Interaction of Alkali Metals with Unsaturated Heterocyclic Compounds. The Reductive Metalation of 1,4-Diphenylphthalazine

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Dedicated to Professor James Graham Smith

1,4-Diphenylphthalazine (**1**) was reduced in tetrahydrofuran by sodium metal to a monomeric dianion **2**. Chemical reactions of this new dianion were examined with various reagents. Generally, the protonation, acylation and alkylation products were 1,2-dihydrophthalazine derivatives. An annulation of the phthalazine ring system was accomplished by treating the dianion with 1,3-dichloropropane or 1,4-dichlorobutane. With 1,2-dichloroethane however, only 1,4-diphenylnaphthalene was detected.

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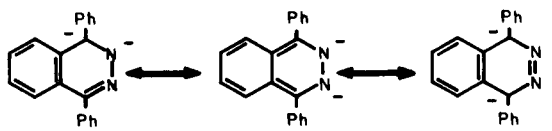
The reduction of some open-chain and cyclic unsaturated nitrogen-containing systems in aprotic solvents by alkali metals has been examined in earlier studies [1,2]. The present report describes the results obtained in the reduction of 1,4-diphenylphthalazine. This compound was selected since it contained the desired conjugative arrangement. The reductive metalation of such conjugated heterocyclic systems can provide dihydro dianionic derivatives capable of further functionalization with electrophiles, thus offering synthetic possibilities.

Experimentally, treatment of 1,4-diphenylphthalazine with sodium metal in tetrahydrofuran (THF) effected the formation of deep purplish blue solution of dianion **2**. When 1,2-dimethoxyethane (DME) was used instead of THF, the reduction was very slow and the yields of the reaction products were very low. Reduction and most of the experiments were effected at −78°.

Under these conditions **1** was clearly converted to a monomeric dianion **2**. The resonance structures of the dianion can be formulated as:



2a **2b** **2c**

The structure shown in **2a** probably provides a better representation of the dianion than the alternative forms **2b** and **2c**. Thus, the chemical behavior of **2** was examined with several reagents and formation of the 1,2-dihydrophthalazine derivatives supported this expectation.

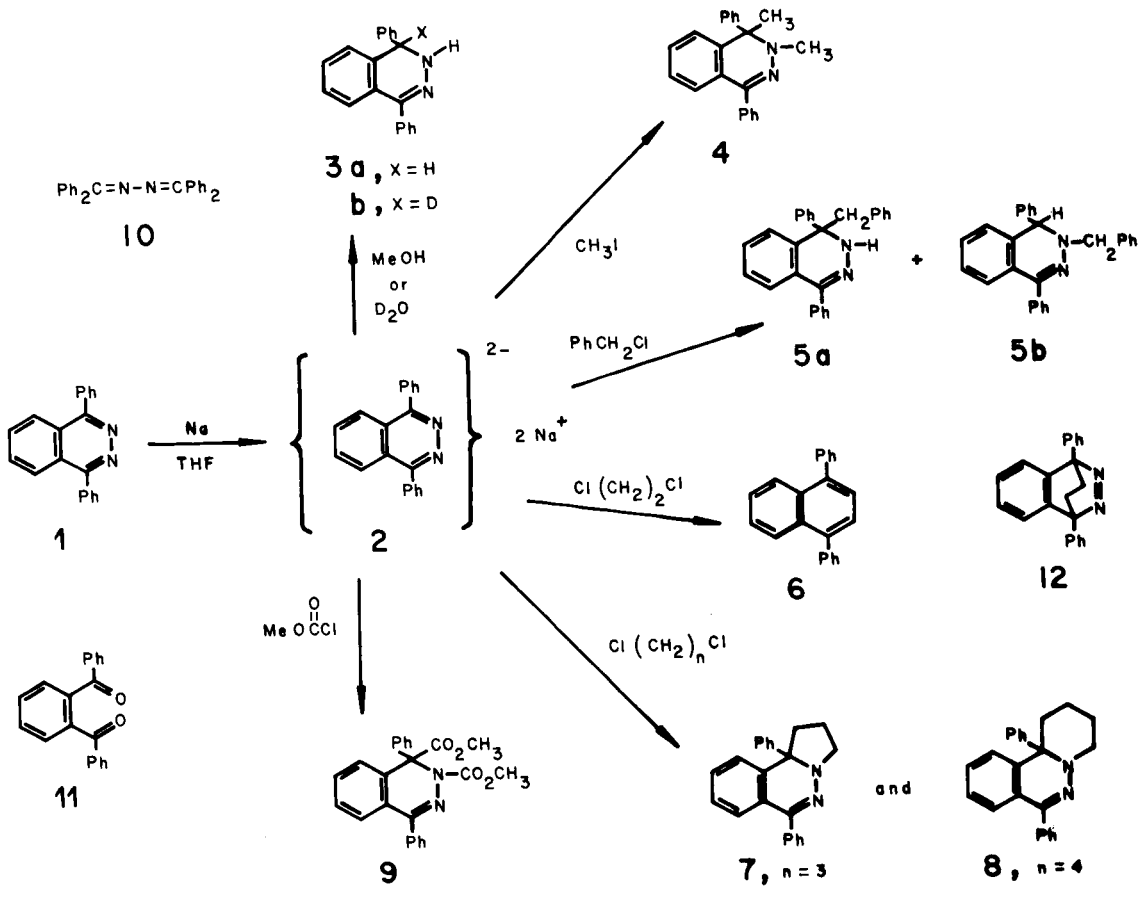
Protonation of the dianion **2** occurred both on the two vicinal anionic centers of **2a** and the product 1,2-dihydro-1,4-diphenylphthalazine (**3a**) was isolated. The structure was characterized from the data obtained. 1-Deuterio-1,2-dihydro-1,4-diphenylphthalazine (**3b**) was formed with deuterium oxide. This identification was based on the nuclear magnetic resonance and infrared spectra of the compound. But the original crude product was readily hydrolyzed and oxidized to the parent compound and only **1** was isolated during purification, as expected.

