[Chem. Pharm. Bull. 23(12)3184—3188(1975)]

UDC 547.752'292.03.04 : 546.185-31.04

# Bischler-Napieralski Reactions of N-(2-Indolylethyl)acetamide

Shunji Naruto and Atsusuke Terada

*Central Research Laboratories, Sankyo Co., Ltd.*[1]

(Received April 28, 1975)

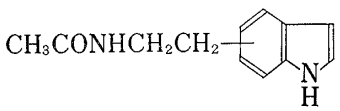
Bischler-Napieralski reaction of N-(2-indol-4-ylethyl)acetamide (II) gave pyridoindole (III) and azepinoindole (IV), N-(2-indol-5-ylethyl)acetamide (V) afforded pyridoindoles (VI and VII), N-(2-indol-6-ylethyl)acetamide (XIII) gave pyridoindoles (XIII and XIV) and N-(2-indol-7-ylethyl)acetamide (XIX) yielded pyridoindole (XX). These reactivity of indole was supported by calculated charge density with CNDO/2.

In a previous paper we have reported the photo induced Friedel-Crafts alkylation of aromatic compounds.[2] The reaction mechanism of these photo alkylations was examined and concluded to be a reaction between an alkyl radical and an aromatic radical cation.[3]

The photoinduced alkylation of indole with chloroacetamide yielded all seven positional isomers of indolylacetamide with 4-indolylacetamide as the major product.[4] The high reactivity of the 4 position of indole has not been previously documented in the literature.[5]

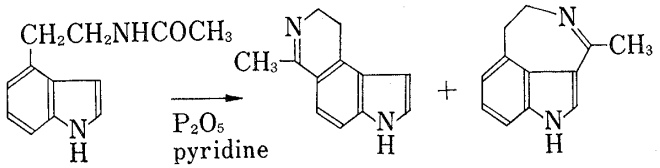
The relative reactivity of the 4, 5, 6, and 7 positions of indole toward alkylation is of considerable importance in connection with the synthesis of naturally occurring alkaloids such as lysergic acid, echinuline, calavinipitic acid and vincristine. The Bischler-Napieralski reaction of indole to $\beta$-carboline[6] is well known, however, there are no other reports on the conversion of indolylethylamine derivatives to pyridoindoles. In a continuation and extension of our studies of indole chemistry we have investigated the Bischler-Napieralski reaction of N-(2-indolylethyl)acetamide (I).

The 2-indolylethylamine of each positional isomer were prepared by the procedure of Troxler,[7] followed by acetylation with dicyclohexylcarbodiimide and acetic acid, to give the



I

Chart 1



II III IV

Chart 2

1) Location: *2-58*, 1-*chome*, *Hiromachi*, *Shinagawa-ku*, *Tokyo*.
2) *a*) O. Yonemitsu and S. Naruto, *Tetrahedron Letters*, **1969**, 2387; *b*) O. Yonemitsu and S. Naruto, *Chem. Pharm. Bull.* (Tokyo), **19**, 1158 (1971).
3) *a*) S. Naruto, O. Yonemitsu, N. Kanamaru, and K. Kimura, *J. Am. Chem. Soc.*, **93**, 4053 (1971); *b*) S. Naruto and O. Yonemitsu, *Tetrahedron Letters*, **1975**, 3399.
4) *a*) S. Naruto and O. Yonemitsu, *Tetrahedron Letters*, **1971**, 2297; *b*) S. Naruto and O. Yonemitsu, *Chem. Pharm. Bull.* (Tokyo), **20**, 2163 (1972).
5) *a*) R.J. Sundberg, Organic Chemistry, a Series of Monographs, Vol. 18, "The Chemistry of Indole," ed. by A.T. Blomquist, Academic Press, New York, N.Y., 1970; *b*) Ed. by W.J. Houlihan, "The Chemistry of Heterocyclic Compounds, Indole part I and II," ed. by A. Weissberger and E.C. Taylor, John Wiley and Sons, Inc., New York, N.Y., 1973.
6) R.A. Abramovitch and I.D. Spenser, "Advances of Heterocyclic Chemistry," Vol. 3, ed. By A.R. Katritzky, Academic Press, New York, N.Y., 1964, p. 79.
7) F. Troxler, A. Harnisch, G. Bormann, F. Seemann, and L. Szabo, *Helv. Chim. Acta.*, **51**, 1616 (1968).

