3(2*H*)Isoquinolones. 2 (1). Studies on the Structure and Formation of Aminonaphthols obtained in the Preparation of 3(2*H*)Isoquinolones

W. E. Kreighbaum, W. F. Kavanaugh, and W. T. Comer

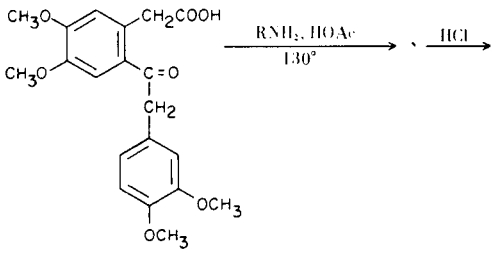
Department of Chemical Research, Mead Johnson Research Center, Evansville, Indiana 47721

Received March 2, 1973

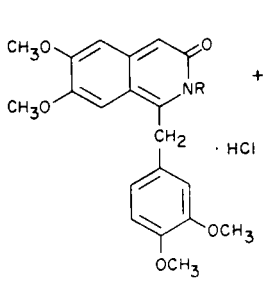
The reaction of a 2-acylphenylacetic acid derivative (I) with primary amines in glacial acetic acid produces novel, colorless aminonaphthols (III) which are isomeric with the brilliant yellow 3(2*H*)isoquinolones (II) obtained in the same reaction. A combination of chemical and spectral techniques allowed identification of the isomers as derivatives of 4-amino-2-naphthol. A plausible mechanism of formation of aminonaphthols *versus* 3(2*H*)isoquinolones is discussed and supported by chemical synthesis of *N*-substituted 2-acylphenylacetamides (VIII) and a 1,4-dihydro-1-hydroxy-3(2*H*)isoquinolone derivative (IX).

During the preparation of a series of pharmacologically interesting *N*-substituted 3(2*H*)isoquinolones, II, (1) by reaction of ketoacid I (2,3,4) with primary amines (Scheme I), we isolated a colorless isomer of the yellow isoquinolone in each case. This report describes our studies on the structure and formation of these isomers, III.

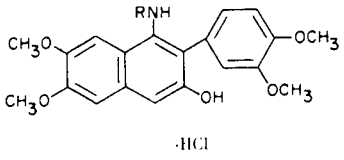
Scheme I



I



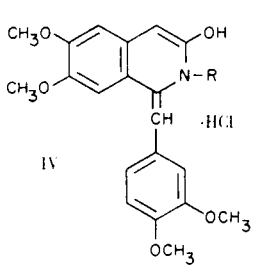
II



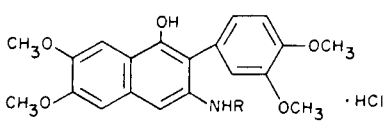
III

The colorless materials (Table I) generally are crystalline, high-melting hydrochlorides giving a positive ferric chloride test. They show no carbonyl band in the infrared spectrum, but exhibit broad absorption in the 2600-3400 cm^{-1} region. The nmr spectrum of one compound (R = CH_3) indicates six aromatic and/or olefinic protons (IV (4) requires seven), and the ir spectrum of the free base in chloroform solution provides evidence for both hydroxyl and secondary amine functions. Reaction of the compound with acetic anhydride gave a crystalline substance which contains both amide and hydroxyl groups as indicated by infrared bands at 1640 cm^{-1} and 3190 cm^{-1}, respectively.

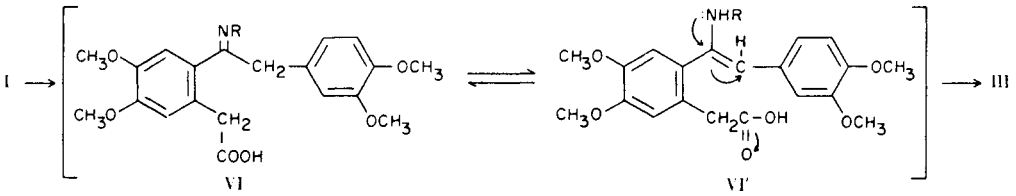
The structure compatible with all the data is an aminonaphthol, of which two position isomers III and V are conceivable, depending upon the steps intermediate to the cyclization. Although the cyclization of I methyl ester with ammonia has been reported (5) to yield a nonnitrogenous naphthoquinone, neither III nor V was isolated.