Alkylation of **2** with methyl iodide smoothly produced 1,2-dimethyl-1,2-dihydro-1,4-diphenylphthalazine (**4**) and its nmr spectrum showed two singlets due to the methyl substituents. The dialkylated product **4** was sufficiently stable that it could be purified easily.

In contrast to the relatively clean methylation reaction of **2**, alkylation with benzyl chloride generated a complex mixture containing both *C*- and *N*-isomers of monobenzyl-1,2-dihydro-1,4-diphenylphthalazine **5a** and **5b**. They were separated by column chromatography and characterized by the benzyl resonance in their nmr spectrum. The major isomer **5a** was assigned the 1-benzyl structure because it contained according to nmr evidence a deuterium oxide exchangeable proton (NH). In addition it also exhibited a band in the NH-region of its ir spectrum. Accompanying this material was a yellow fluorescent oil **5b** which according to its nmr spectrum was assigned the 2-benzylated product. Both **5a** and **5b** proved to be rather unstable compounds, therefore exceptional purification conditions were used for obtaining analytical samples.

An annulation of a five- and six-membered ring to the 1,2-positions of the phthalazine system was accomplished by treating the dianion **2** with a series of polymethylene dichlorides, $Cl(CH_2)_nCl$ (n = 3,4), (*i.e.*, **7** and **8**). The structure assignment of these alkylation products is based on their spectral properties and elemental analyses.

In the case of 1,2-dichloroethane, attempts to annulate a four-membered ring were unsuccessful. Investigation of the spectral data of the isolated material showed that major changes had occurred in the heterocyclic ring system. The only isolable product was in the 77% yield of 1,4-diphenylnaphthalene (**6**). Formation of **6** can be explained



Reactions of the 1,4-diphenylphthalazine dianion.

by the intermediary of **12** which readily looses nitrogen and aromatizes to **6**. This behavior is similar to the known conversion of 1,3-diphenyl-1,3-ethanophthalan to 1,4-diphenylnaphthalene [3].

Acylation of dianion **2** with methyl chloroformate gave one major compound, 1,2-dicarbomethoxy-1,2-dihydro-1,4-diphenylphthalazine (**9**). Since the singlets of the methyl protons of the two carbomethoxy groups were observed near together in its ^{1}H-nmr spectrum, the structure was based mainly on ^{13}C-nmr spectrum evidence by the absorption for the carbonyl groups. The peak at δ 171.5 is assigned to the C=O group attached to position 1 and the C=O peak at δ 149.0 is thought to be due to the carbomethoxy group attached to the nitrogen atom at position 2 [4].