desired starting materials. The Bischler-Napieralski reaction was accomplished by treatment of I, with phosphorous pentoxide in hot xylene containing a catalytic amount of pyridine or tertiary amine.[8]

The Bischler-Napieralski reaction of N-(2-indol-4-ylethyl)acetamide (II) gave two products, 6-methyl-8,9-dihydro-3H-pyrido[4,3-*e*]indole (III) and 3-methyl-5,6-dihydro-1H-azepino-[3,4,5-*cd*]indole (IV) in 70 and 18% yield, respectively. McManus previously reported the synthesis of 4,5-dihydro-3-isopropyl-1H-azepino[3,4,5-*cd*] indole by the Pictet-Spengler reaction.[9]

The structure of III was assigned by the following data coupled with an elemental analysis ($C_{12}H_{12}N_2$). The infrared (IR) spectrum showed an amino band at 3100 $cm^{-1}$ and an imino band at 1630 $cm^{-1}$. The nuclear magnetic resonance (NMR) spectrum integrated for four aromatic protons around 7.0 ppm. Two protons at 7.33 ppm (triplet, $J$=2 Hz) and 6.50 ppm (triplet, $J$=2 Hz) were assigned to the 2 and 1 protons. The remaining singlet at 7.30 ppm integrated for two protons and was assigned to the 4 and 5 protons.

The second product IV had an empirical formula identical to III. The IR spectrum indicated an amino (3200 $cm^{-1}$) and imino band (1580 $cm^{-1}$). The NMR spectrum showed an ABC-type pattern around 7.0 ppm consisting of the 6, 7, and 8 position protons. A singlet at 8.17 ppm integrated for one aromatic proton and was assigned to the 2 position of indole.

The thin-layer chromatography of the ring closure products of N-(2-indol-5-ylethyl) acetamide (V) showed two very closely related spots. Owing to the difficulty of separation and instability of the products, the reaction mixture was reduced with sodium borohydride in methanol, followed by acetylation with acetic anhydride and pyridine to give two products 8-acetyl-9-methyl-6,7,8,9-tetrahydro-3H-pyrido[3,4-*e*]indole (X) and 7-acetyl-8-methyl-5,6,7,8-tetrahydro-1H-pyrido[4,3-*f*]indole (XI) in 35 and 13% yield, respectively.

The elemental analysis of X agreed with an empirical formula, $C_{14}H_{16}ON_2$. The IR spectrum of X had an amino (3180 $cm^{-1}$) and an amide absorption (1620 $cm^{-1}$). The NMR spectrum showed an AB-type pattern at 6.90 ppm and 7.32 ppm ($J$=9 Hz) assigned to the 4 and 5 protons and the typical signals at 6.52 ppm and 7.36 ppm for the 1 and 2 protons of indole. The presence of two methyl singlets at 1.52 ppm and 1.65 ppm, two acetyl methyl singlets at 2.15 ppm and 2.23 ppm, and two quartets at 5.93 ppm and 5.37 ppm due to the methine proton, suggested that the amide group existed as *cis* and *trans* isomers.[10] When the NMR was run at 130° the signals due to the *cis* and *trans* forms collapsed to single peaks. Similarly, the NMR spectra of the N-acetyl-tetrahydro-pyridoindoles, XI, XVII, and XVIII showed the presence of *cis* and *trans* isomers for the amide group.

