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Synthesis of Benz[f] indole-4,9-dione Derivatives *via* Intramolecular Cyclization (II)

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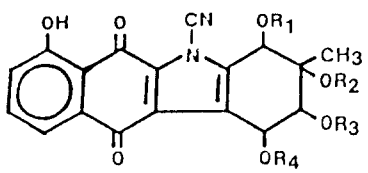
Abstract □ The new N-aryl-benz[f]-indole-4,9-dione derivatives were synthesized *via* intramolecular cyclization when triethylamine was employed as a base for the reaction of 2-chloro-3-(α-cyano-α-ethoxycarbonyl-methyl)-1,4-naphthoquinone and arylamines.

Keywords □ 2-amino-3-ethoxycarbonyl-N-(4-hydroxy-phenyl)-benz[f] indole-4,9-dione, 2-amino-3-ethoxycarbonyl-N-(4-methyl-phenyl)-benz[f] indole-4,9-dione, 2-amino-3-ethoxycarbonyl-N-(5-indanyl-phenyl)-benz[f] indole-4,9-dione, 2-amino-3-ethoxy-carbonyl-N-(4-amino-phenyl)-benz[f]-benz[f]-indole-4,9-dione, 2-amino-3-ethoxy-carbonyl-N-(3-hydroxy-phenyl)-benz[f]-indole-4,9-dione.

1,4-Napthoquinone derivatives with an amino group at the 2-position were reported to show a good antineoplasmic[1], caroinostatic actions[2] and bacterial growth inhibition[3]. Kinamycin A, B, C and D are the antibiotics with the structure of benz [f]-indole-4,9-dione which is a heterocycle with a pyrole ring attatched to 1,4-naphthoquinone[4] Fig. 1.

Mucch attention has been directed to benz[f]-indole-4,9-dione derivatives as antibiotics since S. Ito isolated Kinamycins from Streptomyceus murayamaceusis in 1970. The compounds of this strucutre were found to have an antibacterial action against Gram-positive bacteria[5].



Antibiotic	R_1	R_2	R_3	R_4
Kinamycin A	$COCH_3$	$COCH_3$	$COCH_3$	H
Kinamycin B	H	H	H	H
Kinamycin C	$COCH_3$	H	$COCH_3$	$COCH_3$
Kinamycin D	$COCH_3$		$COCH_3$	H

Fig. 1. The structure of kinamycin A, B, C and D.

The synthesis of benz[f]-indole-4,9-dione from 1, 4-naphthoquinone with an active methylene compound and alkylamines were reported in the previous publication[6] Scheme 1.

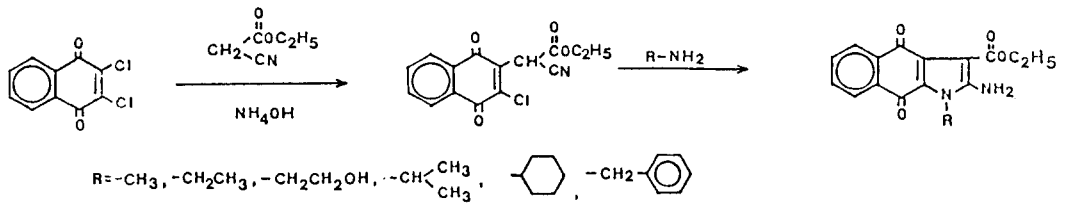
In this study, the new kinds of 2-amino-3-ethoxycarbonyl-N-aryl-benz[f] indole-4,9-diones were prepared when triethylamine was employed as a base catalyst for the reaction of 2-chloro-3-(α-cyano-α-ethoxycarbonyl-methyl)-1,4-naphthoquinone and some arylamines. The overall strategy is illustrated in Scheme 2.

EXPERIMENTAL METHODS

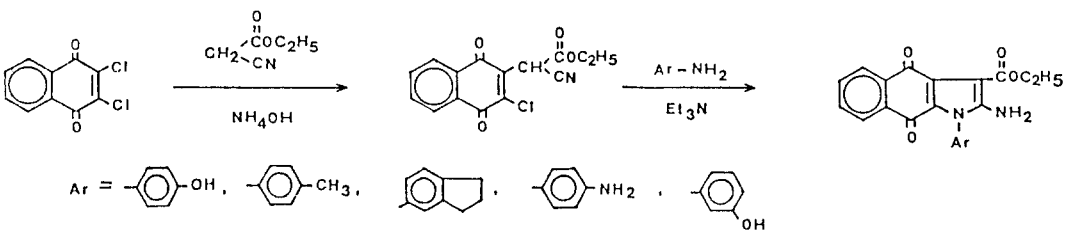
Chemicals and instruments

The reagents and the solvents utilized in this study were the analytical grade and used without further purification.