The mass spectra of these dihydrophthalazines were also compatible with a 1,2-substitution pattern because of the initial fragmentations involved either loss of the second substituent or loss of the phenyl radical of the 1-position resulting in the base peak and a second major fragment. Loss of the 1-phenyl substituent dominated when the second substituent was hydrogen (*i.e.*, **3a**) or when the other substituent was part of a ring (*i.e.*, **7** and **8**). When the second substituent was an alkyl or acyl group, M^+-R fragment formed the base peak (*i.e.*, **4**, **5a** and **9**). In addition, proximity effects were observed in the mass spectra of these compounds by loss of a hydrogen atom from the phenyl-substituted fragments as reported in the literature [5].

In every experiment, some 1,4-diphenylphthalazine (**1**) was recovered, probably, because of only partial reduction of **1** to **2**, or conversion of **2** to **1** by traces of the oxygen introduced into the system during the handling of the reaction reagents. Besides occurrence of **11** (though in small amounts only) is thought to be due to traces of water [6].

Generally speaking, 1,4-diphenylphthalazine (**1**) resembles benzophenone azine (**10**) examined in an earlier report [1a]. The similarities of the cyclic and open-chain conjugated system, C=N-N=C, are the protonation and alkylation (methyl iodide, 1,3-dichloropropane and 1,4-dichlorobutane) at the carbon and adjacent nitrogen positions. Important differences are the alkylations with 1,2-dichloroethane and benzyl chloride. Acylation with methyl chloroformate also deviates from the azine behavior. This

would show the affects that the freedom of rotation about the N-N single bond of benzophenone azine has on the delocalization of the dianion in contrast with the affects imposed by the phthalazine ring system.

EXPERIMENTAL

Melting points are uncorrected and were measured in open capillaries with a Mel-Temp melting point apparatus. Infrared spectra were recorded on a Beckman Acculab 10 spectrometer using infrared grade potassium bromide. Nuclear magnetic resonance spectra were determined on a Bruker WP-80 spectrometer in deuteriochloroform and are reported in parts per million downfield from tetramethylsilane (TMS) as the internal standard (δ scale). Mass spectra were obtained with a VG 7070F mass spectrometer. Chemical analyses were performed by MHW Laboratories, Phoenix, AZ and all new compounds gave satisfactory elemental analyses.

In column chromatography, silica gel 60 (70-230 mesh) from E. Merck AG was used. Thin-layer chromatography (tlc) was performed on Eastman Kodak Chromagram 13181 silica gel sheets with fluorescent indicator.

1,4-Diphenylphthalazine (1,4-diphenyl-2,3-diazanaphthalene) was prepared in 97% overall yield from *o*-dibenzoylbenzene, using methanol instead of ethanol [7]. The required *o*-dibenzoylbenzene was synthesized according to a literature procedure [8]. The properties of the *o*-dibenzoylbenzene (mp 146-147°) and 1,4-diphenylphthalazine (mp 201-202°) agreed with the reported values [9]. Reagents were obtained commercially and redistilled under vacuum immediately prior to use.

Tetrahydrofuran (THF) was purified by refluxing for at least 8 hours over lithium aluminum hydride (LAH) and distilling onto a fresh batch of hydride for storage. When needed, the solvent was refluxed for 2 hours and the required amount redistilled immediately before use.

All operations related to the preparation and reaction of alkali-metal compounds were performed in an atmosphere of purified and dried argon [2b].

The general method for preparing the dianion of 1,4-diphenylphthalazine (**2**) was performed as described earlier [3]. The reductive metalation of **1** was effected by shaking a mixture of 0.565 g (2 mmoles) of **1** with excess sodium metal (circa 1 g) and 100 ml of THF in a modified Schlenk tube [10]. Complete reaction of deep purplish blue **2** was ensured by a 8-16 hours reaction time.

A detailed description of one experiment is given to illustrate the general procedure. All crude reaction products were examined by thin-layer chromatography with toluene as developing solvent and compared against to *o*-dibenzoylbenzene, starting material **1** and reagents to follow the progress of the reaction. The purification procedures and additional comments together with the ir, nmr, ms and analytical data are given in each experiment.

1,2-Dimethyl-1,2-dihydro-1,4-diphenylphthalazine (**4**).