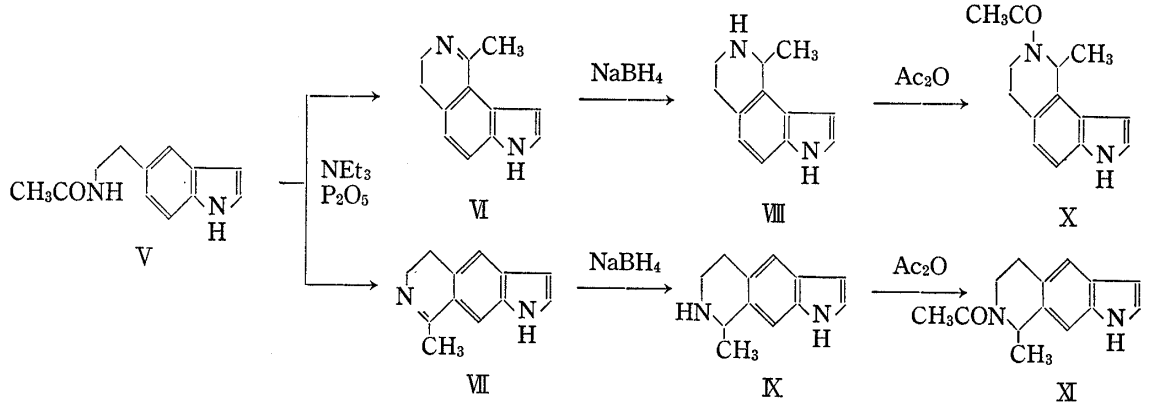



Chart 3

8) N. Itoh and S. Sugasawa, *Tetrahedron*, **1**, 45 (1957).
9) J.M. McManus, Ger. Patent 2306605 (1973) [*C.A.*, **79**, 137117*u* (1973)].
10) *a*) W.E. Stewart and T.H. Siddall III, *Chem. Rev.*, **70**, 517 (1970); *b*) H. Kessler, *Angew. Chem. Intern. Ed. Engl.*, **9**, 219 (1970).

The second product (XI) also had an elemental analysis for $C_{14}H_{16}ON_2$. The IR spectrum showed an amino group at 3300 $cm^{-1}$ and an amide band at 1630 $cm^{-1}$. The NMR signals at 7.22 ppm (doublet, $J$=2 Hz) and 6.40 ppm (doublet, $J$=2 Hz) were assigned to the 2 and 3 protons and the two singlets at 7.20 ppm and 7.33 ppm were assigned to the 4 and 9 protons.

Similarly, treatment of N-(2-indol-6-ylethyl)acetamide (XII) under Bischler-Napieralski reaction conditions afforded two products. The crude product was reduced with sodium borohydride in methanol and acetylated, by the procedure described above, to yield 6-acetyl-5-methyl-5,6,7,8-tetrahydro-1H-pyrido[3,4-*f*]indole (XVII) and 8-acetyl-9-methyl-6,7,8,9-tetrahydro-1H-pyrido[4,3-*g*]indole (XVIII) in 31 and 18% yield, respectively.

The NMR spectrum of the reaction mixture of the dihydropyridoindoles XIII and XIV displayed a singlet at 7.82 ppm and a doublet at 7.62 ppm ($J$=8 Hz), respectively, for 4 position of indole proton. The 1:1 integration ratio of these signals suggested that XIII and XIV had been formed in nearly equal quantities.

Finally, N-(2-indol-7-ylethyl)acetamide (XIX) was allowed to react under Bischler-Napieralski conditions to yield 6-methyl-8,9-dihydro-1H-pyrido[3,4-*g*]indole (XX) and starting material in 54 and 15% yield, respectively.