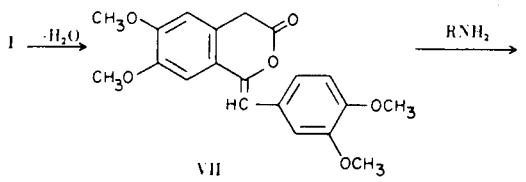
IV

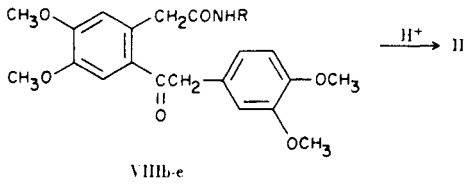


V



We propose that naphthol III is produced from I and amines *via* the imine-enamine intermediate, VI ⇌ VI'. Structure VI', acting as a classical ambident nucleophile, allows attack at the carboxyl carbon by either carbon or nitrogen of the enamine, *C*-attack resulting in β-naphthol III and *N*-attack producing isoquinolone II. This concept is supported by the fact that amines with bulky R groups, which may hinder *N*-attack, give high yields of naphthol and low yields, if any, of isoquinolone; with small R groups, the reverse is generally true.

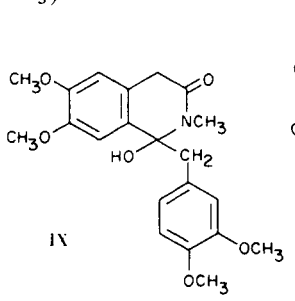


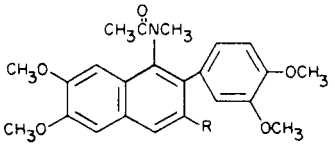


VIIIb-e

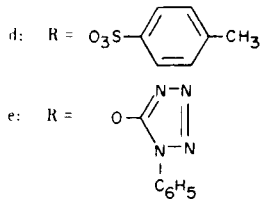
Investigation of a stepwise cyclization of I with amines was informative. If I is converted to lactone VII (1,6) and the latter allowed to react in solution with one equivalent of primary amine under mild conditions, the corresponding open-chain ketoamides (VIIIb-e) are formed in good yield (Table II). These substances could afford naphthol V if such a cyclization occurs. However, treatment of VIIIa-e under the conditions of Scheme I or even milder acidic conditions (Experimental) affords only isoquinolone (thin-layer chromatography). In fact, arylamines, which afford only naphthol when heated directly with I as in Scheme I, produce only isoquinolone *via* the ketoamide route. The *N*,*N*-diethylamide VIIIf, which conceivably could form a tertiary amino-α-naphthol but not an isoquinolone, is unchanged under the reaction conditions of Scheme I or after 24 hours boiling in ethanolic hydrogen chloride. Thus it appears that VIIIa-e could be intermediates for 3(2*H*)isoquinolones but are not responsible for aminonaphthol formation.

Anomalously, treatment of VII with excess methylamine in tetrahydrofuran afforded the 1-hydroxyisoquinolone IX rather than the ketoamide. The ir spectrum of IX is distinguished from that of a ketoamide by the absence of a carbonyl band at 1670-1690 cm^{-1} and the replacement of the amide NH absorption (~ 3350 cm^{-1}) by a broader hydroxyl absorption at 3520 cm^{-1} (7). Acidification of IX in ethyl acetate with one equivalent of ethanolic hydrogen chloride produces an immediate yellow color due to quantitative dehydration to the corresponding *ortho*quinoid 3(2*H*)isoquinolone (II, R = CH_3).





Xa: R = OH
b: R = OC(=O)CH$_3$
c: R = OCH$_3$



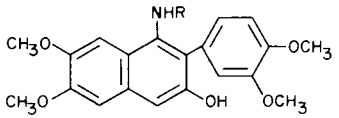
f: R = OC(=S)N(CH$_3$)$_2$
g: R = SC(=O)N(CH$_3$)$_2$
h: R = H

To provide conclusive evidence that the naphthols are indeed III rather than V, we chose to remove one of the functional groups, identify the product by its aromatic substitution pattern in the nmr spectrum, and thus characterize the original naphthol by inference.

