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Studies on the Syntheses of Tetracycline Derivatives. III.[1] Synthetic Approach to Adriamycin—Synthesis of the Linear Tetracyclic Skeleton having the Same BC Ring System with Adriamycin

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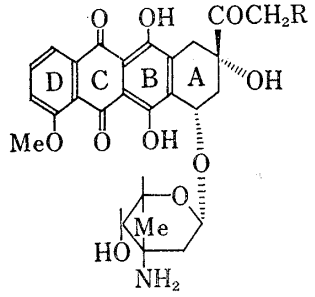
Cycloaddition of 1-acetoxybenzocyclobutene (**21**) with naphthoquinone (**8**) gave naphthacene-5,12-quinone (**22**) which was converted into 6,11-dihydroxynaphthacene-5,12-quinone (**25**) by three steps. Synthetic trial of 6-oxygenated naphthacene-5,12-quinones from naphthacene-5,12-quinones are also described.

Keywords——intermolecular cycloaddition of *o*-quinodimethanes; naphthacene-5,12-quinone; polyoxygenated naphthacene; 6,11-dihydroxynaphthacene-5,12-quinone; Curtius reaction

Adriamycin (**1**)[3] and daunomycin (**2**),[4] antibiotics having a linear tetracyclic skeleton, have shown a very high activity against tumors[5] and have been used successfully as a curative means for acute lymphomas.

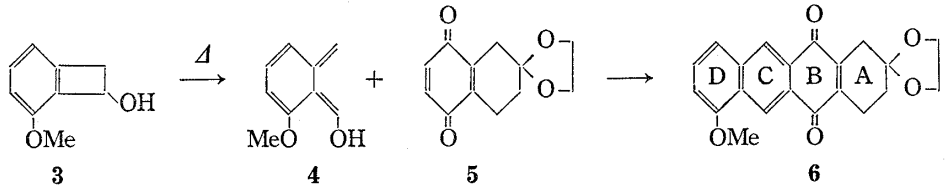


1: R=OH
2: R=H

Chart 1

As these antibiotics produced by fermentation are available in limited quantity, we began to investigate a chemical synthesis of these compounds in order to alleviate the scarcity.[1,6] In this paper we wish to report a synthesis of the linear tetracyclic compound having the same oxygen function on BC ring system with adriamycin.

Previously, we have reported a synthesis of the linear tetracyclic compound (**6**) having the basic skeleton of adriamycin by an intermolecular cycloaddition of the *o*-quinodimethane (**4**), derived thermally from the benzocyclobutene (**3**), to the naphthoquinone (**5**).[1] Adriamycin (**1**) has a naphthazarin system in its BC ring part, but our compound (**6**) lacks two oxygen func-