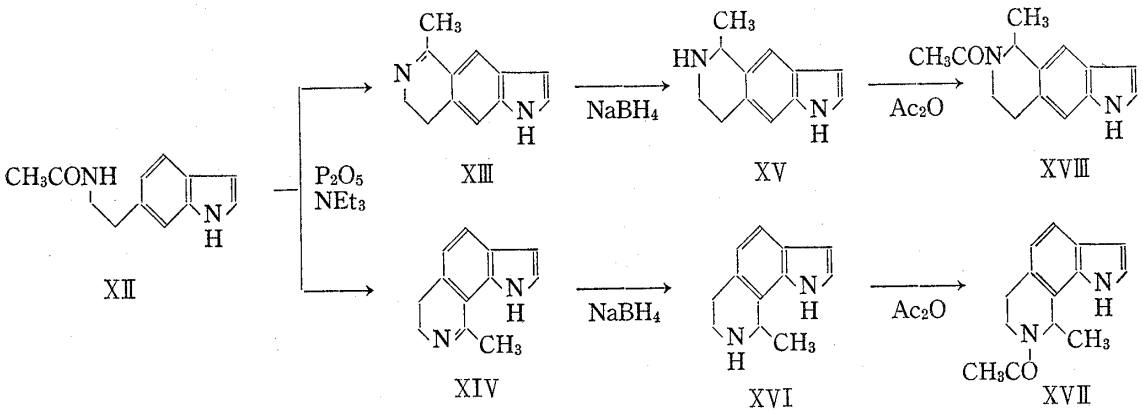



Chart 4

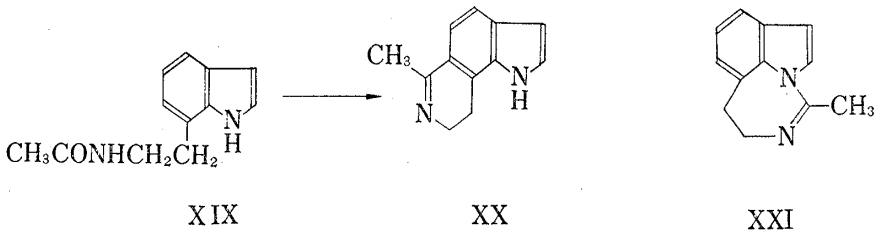



Chart 5

TABLE I

| Position | 5-Me indole model of V. | Yield | 6-Me indole model of XII | Yield |
|---|---|---|---|---|
| 1 | −0.082 | | −0.083 | |
| 2 | 0.076 | | 0.072 | |
| 3 | −0.100 | | −0.096 | |
| 4 | −0.022 | X 35% | 0.002 | |
| 5 | 0.008 | | −0.043 | XIII[a] |
| 6 | −0.012 | XI 13% | 0.038 | |
| 7 | −0.021 | | −0.046 | XIV[a] |

*a*) XIII : XVI=I : I (NMR)

The structure of XX was based on the elemental analysis ($C_{12}H_{12}N_2$) and the IR spectrum, which showed an amino band at 3100 $cm^{-1}$ and an imino band at 1620 $cm^{-1}$. The NMR spectrum exhibited four aromatic proton peaks around 7.0 ppm and an NH proton at 10.45 ppm. The signals at 7.26 ppm (multiplet) and 6.53 ppm (multiplet) were assigned to the 2 and 3 protons of the indole ring and the AB-type pattern at 7.23 ppm and 7.49 ppm ($J$=8 Hz) was assigned to the 4 and 5 protons.

Contrary to our expectations compound XXI could not be isolated. However, 15% of the starting material was recovered. It is possible that the expected ring closure product XXI may be unstable and reverts to XIX.

In order to compare the reactivity of each position of the indole nucleus, molecular orbital calculations were performed. Owing to the difficulty of performing calculations on compounds with a movable side chain, 5-methylindole and 6-methylindole were used as model compounds for the CNDO/2 calculations.[11] The results of the charge density calculations and the yield of the Bischler-Napieralski products (Table I) are in good agreement for compounds V and XII.

## Experimental[12]

**6-Methyl-8,9-dihydro-3H-pyrido[4,3-*e*]indole (III) and 3-Methyl-5,6-dihydro-1H-azepino[3,4,5-*cd*]indole (IV)**——N-(2-Indol-4-ylethyl)acetamide (II) (3.0 g) and 0.5 ml of pyridine were dissolved in 80 ml of xylene. While the solution was stirred and heated (125°) a mixture of $P_2O_5$ (5.0 g) and celite (1.5 g) was added and heated at 125° for an hour.

The reaction mixture was poured into a well stirred mixture of ice (50 g), c·$NH_4OH$ (50 ml) and EtOAc (100 ml). The mixture was filtered and the filtrate was extracted with EtOAc and the extracts were dried over anhydrous $K_2CO_3$. Evaporation *in vacuo* yield 2.6 g of solid, which was chromatographed on $Al_2O_3$. Elution with EtOAc gave (first fraction) 1.80 g (68.9%) of III, which recrystallized from EtOH to give colorless prisms, mp 242—246° (dec.). *Anal.* Calcd. for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.21. Found: C, 78.44; H, 6.63; N, 15.34. NMR $\delta^{DMSO-d_6}$: 2.32 (3H, s), 2.80 (2H, t, $J$=8 Hz), 3.58 (2H, t, $J$=8 Hz), 6.50 (1H, t, $J$=2 Hz), 7.30 (2H, s), 7.33 (1H, t, $J$=2 Hz), 11.30 (1H, bs). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3100, 1630. UV $\lambda_{max}^{EtOH}$ nm ($\varepsilon$): 248 (35900), 254 (35700), 298 (5780).

