtered through alumina. The solution was concentrated and fine maroon needles of an unidentified substance (56 mg.; m. p. 86—92°) were isolated. Recrystallisation did not raise the m. p. and chromatography in alcohol on alumina gave a single band which yielded the unknown *substance* (Found: C, 63·2; H, 5·0; N, 20·3. The expected cinnoline requires C, 68·6; H, 4·8; N, 26·7%).

(b) *With sodium amalgam and methanol.* To 2,2′-diamino-6,6′-dinitrobiphenyl (0·4 g.) in dry methanol (400 ml.) was slowly added 3% sodium amalgam (100 g.) with vigorous stirring. The mixture was cooled in ice and set aside. After 4 hr. the solution was filtered, treated with water, and concentrated. The resulting crystals were dissolved in alcohol, the solution was boiled with charcoal, filtered, and evaporated to give 2,6,2′,6′-tetra-aminobiphenyl (0·21 g.) as colourless needles, m. p. 192—194° (lit.,[3] m. p. 198°).

(c) *With lithium aluminium hydride.* To 2,2′-diamino-6,6′-dinitrobiphenyl (0·5 g.) in dry ether (1 l.) was added ethereal lithium aluminium hydride (2 g. in 100 ml.). The mixture was heated under reflux for 1 hr. The excess of hydride was decomposed with water, and the mixture was filtered. The filtrate was shaken with 20% hydrochloric acid, and the acid layer was basified with dilute aqueous potassium hydroxide. The crystals obtained were recrystallised from alcohol to give golden needles (160 mg.) of *1,10-diaminobenzo*[c]*cinnoline*, m. p. 217—221° (Found: C, 68·3; H, 4·8; N, 26·7. $C_{12}H_{10}N_4$ requires C, 68·6; H, 4·8; N, 26·7%).

[14] Ingersol and Little, *J. Amer. Chem. Soc.*, 1934, **56**, 2124.

(d) *Aqueous-alcoholic sodium sulphide.* Saturated aqueous sodium sulphide (1 g.) did not affect 2,2′-diamino-6,6′-dinitrobiphenyl (0·5 g.) in boiling 90% ethanol (250 ml.).

4,5,9,10-*Tetra-azapyrene* 4,9(?10)-*Dioxide.*—To 1,10-diaminobenzo[*c*]cinnoline (160 mg.) in acetic acid were added 15 ml. of a solution of 85% hydrogen peroxide (6 ml.) in acetic acid (19 ml.). The dark solution obtained was heated on a water-bath until it became orange-yellow (*ca.* 1½ hr.) and then evaporated. The orange precipitate formed was recrystallised from hot dimethylformamide, to give orange needles of 4,5,9,10-*tetra-azapyrene* 4,9(?10)-*dioxide* (110 mg.), decomp. >270° (Found: C, 60·1; H, 2·5; N, 23·5. $C_{12}H_6N_4O_2$ requires C, 60·5; H, 2·5; N, 23·5%).

Reduction of 4,5,9,10-*Tetra-azapyrene* 4,9(?10)-*Dioxide.*—The dioxide (40 mg.) in concentrated hydrochloric acid (10 ml.) was treated with the theoretical quantity of stannous chloride. The mixture immediately became deep blue, indicating the formation of a 1,10-diaminobenzo-[*c*]cinnoline derivative. The mixture was heated on a water-bath for 30 min. and poured into an excess of aqueous sodium hydroxide. The dark red precipitate thus obtained was dissolved in alcohol and filtered through alumina. On concentration the filtrate yielded a red-brown powder (2·5 mg.) which decomposed above 250°.

1,10-*Bishydroxymethylbenzo*[c]*cinnoline.*—Dimethyl 6,6′-dinitrobiphenate (2 g.) in dry benzene (200 ml.) and dry ether (500 ml.) was treated with lithium aluminium hydride (1·25 g.) in ether (120 ml.). The mixture was heated under reflux for 20 min. and the excess of hydride was decomposed with water. The mixture was filtered and concentrated, yielding fine yellow crystals. These were filtered in acetone through alumina, and allowed to recrystallise. Bright yellow needles (m. p. 227—230·5°) of 1,10-*bishydroxymethylbenzo*[c]*cinnoline* (0·18 g.) were obtained (Found: C, 70·0; H, 4·9; N, 11·5. $C_{14}H_{12}N_2O_2$ requires C, 70·0; H, 5·0; N, 11·7%).