Compound **1** (0.425 g, 1.5 mmoles) was placed in a specially designed flask [11] equipped with a Teflon-coated magnetic stirring bar and a septum. The flask was evacuated, filled with Argon and taken into the dry box where the 100 ml of freshly distilled THF and 1 g (0.04 g-atom) of newly cut sodium metal were added. The flask was sealed and removed from dry box. The dianion **2** was obtained by stirring the reaction mixture for 8 hours. After removal of the excess sodium, deep purple solution of **2** was cooled to −78° and 0.24 ml (3.85 mmoles) of methyl iodide was injected. After 1 hour of stirring at −78°, the cooling bath was removed and the reaction mixture was permitted to warm to room temperature, and stirring continued for another 1 hour. The reaction mixture changed from deep purplish blue to red-pink. After addition of water (*ca.* 1 ml) color faded to yellow and the solution was extracted with diethyl ether. The ether layer was washed with water, dried (magnesium sulfate) and evaporated giving 0.44 g of crude product. Investigation of this by thin-layer chromatography with toluene as developer showed that it consisted mainly of **4**, some *o*-dibenzoylbenzene (**11**) and starting material **1**. Chromatography on a short column of silica gel with toluene as eluent gave 0.3 g (64%) of 1,2-dimethyl-1,2-dihydro-1,4-diphenylphthalazine (**4**), an oil which slowly crystallized, mp 151-154°. Two further crystallizations from petroleum ether provided an analytical sample, mp 154-155°; ir (potassium bromide): 1440, 1340, 990, 940, 780, 760, 740, 690 cm^{-1}; nmr (deuteriochloroform): δ 1.72 (s, CCH_3, 3H), 2.86 (s, NCH_3, 3H), 6.4-6.6 (m, aromatic, 1H), 7.1-7.8 (m, aromatic, 13H); ms: m/e (relative intensity) 312 (M^+, 8), 298 (M + 1 − 15, 24), 297 (M-15, 100), 235 (M-77, 48).

Anal. Calcd. for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97. Found: C, 84.60; H, 6.37; N, 9.01.

This was followed by 84 mg (20%) of *o*-dibenzoylbenzene (**11**) [9]. The remaining material was removed from the column with methanol and proved to be 48 mg of starting material **1** (11% recovery) [9].

1,2-Dihydro-1,4-diphenylphthalazine (**3a**).

A solution of the dianion **2** prepared from 0.565 g (2.0 mmoles) of **1** in 100 ml of THF was cooled to 0° and treated with 2 ml of methanol. An immediate color change from deep purplish blue to intense yellow was observed. After 1 hour at 0°, the decolorized solution was stirred for an additional hour during which time it was allowed to rise to room temperature. It was then quenched with water and the crude product was isolated as described above. For purification it was chromatographed on silica gel with toluene. In order of elution there were obtained 22 mg of an as yet unidentified fluorescent material, 0.35 g (62%) of **3a** and 50 mg (8.7%) of **11**, [9]. Further elution of the column with methanol gave 0.11 g (20% recovery) of starting material **1** [9].

Under usual conditions, several attempts for recrystallization of **3a** were not successful and led to quantitative recovery of **1**. An analytical sample was obtained by recrystallization from a cold mixture of diethyl ether and 30-60° petroleum ether (1:1) in an atmosphere of purified and dried nitrogen, pale yellow crystals of 1,2-dihydro-1,4-diphenylphthalazine (**3a**), mp 114-115°, raised by a further recrystallization from cold 30-60° petroleum ether to 119-120°; ir (potassium bromide): 3240, 1490, 1450, 1350, 1110, 1070, 970, 740, 690 cm^{-1}; nmr (deuteriochloroform): δ 5.39 (s, CH, 1H), 6.28 (s, 1, exchanges with deuterium oxide, NH), 6.7-6.9 (m, aromatic, 1H), 7.2-7.8 (m, aromatic, 13H); ms: m/e (relative intensity) 284 (M^+, 22), 283 (M-1, 11), 281 (M-3, 11), 208 (M + 1 − 77, 15), 207 (M-77, 100).

Anal. Calcd. for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85. Found: C, 84.68; H, 5.89; N, 9.89.