The second fraction was eluted with EtOH to yield 490 mg (17.9%) of IV. Recrystallization from EtOH gave colorless prisms, mp 228—230° (dec.). *Anal.* Calcd. for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.21. Found: C, 78.11; H, 6.57; N, 15.24. NMR $\delta^{DMF-d_7}$: 2.53 (3H, s), 3.10 (2H, t, $J$=8 Hz), 3.80 (2H, t, $J$=8 Hz), 6.83 (1H, q, $J$=2 and 8 Hz), 7.06 (1H, t, $J$=8 Hz), 7.40 (1H, q, $J$=2 and 8 Hz), 8.17 (1H, s). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3200, 1580. UV $\lambda_{max}^{EtOH}$ nm ($\varepsilon$): 243 (7800), 256 (7480), 272 (8990), 279 (7140), 299 (6000), 308 (5940), 346 (9740).

**8-Acetyl-9-methyl-6,7,8,9-tetrahydro-3H-pyrido[3,4-*e*]indole (X) and 7-Acetyl-8-methyl-5,6,7,8-tetrahydro-1H-pyrido[4,3-*f*]indole (XI)**——N-(2-Indol-5-ylethyl)acetamide (V) (1.0 g) and triethylamine (2 ml) were dissolved in 20 ml of xylene. While the solution was stirred and heated (125°) a mixture of $P_2O_5$ (3.5 g) and celite (1.0 g) was added and heated for an hour. After cooling, the reaction mixture was pouted into well stirred mixture of ice (20 g), c·$NH_4OH$ (30 ml) and EtOAc (50 ml). The mixture was filtered and filtrate was extracted with EtOAc and the extracts were dried over anhydrous $K_2CO_3$. Evaporation *in vacuo* afforded a brown oil which was dissolved in MeOH (30 ml). To the ice-cooled solution, $NaBH_4$ (120 mg) was added with stirring. After an hour the solvent was evaporated in vacuo and $Ac_2O$ (30 ml) was added. After standing 20 hr at room temperature the solvent was evaporated *in vacuo*. The residual solid was dissolved in a trace of EtOH and chromatographed on silica gel and eluted with a mixture of EtOAc and EtOH to give a solid. Recrystallization from tetrahydrofurane (THF) gave colorless prisms of X (350 mg), mp 211—212°. *Anal.* Calcd. for $C_{14}H_{16}ON_2$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.66; H, 7.16; N, 12.57. NMR $\delta^{DMF-d_7}$: 1.52 (d), 1.65 (d) (3H, $J$=7 Hz), 2.15 (s), 2.23 (s) (3H), 3.0—4.0 (4H, m), 5.93 (q), 5.37 (q) (1H, $J$=7 Hz), 6.52 (1H, t), 6.90 (1H, d, $J$=9 Hz), 7.32 (1H, d, $J$=9 Hz), 7.36 (1H, t). NMR $\delta^{DMSO-d_6}$ (at 130°): 1.48 (3H, d, $J$=7 Hz), 2.18 (3H, s), Ca 2.90 (4H, m), 5.63 (1H, q, $J$=7 Hz), 6.42 (1H, d, $J$=3 Hz), 6.82 (1H, d, $J$=9 Hz), 7.24 (1H, d, $J$=9 Hz), 7.24 (1H, d, $J$=3 Hz). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3180, 1620. UV $\lambda_{max}^{EtOH}$ nm ($\varepsilon$): 272 (8340), 282 (7140), 293 (4030).