Infrared spectra were recorded on a Perkin-Elmer Model 1420 Ratio Recording Infrared Spectrophoremeter using pressed KBr pellet. ^{1}H-NMR spectra were obtained with JEOL JNN-PMX 60 SI, Bruker AW 90 NMR Spectrometer, AM-200-SY 200 MHz Brucker and Gemini 300 HMz Varian nmr spectrometer, using trimethylsilane as an internal standard. The multiplicity was specified as follows; s=singlet,



Scheme 1. The synthesis of 2-amino-3-ethoxycarbonyl-N-alkyl-benz[f] indole-4,9-dione derivaties.



Scheme 2. The synthesis of 2-amino-3-ethoxycarbonyl-N-alkyl-benz[f] indole-4,9-dione.

d=doublet, t=triplet, q=quartet and m=multiplet.

Melting point were determined with a Electrothermal Digital Melting Point Apparatus and uncorrected. Elementary analysis were performed on Perkin-Elmer Model 240℃ elemental analyzer. TLC was carried in plastic plates precoated with Kieselgel 60 F-254 (0.2 nm, Merck), under UV 254 nm lamp. Kieselgel 60 (70-230 mesh ASTM, Merck) was used for column chromatography.

Preparation of 2-amino-3-ethoxycarbonyl-N-aryl-benz[f] indole-4,9-diones, 1a-e

A suspension of 2-chloro-3-(α-cyano-α-ethoxycarbonyl-methyl)-1,4-naphthoquinone in methanol or ethanol was placed in a two-necked round bottomed flask equipped with a reflux condenser, a drying calcium chloride guard tube, a magnetic stirring bar and an oil bath. Arylamines and triethylamine were added slowly to this suspension respectively, and the reaction mixture was heated to reflux, concentrated under reduced pressure and cooled at the room temperature. The filtered precipitate was purified by recrystalization or column chromatgraphy followed by washing with hexane. The resulting solid was dried *in vacuo*.

2-Amino-3-ethoxycarbonyl-N-(4-hydroxy-phenyl)-benz[f] indole-4,9-dione 1a

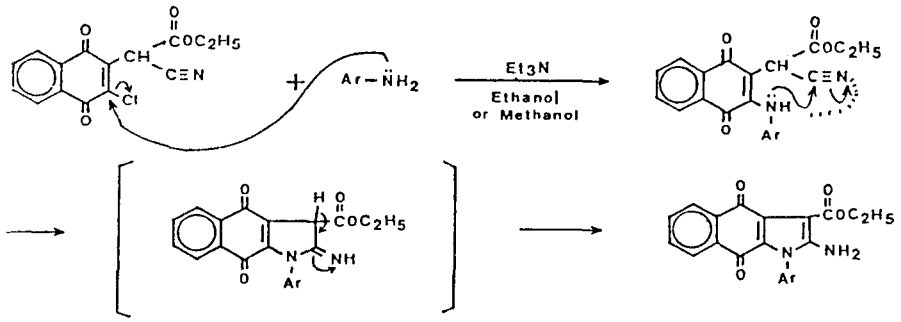
To a mixture of 2-chloro-3-(α-cyano-α-ethoxycarbonyl-methyl)-1,4-naphthoquinone 0.5g (0.00165 mole) and p-hydroxyanile 0.4g (0.0063 mole) in 20 m*l* of ethanol, triethylamine 0.4 m*l* (0.0028 mole) was added. The reaction mixture was heated to reflux for 1½ hours, concentrated and cooled. The precipitate was filtered and washed with ethanol to give 0.32g (52.5%) of orange powder **1a**.

mp. 279℃; IR (KBr, cm^{-1}): 3250, 3350, 3470 (-OH, $-NH_2$), 1630 (-COO). ^{1}H-NMR (DMSO-d_6): δ 1.3 (t, 3H, $-COOCH_2\underline{CH_3}$), 4.3 (q, 2H, $-COO\underline{CH_2}CH_3$), 6.4 (s, 2H, $-\underline{NH_2}$), 6.8-8.0 (m, 8H, aromatic), 9.9 (s, 1H, -OH).