The above experiment was repeated with 0.145 ml (8.0 mmoles) of deuterium oxide instead of methanol. Chromatography of the crude product yielded mainly a yellow solid. This was dissolved in 50 ml of hexane, the solution was filtered to remove a small amount of insoluble material and 5 ml of ethanol was added. The only isolable product was the solid which precipitated. It amounted to 0.46 g (81%) of **3b**, mp 128-135°; ir (potassium bromide): 3240, 2860, 1480, 1450, 750 cm^{-1}; nmr (deuteriochloroform): δ 6.34 (s, 1, exchanges with deuterium oxide, NH), 6.72-6.88 (m, aromatic, 1H), 7.27-8.23 (m, aromatic, 13H). On the basis of its ir and nmr spectral properties the structure was considered to be 1-deuterio-1,2-dihydro-1,4-diphenylphthalazine (**3b**). But its purification could not be effected for a satisfactory elemental analysis and led to recovery of **1**.

Thirty-two mg (5.6%) of the starting material **1** was recovered from the column [9].

1-Benzyl-1,2-dihydro-1,4-diphenylphthalazine (**5a**).

Treatment of a 2 mmoles solution of the dianion **2** in THF at −24° (dry ice-carbon tetrachloride) with 0.92 ml (8.0 mmoles) of benzyl chloride gave a rapid color change from deep purplish blue to brownish red. Changing of the color to an intense yellow occurred by quenching with 2 ml of methanol and 1 ml of water. The crude product was isolated as described previously. Chromatography of the product on silica gel using toluene gave three fractions. The first fraction, 0.17 g of a yellow fluorescent oil, was determined to be the 2-benzyl isomer by its spectral properties, **5b**; ir (film): 1490, 1450, 1350, 1260, 1110, 1070, 970, 760, 695 cm^{-1}; nmr (deuteriochloroform): δ 4.5-4.7 (s, CH_2Ph, 2H), 6.7-6.9 (m, CH, 1H),

7.0-7.85 (m, aromatic, 19H). Various purification conditions were used but an analytical sample could not be obtained and it was completely converted to **1**.

The second fraction was a viscous oil and subjected to high vacuum until it solidified, mp 143-145° (0.32 g, 43%). Repeated attempts to purify this material failed and led to recovery **1**. Purification was effected by low temperature dissolution in a mixture of 30-60° petroleum ether and diethyl ether (1:1) in a nitrogen atmosphere. Crystallization occurred slowly during three days. Under the same conditions, a second recrystallization from a minimum amount of diethyl ether provided 1-benzyl-1,2-dihydro-1,4-diphenylphthalazine (**5a**), mp 143-144°; ir (potassium bromide): 3370, 1590, 1490, 1440, 1335, 1100, 740, 690 cm^{-1}; nmr (deuteriochloroform): δ 3.6 (s, CH_2Ph, 2H), 6.5 (s, exchanges with deuterium oxide, NH), 6.8-6.95 (m, aromatic, 2H), 7.0-7.8 (m, aromatic, 17H); ms: m/e (relative intensity) 297 (M-77, 2), 284 (M + 1 −91, 25), 283 (M-91, 100), 282 (M-92, 49).

The analytical data suggested that this compound contained solvent of crystallization [2a]. It is considered to be a rather stable ether of hydration compound, probably a clathrate.

Anal. Calcd. for $C_{27}H_{22}N_2 \cdot \frac{1}{4}C_4H_{10}O$: C, 85.60; H, 6.24; N, 7.13. Found: C, 85.74; H, 6.21; N, 7.26. When dried at 20° over phosphorus pentoxide, 6-8 hours, the following data was obtained: C, 85.75; H, 6.10; N, 7.29.

The third fraction was identified as **11** (37 mg, 6.5%) [9]. The final elution from the column with methanol yielded 119 mg (21% recovery) of impure starting material, **1** [9].

1,4-Diphenylnaphthalene (**6**).

The deep purplish blue solution of **2** prepared from 0.34 g (1.2 mmoles) of **1** was treated at −78° with 0.4 ml (4.75 mmoles) of 1,2-dichloroethane. When the temperature was increased to room temperature the color of the resulting brownish green solution turned orange. The crude product was isolated by ether extraction. Chromatography on silica gel with toluene as eluent provided one major fraction, 0.26 g (77%) of **6** as a viscous oil from which crystallized on the addition of a small amount of ethanol, mp 132-135°. Two recrystallizations from ethanol gave an almost colorless sample of 1,4-diphenylnaphthalene **6**, mp 136-137° (reported 135-136°, 136° [12]), mixture mp with an authentic sample, 136-137°. Spectroscopic properties were also identical to those of the reference sample.