Removal of the primary amine group in IIIa *via* the diazonium salt (8) failed in this case due to rapid self-coupling of the diazonium intermediate. To study replacement of the phenolic hydroxyl with hydrogen, we utilized the *N*-methylacetamidonaphthol (Xa), which was also characterized as Xb, c. Catalytic replacement of the *O*-tosyl (9) or *O*-(1-phenyl-5-tetrazoyl) moiety (10) with hydrogen was unsuccessful; both derivatives (Xd, e) were cleaved to regenerate naphthol Xa. A successful conversion was accomplished *via* a four-step sequence (11) involving rearrangement of thiocarbamate Xf to Xg, hydrolysis to the thiol and reduction with Raney nickel to the desired Xh. The nmr spectrum of Xh shows a downfield pair of *ortho*-coupled aromatic protons not

TABLE I

4-Substituted Amino-3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-naphthols

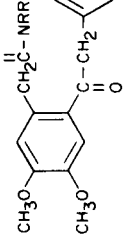


Compound	R	% Yield	M.p., °C	Recrystn. Solvent (b)	Formula	λ max (ε) nm (ε)	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIIa (d)	H	25	242.0-245.0 dec.	M-W	$C_{20}H_{21}NO_5$·HCl	340 (2,000)	61.29	5.66	3.57	60.97	5.64	3.29
b	CH_3	6	242.0-244.0 dec.	M-I	$C_{21}H_{23}NO_5$·HCl	345 (11,320)	62.14	5.96	3.45	62.19	5.70	3.40
c	CH_2CH_3	30	251.0-254.0 dec.	M-EA	$C_{22}H_{25}NO_5$·HCl	341 (5,200)	62.94	6.24	3.34	62.80	6.14	3.28
d	$CH_2C_6H_5$	28	197.5-200.0 dec.	M-EA	$C_{27}H_{27}NO_5$·HCl	342 (5,300)	67.28	5.86	2.91	67.35	5.92	3.01
e	$CH_2CH{=}CH_2$	23	205.5-210.0 dec.	M-EA	$C_{23}H_{25}NO_5$·HCl	340 (6,400)	63.96	6.07	3.24	63.71	5.90	3.23
f	$\overline{CH(CH_2)_4CH_2}$	22	231.0-236.0 dec.	EA	$C_{26}H_{31}NO_5$·HCl	342 (4,700)	65.88	6.81	2.96	65.98	6.84	2.93
g	C_6H_5	30	183.0-185.0	M	$C_{26}H_{25}NO_5$	340 (7,500)	72.37	5.84	3.25	72.48	5.75	3.25
h	$CH_2CH_2C_6H_3$-3,4-$(OCH_3)_2$	32	237.0-239.0 dec.	M-D	$C_{30}H_{33}NO_7$·HCl	340 (3,900)	64.80	6.16	2.52	64.91	6.10	2.68

(a) Melting points are corrected (12). (b) M = methanol, EA = ethyl acetate, I = isopropyl alcohol, E = absolute ethanol, D = ethyl ether, W = water. (c) Longest wavelength ultraviolet absorption in 95% ethanol. (d) Prepared by catalytic debenzylation of IIId; see Experimental.

TABLE II

N-Substituted 2-[2-[(3,4-Dimethoxyphenyl)acetyl]-4,5-dimethoxyphenyl]acetamides



Compound	R	R_1	% Yield	M.p., °C (a)	Recryst'd from (b)	Formula	Calcd. C	Calcd. H	Analysis N	Found C	Found H	Found N
VIIIa	H	$CH_2(CH_2)_2CH_3$	19	95.0-96.5	A-B	$C_{24}H_{31}NO_6$	67.11	7.28	3.26	67.38	7.00	3.24
b	H	$CH(CH_2)_4CH_2$	91	138.0-139.0	A	$C_{26}H_{33}NO_6$	68.55	7.30	3.08	68.49	7.29	2.87
c	H	$CH_2CH{=}CH_2$	73	126.5-127.5	A	$C_{23}H_{27}NO_6$	66.81	6.58	3.39	66.73	6.65	3.45
d	H	p-$C_6H_4OCH_3$	77	156.0-157.5	A	$C_{27}H_{29}NO_7$	67.63	6.10	2.92	67.72	6.46	2.85
e	H	$CH_2CH_2CH_2\rangle_2$	45	138.0-144.5	A	$C_{46}H_{56}N_2O_{12}$	66.65	6.81	3.38	66.41	6.93	3.40
f	CH_2CH_3	CH_2CH_3	59	112.0-114.0	A	$C_{24}H_{31}NO_6$	67.11	7.28	3.26	67.09	7.37	3.20

(a) Melting points are corrected (12). (b) A = ethyl acetate, B = cyclohexane.

present in Xa-g, indicating that the hydroxyl was removed from the β-position of Xa, and substantiating structure III for the colorless products.