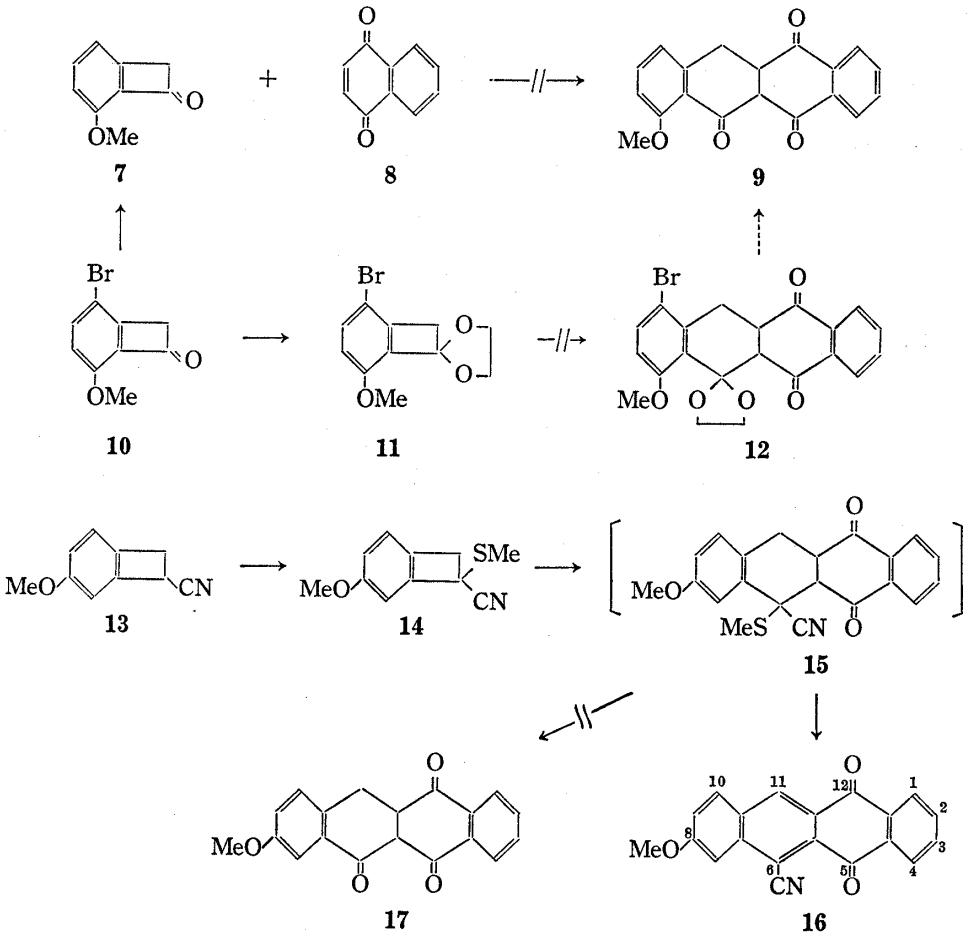
3 **4** **5** **6**

Chart 2

1) Part II: T. Kametani, M. Takeshita, H. Nemoto, and K. Fukumoto, *Chem. Pharm. Bull.* (Tokyo), **26**, 556 (1978).
2) Location: *Aobayama, Sendai 980, Japan.*
3) F. Arcamone, G Franceschi, S. Penco, and A. Selva, *Tetrahedron Lett.*, **1969**, 1007.
4) F. Arcamone, G. Franceschi, P. Orezzi, G. Cassinelli, W. Barbiere, and R. Mondelli, *J. Am. Chem. Soc.*, **86**, 5334 (1974).
5) J.F. Halazun, H.R. Wagner, J.F. Gaeta, and L.F. Sinks, *Cancer*, 33, 545 (1974).
6) T. Kametani, T. Takahashi, M. Kajiwara, Y. Hirai, C. Ohtsuka, F. Satoh, and K. Fukumoto, *Chem. Pharm. Bull.* (Tokyo), **22**, 2159 (1974).

tional groups on C ring. Therefore, we investigated a synthesis of the C ring-oxygenated tetracyclic compounds and also an introduction of oxygen function to our compound[1,6] obtained previously, all of which have no oxygen functional groups on ring C.

Firstly, we examined a synthesis of 6-oxygenated naphthacene-5,12-quinones (**9**, **12**, **17**) by three methods. Heating a mixture of the benzocyclobutenone-1 (**7**)[1] and naphthoquinone (**8**) gave no tetracyclic compound (**9**) but the starting materials have been recovered. The reaction of naphthoquinone (**8**) with the ketal (**11**), obtained by treatment of the benzocyclobutenone-1 (**10**)[1] with ethylene glycol in boiling benzene in the presence of *p*-toluenesulfonic acid, afforded the unidentified compound, mp 231—232°, and did not form the expected compound (**12**), a precursor to **9**. The third trial was intermolecular cycloaddition of naphthoquinone (**8**) to the 1-cyano-1-methylthiobenzocyclobutene (**14**), which was a chemical equivalent with benzocyclobutenone, because it is well known that the benzocyclobutenes having a cyano or hydroxyl group at C-1 position were reactive compounds in a cycloaddition.[7] Treatment of the 1-cyanobenzocyclobutene (**13**)[8] with dimethyl disulfide in the presence of *n*-butyllithium gave the sulfide (**14**), which was heated with naphthoquinone (**8**) in boiling xylene to afford, in 59% yield, the known 6-cyanonaphthacene-5,12-quinone (**16**)[6] but not the expected 6,6-disubstituted compound (**15**), congener of **17**. Since our first trial which would afford 6-oxygenated tetracyclic compounds by a direct synthetic method had resulted in failure, our attention turned to a conversion of the substituent presented already at C-6 position into the oxygen function.