Finally, 79 mg (22% recovery) of **1** was removed from the column with methanol [9].

6,10b-Diphenylpyrrolidino[2,1-*a*]phthalazine (**7**).

Dianion **2** derived from 0.565 g (2.0 mmoles) of **1**, was treated at −78° as usual with 0.76 ml (8.0 mmoles) of 1,3-dichloropropane. The reaction product was isolated as described previously. An examination of the thin-layer chromatogram of this material showed that it mainly consisted of **7**. Chromatography on silica gel using toluene gave 0.45 g (70%) of a yellow solid of **7**. Purification was effected by rechromatography and rapid recrystallization from hexane, mp 121-122°; ir (potassium bromide): 1450, 1440, 1310, 1270, 1150, 760, 690 cm^{-1}; nmr (deuteriochloroform): δ 1.8-2.2 (m, CH_2, 2H), 2.5-2.9 (m, CH_2, 2H), 3.8-4.3 (m, CH_2, 2H), 7.0-7.7 (m, aromatic, 14H); ms: m/e (relative intensity) 324 (M^+, 8), 248 (M + 1 −77, 19), 247 (M-77, 100).

Anal. Calcd. for $C_{23}H_{20}N_2$: C, 85.15; H, 6.21; N, 8.63. Found: C, 85.35; H, 6.29; N, 8.56.

Further elution of the column with methanol gave 0.13 g (23% recovery) of starting material, **1** [9].

7,11b-Diphenylpiperidino[2,1-*a*]phthalazine (**8**).

The above reaction was repeated using 0.88 ml (8 mmoles) of 1,4-dichlorobutane in place of the 1,3-dichloropropane and worked up as described to give an intense yellow oil which slowly became solid under vacuum (0.55 g). Rechromatography and rapid crystallization of this material from hexane afforded 0.40 g (59%) of an analytical sample of **8**, mp 66-67°; ir (potassium bromide): 2940, 1440, 980, 960, 770, 760, 750, 700 cm^{-1}; nmr (deuteriochloroform): δ 1.4-2.0 (m, 2 × CH_2, 4H), 2.4-2.7 (m, CH_2, 2H), 3.5-3.8 (m, CH_2, 2H), 6.8-7.7 (m, aromatic, 14H); ms: m/e (relative intensity) 338 (M^+, 12), 281 (M −57, 15), 262 (M + 1 −77, 20), 261 (M-77, 100).

Anal. Calcd. for $C_{24}H_{22}N_2$: C, 85.16; H, 6.56; N, 8.27. Found: C, 85.07; H, 6.69; N, 8.11.

Continued elution of the column with methanol gave 0.15 g (27% recovery) of impure starting material, **1** [9].

1,2-Dicarbomethoxy-1,2-dihydro-1,4-diphenylphthalazine (**9**).

Methyl chloroformate (0.62 ml, 8.0 mmoles) was added to the chilled solution (−78°) of the dianion **2** prepared from 0.565 g (2.0 mmoles) of **1**. The solution immediately became intense red and after warming to room temperature the color faded yellow. The crude product, 0.82 g red colored solid, was isolated and chromatographed as previously described. Elution with toluene gave 90 mg of unidentified material first. Continuing the elution yielded 0.50 g (62%) of **9**, mp 190-191°, as colorless crystals. An analytical sample was obtained by recrystallization from a mixture of methanol and acetone (1:1), mp 191-192°; ir (potassium bromide): 1750, 1705, 1450, 1440, 1370, 1320, 1305, 1240, 1145, 1030, 1000 cm^{-1}; nmr (deuteriochloroform): δ 3.84 (s, CO_2CH_3, 3H), 3.90 (s, CO_2CH_3, 3H), 7.2-7.8 (m, aromatic, 14H); ms: m/e (relative intensity) 400 (M^+, 1), 342 (M + 1 −59, 27), 341 (M-59, 100), 297 (M-103, 41), 282 (M-118, 7), 281 (M-119, 15).

Anal. Calcd. for $C_{24}H_{20}N_2O_4$: C, 71.99; H, 5.04; N, 6.99. Found: C, 72.16; H, 5.18; N , 7.16.

Two tenths g (35% recovery) of the impure starting material **1** was obtained from the column with methanol [9].

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