We conclude that in the reaction of I with amines, 3(2*H*)isoquinolone formation occurs either through ketoamide VIII or enamine VI′, but the only feasible path to aminonaphthol formation is *via* VI′.

EXPERIMENTAL (12)

Reaction of 2-[3,4-(Dimethoxyphenyl)acetyl]-4,5-dimethoxyphenyl Acetic Acid (I) with Amines. General Preparation of the Aminonaphthols (IIIb-h) (Table I).

A solution of 10 g. (0.027 mole) of ketoacid I and 0.44 mole of amine in 40 ml. of glacial acetic acid was stirred at 130° for 2 hours, then poured into 800 ml. of ice water. Ammonium hydroxide was added to the mixture until no more precipitate formed and the suspension was extracted with chloroform. Separation and acidification of the organic layer (5*N* ethanolic hydrogen chloride to *p*H 2), followed by distillation of the volatile material *in vacuo* gave an impure brown solid. Fractional recrystallization afforded yellow crystalline material (II) in addition to the corresponding colorless naphthol (III) indicated in Table I. Compound IIIb shows the following spectral properties; nmr δ (dimethylsulfoxide-d_6): 7.83 (1H, singlet, aromatic), 6.80-7.40 (5H, multiplet, aromatic), 3.83-4.00 (12H, four singlets, OCH_3), 3.00 (3H, singlet, NCH_3); ν max (chloroform) cm^{-1} (free base): 3550 (OH), 3370 (NH).

4-Amino-3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-naphthol Hydrochloride (IIIa).

Two g. (0.00415 mole) of the *N*-(benzyl)aminonaphthol IIId suspended in 125 ml. of absolute methanol was reduced at 60° for 6 hours on a Parr shaker with 0.2 g. of palladium-on-carbon. The catalyst was separated (Celite) and the filter cake leached with methanol until the leachings were colorless. The filtrate and leachings were evaporated and the residue recrystallized as indicated in Table I.

N-Butyl-2-[2-[(3,4-dimethoxyphenyl)acetyl]-4,5-dimethoxyphenyl]acetamide (VIIIa).

This compound was prepared from ketoacid I and *n*-butylamine by a mixed anhydride procedure (13) and was purified as indicated in Table II; ν max (Nujol) cm^{-1}: 3350 (NH), 1685 (ketone), 1645 (amide).

Reaction of 6,7-Dimethoxy-1-veratrylidene-3-isochromanone (VII) with Amines. General Preparation of the Ketoamides (VIIIb-f) (Table II).

A solution of lactone VII in dry tetrahydrofuran was treated with an equimolar amount of the appropriate amine at 25°. Overnight stirring followed by removal of the volatile material *in vacuo* afforded a syrupy residue which generally crystallized from ether. Purification is indicated in Table II.

Reaction of Ketoamide VIIIc with Ethanolic Hydrogen Chloride.

One-half g. (0.0012 mole) of VIIIc was boiled under reflux for one hour in 20 ml. of 2.5*N* hydrogen chloride in ethanol. Evaporation of the solvent and recrystallization of the residue from ethanol-ethyl acetate afforded 0.5 g. (99%) of bright yellow crystalline material identical (m.m.p., ir, nmr, tlc) with 2-allyl-6,7-dimethoxy-1-veratryl-3(2*H*)isoquinolone hydrochloride (1).

1,4-Dihydro-1-hydroxy-6,7-dimethoxy-2-methyl-1-veratryl-3(2*H*)-isoquinolone (IX).