The mother liquid was chromatographed on silica gel. Elution with EtOAc gave 50 mg of X, and elution with EtOH afforded 150 mg of XI which was recrystallized from EtOAc to yield prisms, mp 200—201°. *Anal.* Calcd. for $C_{14}H_{16}ON_2$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.49; H, 7.12; N, 12.53. NMR $\delta^{MeOH-d_4}$:

11) J.A. Pople and G.A. Segal, *J. Chem. Phys.*, **44**, 3289 (1966).

12) All melting points are uncorrected. The NMR spectra were taken on Varian T-60 spectrometer with tetramethylsilane as an internal standard.

1.41 (d), 1.51 (d) (3H, $J$=7 Hz), 2.10 (s), 2.20 (s) (3H), 2.90 (2H, t, $J$=6 Hz), 3.60 (2H, t, $J$=6 Hz), 5.16 (q), 5.61 (q) (1H, $J$=7 Hz), 6.40 (1H, d, $J$=2 Hz), 7.20 (1H, s), 7.22 (1H, d, $J$=2 Hz), 7.33 (1H, s). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3300, 1630. UV $\lambda_{max}^{EtOH}$ nm ($\varepsilon$): 286 (7260).

**6-Acetyl-5-methyl-5,6,7,8-tetrahydro-1H-pyrido[3,4-*f*]indole (XVII) and 8-Acetyl-9-methyl-6,7,8,9-tetrahydro[4,3-*g*]indole (XVIII)**——N-(2-Indol-6-ylethyl)acetamide (XII) (1.0 g) was treated in the same manner as V to yield a mixture of XVII and XVIII. When the reaction mixture was chromatographed on silica gel the first fraction contained 350 mg of XVII which was recrystallized from EtOAc to yield prisms, mp 156—157°. *Anal.* Calcd. for $C_{14}H_{16}ON_2$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.55; H, 6.89; N, 12.54. NMR $\delta^{DMF-d_7}$: 1.38 (d), 1.53 (d) (3H, $J$=7 Hz), 2.08 (s), 2.16 (s) (3H), 2.97 (2H, t, $J$=6 Hz), 3.70 (2H, t, $J$=6 Hz), 5.13 (q), 5.66 (q) (1H, $J$=7 Hz), 6.43 (1H, bs), 7.26 (1H, s), 7.31 (1H, s), 7.43 (1H, s). UV $\lambda_{max}^{EtOH}$ nm ($\varepsilon$): 286 (6810), 296 (5530). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3220, 1620.

The second fraction afforded 130 mg of XVIII which was recrystallized from THF–EtOAc to give prisms, mp 205—206°. *Anal.* Calcd. for $C_{14}H_{16}ON_2$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.85; H, 7.11; N, 12.35. NMR $\delta^{DMF-d_7}$: 1.46 (d), 1.59 (d) (3H, $J$=7 Hz), 2.13 (s), 2.19 (s) (3H), 2.80—4.00 (4H, m), 5.55 (q), 6.05 (q) (1H, $J$=7 Hz), 6.46 (1H, bs), 6.82 (1H, d, $J$=8 Hz), 7.33 (1H, bs), 7.42 (1H, d, $J$=8 Hz). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3200, 1620. UV $\lambda_{max}^{EtOH}$ nm ($\varepsilon$): 268 (6410), 278 (5590), 289 (3610).

**6-Methyl-8,9-dihydro-1H-pyrido[3,4-*g*]indole (XX)**——N-(2-Indol-7-ylethyl)acetamide (XIX) (400 mg) was treated in the same manner as II. Chromatography on $Al_2O_3$ gave 60 mg of starting material and 195 mg of XX which was recrystallized from EtOAc to yield needles, mp 166—167°. *Anal.* Calcd. for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.21. Found: C, 78.12; H, 6.59; N, 15.20. NMR $\delta^{CDCl_3}$: 2.45 (3H, s), 2.86 (2H, t, $J$=8 Hz), 3.70 (2H, t, $J$=8 Hz), 6.53 (1H, m), 7.23 (1H, d, $J$=8 Hz), 7.26 (1H, m), 7.49 (1H, d, $J$=8 Hz), 10.45 (1H, bs). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3100, 1620. UV $\lambda_{max}^{EtOH}$ nm ($\varepsilon$): 249 (26400), 298 (11200), 325 (6490).