7 **8** **9**
10 **11** **12**
13 **14** **15**
17 **16**

Chart 3

7) T. Kametani and K. Fukumoto, *Heterocycles*, **8**, 465 (1977).
8) T. Kametani, M. Kajiwara, and K. Fukumoto, *Tetrahedron*, **30**, 1053 (1974).

It is well known that quinones could be obtained from aromatic amines by an oxidation with Fremy's radical.[9] Therefore, we investigated a synthesis of the 6-aminonaphthacene-5, 12-quinone (**20**), which would be a key intermediate to 5,6,11,12-tetraoxygenated tetracyclic compounds, from the 6-cyano one (**16**) by Curtius reaction modified by Yamada.[10]

Hydrolysis of the nitrile (**16**) with methanolic potassium hydroxide gave the carboxylic acid (**18**), which was treated firstly with diphenylphosphoryl azide (DPPA)[9] in the presence of triethylamine in dioxane at 80—90°, and then with boiling ethanol for 20 hr to furnish the urethane (**19**) in 47% yield. However, this urethane (**19**) could not be converted into the amine (**20**) by a hydrolysis under several conditions.

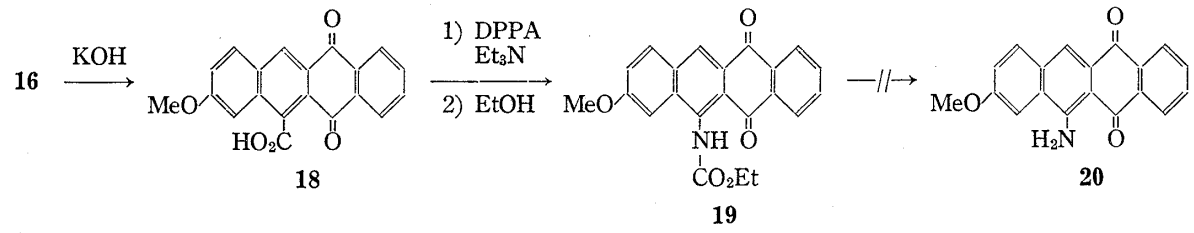


Chart 4

Finally, we examined a synthesis of the tetracyclic compound (**25**) having a naphthazarin system in its BC ring part by an oxidation of naphthacene-5,12-quinone (**22**) according to Kende's method.[11]

Thermolysis of 1-acetoxybenzocyclobutene (**21**)[12] in the presence of naphthoquinone (**8**) in *o*-dichlorobenzene at 180° for 6 hr gave the starting naphthacene-5,12-quinone (**22**)[13,14], mp 280° (lit.,[13] mp 285°), which was reduced with zinc in acetic anhydride in the presence of sodium acetate at 110° for 3 hr to afford, in 36% yield, 5,12-diacetoxynaphthacene (**23**),