Methylamine was passed into a suspension of lactone VII (3.2 g., 0.009 mole) in 125 ml. of dry tetrahydrofuran until all the solid material had dissolved. The solution was stirred 18 hours at 25° after which the solvent was evaporated *in vacuo* and the residue recrystallized twice from acetonitrile-isopropyl ether to give 2.1 g. (60%) of 1-hydroxyisoquinolone as colorless crystals, m.p. 141.5-143.5°; nmr δ (dimethylsulfoxide-d_6): 7.16, 6.20-6.80, 6.03 (5H, aromatic), 6.70 (1H, singlet, OH), 3.45-3.83 (12H, multiplet, OCH_3), 3.08 (3H, singlet, NCH_3), 2.70-3.20 (2H, multiplet, CH_2), 1.80-2.10 (2H, doublet, CH_2); ν max (Nujol) cm^{-1}: 3520 (OH), 1645 (amide).

Reaction of the Lactam IX with Acid.

A solution of 0.50 g. (0.0013 mole) of IX in 10 ml. of ethyl acetate was treated dropwise with 1 equivalent of 5*N* ethanolic hydrogen chloride. The resulting yellow precipitate was dissolved by addition of hot methanol and the solution was allowed to cool, affording 0.49 g. (98%) of yellow crystals identical (m.m.p., ir, tlc) with 6,7-dimethoxy-2-methyl-1-veratryl-3(2*H*)isoquinolone hydrochloride (I).

N-[3-Hydroxy-2-(3,4-dimethoxyphenyl)-6,7-dimethoxy-1-naphthyl]-*N*-methylacetamide (Xa).

Twenty-five g. (0.068 mole) of methylaminonaphthol IVb (free base) was heated with 25 g. (0.245 mole) of acetic anhydride in 450 ml. of dioxane at 95° for 3 hours. The volatile material was distilled under vacuum and the residue recrystallized from ethyl acetate and then from butanone to give 10 g. (36%) of *N*-acetylated material, m.p. 225.5-226.5°; nmr δ (dimethylsulfoxide-d_6): 9.42 (1H, singlet, OH), 6.80-6.95 (6H, aromatic), 3.70-3.95 (12H, OCH_3), 2.92 (3H, singlet, NCH_3), 1.60 (3H, singlet, CH_3CO); ν max (Nujol) cm^{-1}: 3190 (OH), 1640 (CO).

Anal. Calcd. for $C_{23}H_{25}NO_6$: C, 67.14; H, 6.12; N, 3.40. Found: C, 67.10; H, 5.88; N, 3.40.

N-[3-Acetoxy-2-(3,4-dimethoxyphenyl)-6,7-dimethoxy-1-naphthyl]-*N*-methylacetamide (Xb).

The liquors from the recrystallization of Xa afforded, upon concentration, 9 g. of gray solid. Recrystallization from butanone and then from ethyl acetate gave 6.0 g. (19%) of the acetoxy derivative of Xa, m.p. 202.0-204.0°.

Anal. Calcd. for $C_{25}H_{27}NO_7$: C, 66.21; H, 6.00; N, 3.09. Found: C, 66.28; H, 6.22; N, 3.12.

N-[2-(3,4-Dimethoxyphenyl)-3,6,7-trimethoxy-1-naphthyl]-*N*-methylacetamide (Xc).

A mixture of 2.0 g. (0.00486 mole) of the naphthol Xa, 2.0 g. (0.0145 mole) of potassium carbonate and 11.4 g. (0.08 mole) of methyl iodide in 100 ml. of acetone was boiled under reflux with stirring for 24 hours. The volatile material was removed and the residue taken up in 100 ml. of water. The precipitated methyl ether of Xa was collected and recrystallized from acetonitrile and then methanol-isopropyl acetate to give 1.0 g. (48%) of white powder, m.p. 222.5-223.5°.

Anal. Calcd. for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40; N, 3.29. Found: C, 67.95; H, 6.26; N, 3.36.

2-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-1-(*N*-methylacetamido)-3-naphthyl *p*-toluenesulfonate (Xd).

A solution of naphthol Xa (4.1 g., 0.01 mole) and 1.95 g. (0.01 mole) of *p*-toluenesulfonyl chloride in 25 ml. of pyridine was heated on a steam bath for 1.5 hours. The mixture was poured into 600 ml. of water and allowed to stand at 25° for several hours, after which the precipitated solid was filtered off and recrystallized from aqueous methanol to give 2.1 g. (37%) of *p*-toluenesulfonate ester, m.p. 227.5-229.5°.

Anal. Calcd. for $C_{30}H_{31}NO_8S$: C, 63.70; H, 5.52; N, 2.48. Found: C, 63.31; H, 5.64; N, 2.61.