2-Amino-3-ethoxycarbonyl-N-(4-methyl-phenyl)-benz[f] indole-4,9-dione, 1b

To a mixture of 2-chloro-3-(α-cyano-α-ethoxycarbonyl-methyl)-1,4-naphthoquinone 0.5g (0.00165 mole) and p-toluidine 0.34g (0.0032 mole) in 20 m*l* of ethanol, triethylamine 0.4 m*l* (0.0028 mole) was added. The reaction mixture was heated to reflux for 4 hours, concentrated and cooled. The precipitate was filtered and washed with hexane to give 0.19g (30.7%) of red pellet **1b**.

mp. 263℃; IR (KBr, cm $^{-1}$); 3280, 3400 ($-NH_2$, OH), 1660 (-CO). ^{1}H-NMR (DMSO-d_6): δ 1.3 (t, 3H, $-COOCH_2\underline{CH_3}$), 2.5 (s, 3H, $-CH_3$), 4.3 (q, 2H, $-COO\underline{CH_2}CH_3$), 6.54 (s, 2H, $-NH_2$), 7.3-8.0 (m,



Scheme 3. Reaction mechanism of 2-chloro-3-(α-cyano-α-ethoxycarbonyl-methyl)-1,4-naphthoquinone with arylamines in the presence of triethylamine.

8H, aromatic). Anal. cald. for $C_{22}H_{18}N_2O_4$Cmw=374: C 70.6, H 4.81, N 7.49, Found: C 70.5, H 4.73, N 7.49.

2-Amino-3-ethoxycarbonyl-N-(5-indanyl)-benz[f] indole-4, 9-dione, 1c

To a mixture of 2-chloro-3-(α-cyano-α-ethoxycarbonyl-methyl)-1,4-naphthoquinone 0.5g (0.00165 mole) and 5-inadanamine 0.3g (0.0023 mole) in 20 m*l* of ethanol, triethylamine 0.4 m*l* (0.0028 mole) was added. The reaction mixture was heated to reflux for 4 hours, concentrated and cooled. The precipitate was filtered and recrystallized from methanol to give 0.26g (40%) of red powder **1c**.

mp. 248℃; IR (KBr, cm^{-1}): 3300, 3400 (-NH_2), 1660 (-COO). ^{1}H-NMR (DMSO-d_6): δ 1.3 (t, 3H, -$COOCH_2\underline{CH_3}$), 2.1-3.0 (m, 6H, -$CH_2CH_2\underline{CH_2}$-), 4.3 (q, 2H, -$COO\underline{CH_2}CH_3$), 6.4 (s, 2H, -NH_2), 7.1-8.0 (m, 8H, aromatic). Anal. cald. for $C_{24}H_{20}N_2O_4$ (MW=400): C 72.0, H 5.00, N 7.00, Found: C 71.9, H 4.98, N 7.05.

2-Amino-3-ethoxycarbonyl-N-(4-amino-phenyl)-benz[f] indole-4,9-dione, 1d

To a mixture of 2-chloro-3-(α-cyano-α-ethoxycarbonyl-methyl)-1,4-naphthoquinone 0.5g (0.00165 mole) and p-phenylenediamine 0.3g (0.0028 mole) in 20 m*l* of ethanol, triethylamine 0.4 m*l* (0.0028 mole) was added. The reaction mixture was heated to refulx for 3½ hours, concentrated and cooled. The precipitate was filtered, chromatgraphed (hexane-ethylacetate, 1.5 : 1 v/v%) and washed with hexane to give 0.21g (33.9%) of red powder **1d**.

mp. 249℃; IR (KBr, cm^{-1}): 3360, 3460 (-NH_2), 1720 (-COO). ^{1}H-NMR (DMSO-d_6): δ 1.3 (t, 3H, -$COOCH_2\underline{CH_3}$), 4.3 (q,2H, -$COO\underline{CH_2}CH_3$), 5.5 (s, 2 H, -$\underline{NH_2}$), 6.4 (s, 2H, -$\underline{NH_2}$), 6.7-8.0 (m, 8H, aromatic).