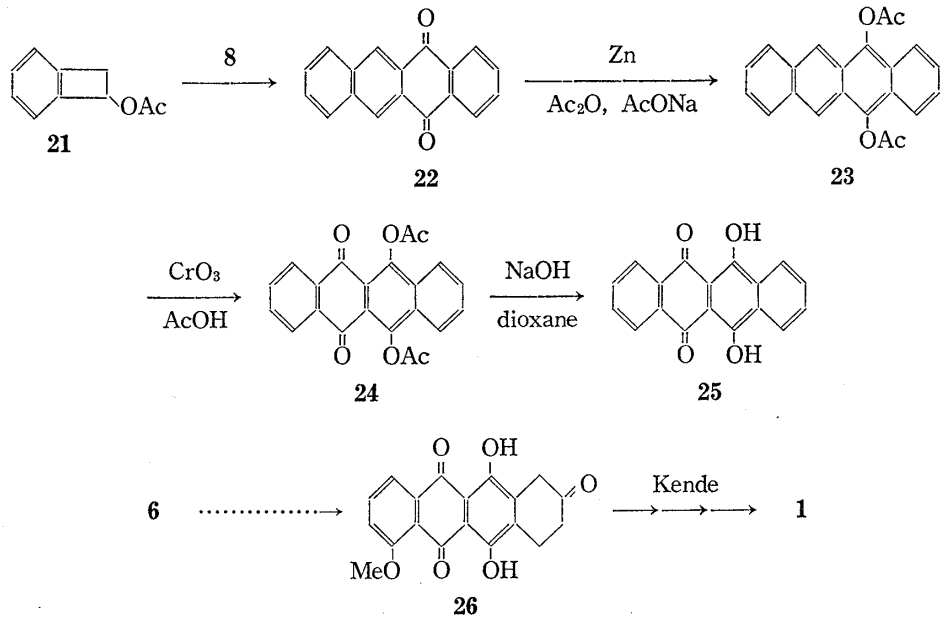


Chart 5

9) H. Zimmer, D.C. Lankin, and S.T. Horgan, *Chem. Rev.*, **71**, 229 (1971).
10) K. Ninomiya, T. Shioiri, and S. Yamada, *Tetrahedron*, **30**, 2151 (1974).
11) A.S. Kende, D.P. Curran, Y. Tsay, and J.E. Mills, *Tetrahedron Lett.*, **1977**, 3537.
12) H.H. Wasserman and J. Solodar, *J. Am. Chem. Soc.*, **87**, 4002 (1965).
13) L.F. Fieser, *J. Am. Chem. Soc.*, **53**, 2329 (1931).
14) B.J. Arnold, P.G. Sammes, and T.W. Wallace, *J. Chem. Soc. Perkin I*, **1974**, 409.

mp 250° (lit.,[15] mp 250°), showing the methyl resonance in acetyl group at δ 2.73 in its nuclear magnetic resonance (NMR) spectrum and carbonyl band in acetoxyl at 1760 cm^{-1} in its infrared (IR) spectrum. Oxidation of the diacetoxynaphthacene (**23**) was carried out with chromic anhydride in 80% acetic acid at room temperature to give the quinone (**24**), mp 215° (sublimation) [(lit.,[16] mp 215° (sublimation)], *m/e* 374 (M^+), in 48% yield, which showed the presence of acetoxyl and quinone groups at 1770 and 1675 cm^{-1}, respectively in its IR spectrum. Treatment of **24** with sodium hydroxide in boiling dioxane for 3 hr afforded in 75.5% yield the 6,11-dihydroxynaphthacene-5,12-quinone (**25**), mp 340° (lit.,[17] mp 340°), *m/e* 290 (M^+), whose ultraviolet (UV) spectrum was identical with that of reported one.[18]

Thus we could develop a synthetic route of linear tetracyclic compound having naphtharazin system in its BC ring by a cycloaddition reaction of benzocyclobutene, followed by oxidation. Now we are investigating an oxidation of our compound **6** to the keto-quinone (**26**), which had been correlated with adriamycin (**1**) by Kende.[19]

Experimental[20]

3-Bromo-6-methoxybenzocyclobuten-1-one Ethylene Ketal (**11**)——A mixture of 3-bromo-6-methoxybenzocyclobuten-1-one (**10**)[1] (12 g), ethylene glycol (12 g), *p*-toluenesulfonic acid (20 mg), and dry benzene (30 ml) was refluxed for 24 hr, and after cooling, the reaction mixture was digested with water (30 ml). The organic layer separated was washed with sat. $NaHCO_3$ solution and water, and dried over Na_2SO_4. Evaporation of the solvent gave a viscous syrup, which was purified by high-pressure liquid chromatography (HPLC) with methanol to give the ketal (**11**) (1 g; 74%) as a colorless viscous oil. *Anal.* Calcd. for $C_{11}H_{11}BrO_3$: C, 48.79; H, 4.09; *m/e* (M^+) 269.9891 and 271.9870. Found: C, 48.49; H, 3.92; M^+, 269.9841 and 271.9844. NMR (CCl_4) δ: 3.36 (2H, s, $ArCH_2$), 3.86 (3H, s, OMe), 4.20 (4H, s, OCH_2CH_2O), 6.66 (1H, d, J=9 Hz, 5-H), 7.33 (1H, d, J=7 Hz, 4-H).