On treatment with methyl iodide in hot nitromethane this compound forms a *methiodide*, m. p. 160° (decomp.) (Found: C, 47·1; H, 4·1; N, 7·6; I, 32·9. $C_{15}H_{15}IN_2O_2$ requires C, 47·2; H, 3·9; N, 7·3; I, 33·2%).

Action of Hydrobromic Acid on 1,10-*Bishydroxymethylbenzo*[c]*cinnoline.*—The alcohol (0·14 g.) in 60% hydrobromic acid (10 ml.) was heated at *ca.* 75° for 30 min. The solution was left overnight and then poured into dilute aqueous sodium hydroxide. The pale yellow flocculent precipitate was washed with water, dissolved in acetone, and filtered through alumina. The filtrate yielded pale yellow needles (89 mg.) of 9,11-*dihydro*-10-*oxa*-4,5-*diazacyclohepta*[de]-*phenanthrene*, m. p. 171—172° (Found: C, 75·0; H, 4·6; N, 12·9. $C_{14}H_{10}N_2O$ requires C, 75·6; H, 4·5; N, 12·6%).

If the reaction is carried out at 200° for 16 hr. a black, infusible, insoluble polymer is obtained (Found: C, 76·6; H, 3·2; N, 8·7%; Br, 0).

On treatment with 80% hydrogen peroxide in acetic acid the cyclic ether forms an N-*oxide*, m. p. 224—226° (Found: C, 70·1; H, 4·1; N, 11·8. $C_{14}H_{10}N_2O_2$ requires C, 70·6; H, 4·2; N, 11·8%), and with methyl iodide in hot nitromethane a *methiodide*, m. p. 185—188° (Found: C, 49·6; H, 3·7; N, 7·8; I, 35·2. $C_{15}H_{13}IN_2O$ requires C, 49·4; H, 3·6; N, 7·7; I, 34·9%).

1-*Chloromethyl*-10-*hydroxymethylbenzo*[c]*cinnoline and* 1,10-*Bischloromethylbenzo*[c]*cinnoline.*—The bishydroxymethylbenzo[*c*]cinnoline (115 mg.) was dissolved in thionyl chloride (3 ml.). After effervescence had ceased the solution was heated under reflux for 10 min. and then added slowly to dilute aqueous potassium hydroxide. The resulting precipitate was washed with water, dissolved in acetone, and filtered through alumina. The filtrate was concentrated and water was added until crystallisation commenced. Greenish-yellow crystals (68 mg.) of 1-*chloromethyl*-10-*hydroxymethylbenzo*[c]*cinnoline*, m. p. 131—133° (decomp.), were obtained (Found: C, 65·8; H, 4·3; N, 10·7; Cl, 13·6. $C_{14}H_{11}ClN_2O$ requires C, 65·0; H, 4·3; N, 10·8; Cl, 13·7%).

When the reaction time was extended to 2 hr., 1,10-*bischloromethylbenzo*[c]*cinnoline*, m. p. 171° (decomp.), was obtained as yellow needles (from acetone) (57·5% yield) (Found: C, 61·0; H, 3·7; N, 10·1; Cl, 25·4. $C_{14}H_{10}Cl_2N_2$ requires C, 60·7; H, 3·6; N, 10·1; Cl, 25·6%).

Wurtz Reaction of 1,10-*Bischloromethylbenzo*[c]*cinnoline.*—Sodium (0·4 g.) was melted in boiling dry toluene (30 ml.) under nitrogen. To the stirred mixture was slowly (15 min.) added 1,10-bischloromethylbenzo[*c*]cinnoline (0·3 g.) in dry toluene (50 ml.). The mixture was then heated under reflux for 30 min., cooled, and filtered to remove sodium and some black material. The solution was concentrated and filtered through alumina. It gave a series of ill-defined bands which ranged from orange to dark brown. The column was eluted with alcohol. On

evaporation, the eluate gave only a brown sticky polymeric material. The solid was redissolved in alcohol, boiled with charcoal, filtered, and concentrated but no crystalline product was isolated.

Ultraviolet absorption spectra were determined with a Unicam S.P. 500 spectrophotometer.

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