N-[2-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-3-[(1-phenyl-5-tetrazolyl)oxy]-1-naphthyl]-*N*-methylacetamide (Xe).

A mixture of 4.11 g. (0.01 mole) of naphthol Xa, 1.8 g. (0.01 mole) of 5-chloro-1-phenyltetrazole (Aldrich Chemical Co.), 2.0 g. (0.0145 mole) of anhydrous potassium carbonate and 150 ml. of acetone was heated under reflux for 72 hours. The insoluble material was filtered, the filtrates evaporated and the residue recrystallized from 50% ethanol-acetone to give 3.5 g. (63%) of Xe as colorless prisms, m.p. 223.0-225.0° dec.

Anal. Calcd. for $C_{30}H_{29}N_5O_6$: C, 64.86; H, 5.26; N, 12.60. Found: C, 64.80; H, 5.31; N, 12.34.

O-[3-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-4-(*N*-methylacetamido)-2-naphthyl]dimethylthiocarbamate (Xf).

A solution of 2.5 g. (0.006 mole) of naphthol Xa and 3 g. (0.024 mole) of *N,N*-dimethylthiocarbamoyl chloride (Aldrich Chemical Co.) in 30 ml. of pyridine was heated overnight on a steam bath at 65-85°. The pyridine was removed *in vacuo* at 85°, after which the dark residue was diluted with water and extracted with chloroform. Evaporation of the organic layer afforded 1.3 g. of tan solid which was recrystallized from acetonitrile to give 1.0 g. (33%) of thiocarbamate Xf, m.p. 234.0-235.0°.

Anal. Calcd. for $C_{26}H_{30}N_2O_6S$: C, 62.63; H, 6.06; N, 5.62. Found: C, 62.27; H, 6.17; N, 5.56.

S-[3-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-4-(*N*-methylacetamido)-2-naphthyl]dimethylthiocarbamate Ethyl Acetate Solvate (Xg).

Seven g. (0.014 mole) of carbamate Xf was heated at 285-290° for 17 minutes. The resulting melt, after cooling, was taken up in hot ethyl acetate, whereupon the mixture solidified to a mass of crystals. Recrystallization of the solid material from 50% ethyl acetate-acetone afforded 3.9 g. (56%) of thiocarbamate Xg, m.p. 122.0-124.0°.

Anal. Calcd. for $C_{26}H_{30}N_2O_6S \cdot C_4H_8O_2$: C, 61.42; H, 6.53; H, 4.77. Found: C, 61.73; H, 6.57; N, 5.11.

After several days exposure to the atmosphere, the melting point was 173.5-175.5° presumably reflecting loss of the solvate.

N-[2-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-1-naphthyl]-*N*-methylacetamide (Xh).

Carbamate Xg (3.8 g., 0.006 mole) in 200 ml. of methanol containing 40 ml. of 1*N* sodium hydroxide solution was heated under reflux for 24 hours and then evaporated to dryness *in vacuo*. The yellow solid residue was taken up in 100 ml. of water, after which the solution was filtered (Celite) and adjusted to pH 2 with 1*N* hydrochloric acid. The pale-yellow precipitate was collected on a Buchner funnel and transferred to a suspension of 40 g. of Raney nickel (W-2) in 200 ml. of ethanol which was subsequently boiled under reflux for 9 hours. Removal of the nickel and evaporation of the filtrates afforded a stiff syrup which crystallized from 2-propanol. Recrystallization from 2-propanol gave 1.5 g. (50%) of tiny, colorless prisms, m.p. 166.0-169.0°; nmr δ (deuteriochloroform): 7.84, 7.42 (2H, two doublets, J = 9 cps, *ortho* aromatic C-H on naphthalene ring), 7.28 (1H, singlet, aromatic), 6.90-7.10 (4H, multiplet, aromatic), 3.80-4.05 (12H, four singlets, OCH_3), 3.10 (3H, singlet, NCH_3), 1.75 (3H, singlet, CH_3CO); ν max (Nujol) cm^{-1}: 1645 (CO).

Anal. Calcd. for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37; N, 3.54. Found: C, 70.04; H, 6.36; N, 3.60.

Acknowledgement.

The authors express their appreciation to Mr. Charles M. Combs and his group for microanalyses and spectral data.

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