1-Cyano-5-methoxy-1-methylthiobenzocyclobutene (**14**)——*n*-Butyllithium (5 ml; 10 w/v % in *n*-hexane) was added to a solution of the 1-cyanobenzocyclobutene (**13**)[8] (1 g) and three drops of HMPA in dry tetrahydrofuran (50 ml) at −70° in a current of nitrogen and the mixture was stirred for 10 min at the same temperature. To this mixture was added dimethyl disulfide (0.6 g) at −70° and stirred for further 1 hr at this temperature and then at room temperature for 1 hr. After the reaction mixture was decomposed with water, this was extracted with ether. The extract was washed with 10% NaOH solution and water, and dried over Na_2SO_4. Evaporation of the solvent left an oil, which was purified by column chromatography on silica gel with benzene and then by HPLG with methanol to give the sulfide (**14**) (0.79 g; 50%). *Anal.* Calcd. for $C_{11}H_{11}NOS$: N, 6.82. Found: N, 6.81. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2240 (CN). NMR ($CDCl_3$) δ: 2.50 (3H, s, SMe), 3.43 (1H, d, J=14 Hz, ArCHH), 3.83 (3H, s, OMe), 3.95 (1H, d, J=14 Hz, ArCHH), 6.66—7.20 (3H, m, ArH).

6-Cyano-8-methoxynaphthacene-5,12-quinone (**16**)——A solution of naphthoquinone (**8**) (609 mg) and the benzocyclobutene (**14**) (790 mg) in xylene (30 ml) was heated at 160° for 2 hr, and the separated yellow solid was collected by filtration. Recrystallization of this from chloroform gave the naphthacene-5,12-quinone (**16**) (890 mg; 59%), mp 236—238° (lit.,[6] mp 237—238°) which was identical with the authentic specimen[6] in mp and spectral comparisons.

6-Carboxy-8-methoxynaphthacene-5,12-quinone (**18**)——A mixture of the nitrile (**16**) (150 mg), KOH (2 g) and methanol (2 ml) was refluxed for 48 hr and then methanol was removed by distillation under reduced pressure. The residue was digested with water (50 ml) and washed with ether. After acidification of the residue with 10% HCl, the separated solid was extracted with ether and the extract was washed with brine and dried over Na_2SO_4. Evaporation of ether gave the carboxylic acid (**18**) (75 mg; 47%) as red needles, mp 290—294°, after recrystallization from chloroform–benzene–methanol. *Anal.* Calcd. for $C_{20}H_{12}O_5$:

15) H. Brockmann and B. Franck, *Chem. Ber.*, **88**, 1792 (1955).
16) S. Gabriel and E. Leupold, *Ber.*, **31**, 1281 (1898).
17) R.G. Beĭles and I. Ya. Postovskiĭ, *Zhur. Obshchei Khim.*, **20**, 518 (1950) [*C.A.*, **45**, 599*f* (1951)].
18) H. Brockmann and W. Müller, *Chem. Ber.*, **92**, 1164 (1959).
19) A.S. Kende, Y. Tsay, and J.E. Mills, *J. Am. Chem. Soc.*, **98**, 1968 (1976).
20) All melting points are uncorrected and were measured with a Yanagimoto micromelting point apparatus (MP-22). IR spectra were measured with a Hitachi 215 grating spectrophotometer, NMR spectra with a JEOL PMX-60 spectrometer with tetramethylsilane as an internal standard, and mass spectra with a JEOL D-300 and a Hitachi M-52 spectrometer. High-pressure liquid chromatography was carried out with a Hitachi 635 instrument equipped with 4×250 mm of Hitachi Gel 3011.

C, 72.29; H, 3.64. Found: C, 72.08; H, 3.62. IR ν_{max}^{Nujol} cm^{-1}: 1730 (CO_2H), 1630 (>C=O). NMR (CF_3CO_2H) δ: 4.08 (3H, s, OMe), 7.56—8.60 (7H, m, ArH), 9.03 (1H, s, 11-H), MS *m/e*: 332 (M^+).

6-Ethoxycarbonylamino-8-methoxynaphthacene-5,12-quinone (19)——A solution of the carboxylic acid (**18**) (1 g), DPPA (1.2 g) and triethylamine (0.5 g) in dioxane (25 ml) was heated at 80—90° for 15—20 min, and then ethanol (5 ml) was added to this mixture and refluxed for 20 hr. After evaporation of solvent, the residue was extracted with chloroform. The extract was washed with sat. $NaHCO_3$, water, 10% HCl and brine and dried over Na_2SO_4. After evaporation of chloroform, the residue was chromatographed on silica gel (20 g) with benzene to give the solid, which was recrystallized from benzene to afford the urethane (**19**) (530 mg; 47%) as orange needles, mp 208—210°. *Anal.* Calcd. for $C_{22}H_{17}NO_5$: C, 70.39; H, 4.53; N, 3.73. Found: C, 70.20; H, 4.55; N, 3.61. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740 (COOEt), 1678 (>C=O). NMR ($CDCl_3$) δ: 1.43 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 4.02 (3H, s, OMe), 4.25 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 7.66—8.56 (7H, m, ArH), 8.70 (1H, s, 11-H).

Naphthacene-5,12-quinone (22)——A solution of 1-acetoxybenzocyclobutene (**21**)[12] (5.7 g) and naphthoquinone (**8**) (6.0 g) in *o*-dichlorobenzene (100 ml) was heated with stirring for 6 hr in a current of nitrogen. After cooling, the crystal separated was collected by filtration and recrystallized from benzene to give naphthacene-5,12-quinone (**22**) (5.0 g; 54%) as yellow needles, mp 280° (lit.,[13] mp 285°). NMR ($CDCl_3$) δ: 7.65—8.60 (8H, m, ArH), 8.85 (2H, s, 6- and 11-H). MS *m/e*: 258 (M^+).

5,12-Diacetoxynaphthacene (23)——To a mixture of the naphthacenequinone (**22**) (2.2 g), acetic anhydride (42 ml) and sodium acetate (722 mg) was added slowly zinc dust (1.3 g) in a current of nitrogen, and the mixture was stirred for 3 hr at 110°. After cooling, the reaction mixture was poured into ice, and to this solution was added an excess of chloroform. The mixture was stirred at room temperature for 12 hr and the organic layer was washed with sat. $NaHCO_3$ solution and water, and dried over Na_2SO_4. Evaporation of solvent afforded the diacetoxynaphthacene (**23**) (1.035 g; 36%) as orange needles, after recrystallization from benzene, mp 250° (lit.,[15] mp 250°). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760 (OAc). NMR ($CDCl_3$) δ: 2.73 (6H, s, OCOMe), 7.35—8.26 (8H, m, ArH), 8.65 (2H, s, 6- and 11-H). MS *m/e*: 344 (M^+).

6,11-Diacetoxynaphthacene-5,12-quinone (24)——To a solution of CrO_3 (300 mg) in 80% acetic acid (8 ml) was added slowly the diacetoxynaphthacene (**23**) (172 mg) with stirring, and the mixture was stirred for 6 hr at room temperature. After neutralization with sat. $NaHCO_3$ solution, the mixture was extracted with chloroform, and the extract was washed with water and dried over Na_2SO_4. Evaporation of the solvent left a solid, which was recrystallized from benzene–*n*-hexane to give the diacetoxy-quinone (**24**) (89 mg; 48%) as pale yellow needles, mp 215° (sublimation) [lit.,[16] mp 215° (sublimation)]. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770 (OAc), 1675 (>C=O). NMR ($CDCl_3$) δ: 2.67 (6H, s, OCOMe), 7.7—8.0 (4H, m, 2-, 3-, 8-, and 9-H), 8.17—8.45 (4H, m, 1-, 4-, 7- and 10-H). MS *m/e*: 374 (M^+), 332 (M^+-COCH_2), 290 ($M^+-2\times COCH_2$).

6,11-Dihydroxynaphthacene-5,12-quinone (25)——A mixture of the diacetoxy-quinone (**24**) (50 mg), 5% NaOH (0.5 ml) and dioxane (2 ml) was refluxed for 3 hr and then extracted with an excess of chloroform. This solution was washed with water, dried over Na_2SO_4 and evaporated to leave a solid, which was recrystallized from nitrobenzene to give the dihydroxynaphthacenequinone (**25**) (28.5 mg; 75.5%) as reddish needles, mp 340° (lit.,[17] mp 340°). $\lambda_{max}^{cyclohexane}$ nm: 457, 486, 512, 520.

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