2-Amino-3-ethoxycarbonyl-N-(3-hydroxy-phenyl)-benz[f] indole-4,9-dione, 1e

To a mixture of 2-chloro-3-(α-cyano-α-ethoxycarbonyl-methyl)-1,4-naphthoquinone 0.5g (0.0023 mole) and m-hydroxyaniline 0.3g (0.0023 mole) in 20 m*l* of ethanol, triethylamine 0.4 m*l* (0.0056 mole) was added. The reaction mixture was heated to reflux for 14½ hours, concentrated and cooled. The filtered precipitate was chromatgraphed (hexane-ethylacetate, 4 : 1 v/v%) to give 0.07g (11.3%) of orange powder, **1e**.

mp. 251℃; IR (KBr, cm^{-1}): 3360, 3470 (-OH, -NH_2), 1650 (-COO). ^{1}H-NMR (DMSO-d6): δ 1.3 (t, 3H, -$COOCH_2\underline{CH_3}$), 4.3 (q, 2H, -$COO\underline{CH_2}CH_3$), 6.5 (s, 2H, -$\underline{NH_2}$), 6.8-8.0 (m, 8H, aromatic) 9.9 (s, 1H, -$\underline{OH}$). Anal. cald. for $C_{21}H_{16}N_2O_5$ (MW=376): C 67.0, H 4.26, N 7.40 Found: C 67.8, H 4.39, N 6.87.

RESULTS

Reaction of 2-chloro-3-(α-cyano-α-ethoxycarbonyl-methyl)-1,4-naphthoquinone with arylamines in the presence of triethylamine.

Since it was assumed that the different basicities between alkyl and arylamines caused the different results, it seemed reasonable that 2-chloro-3-(α-cyano-α-ethoxycarbonyl-methyl)-1,4-naphthoquinone sould react with arylamines under a basic condition to give the cyclized compounds. The attempted basic catalysts were ammonia, NaOH, KOH, triethylamine, pyridine and sodium ethoxide. Among these,

the ring closed compounds, 2-amino-3-ethoxycarbonyl-N-aryl-benz[f] indole-4,9-diones were yielded when triethylamine-ethanol solution was employed.

In this case, corresponding 2-arylamino-3-(α-cyano-α-ethoxycarbonyl-methyl)-1,4-naphthoquines which were the proposed intermediates for the intramolecular cyclization were isolated as minor products along with the compounds **1a-e**.

The structure of 2-amino-3-ethoxycarbonyl-N-aryl-benz[f]-indole-4,9-diones were characterized by IR and NMR spectral data. The absorption in the region of 3400-3500 cm^{-1} in IR and the signal at δ 6.5-7.0 (s, 2H, $-NH_2$) in NMR spectra show the presence of the primary amine thereby suggesting the ring-closed structure.

This reaction was also greatly influenced by the electron donating ability and the steric hindrance of the arylamines.

When 2-chloro-3-(α-cyano-α-ethoxycarbonyl-methyl)-1,4-naphthoquinone was reacted with arylamines which have electron withrawing groups, or with ortho- or meta- substituens, it gave either compex mitures or no reaction.

CONCLUSION

The new N-aryl-benz[f]-indole-4,9-dione derivatives (2-amino-3-ethoxycarbonyl-N-(4-hydroxy-phenyl)-benz[f] indole-4,9-dione, 2-amino-3-ethoxycarbonyl-N-(4-methyl-phenyl)-benz[f]-indole-4,9-dione, 2-amino-3-ethoxycarbonyl-N-(5-indanyl-phenyl)-benz [f]-indole-4,9-dione, 2-amino-3-ethoxy-carbonyl-N-(4-amino-phenyl)-benz[f]-indole-4,9-dione, 2-amino-3-ethoxy-carbonyl-N-(3-hydroxy-phenyl)-benz[f]-indole-4,9-dione) were synthesized *via* intramolecular cyclization when triethylamine was employed as a base for the reaction of 2-chloro-3-(α-cyano-α-ethoxycarbonyl-methyl)-1,4-naphthoquinone and arylamines. In this case, corresponding 2-arylamino-3-(α-cyano-α-ethoxycarbonyl-methyl)-1,4-naphthoquinones were isolated as minor products along with the cyclized products (compounds **1a-e**).

LITERATURE CITED

1. Robert, K. Y., Zee-Cheng, Podrebarao, Eugene, G., Menon, C. S., Cheng, C. C.: Structural modification study of bis (substituted aminoalkylamino) anthraquinones. *J. Med. Chem.* **22**, 501 (1979).
2. Petersen, S., Gauss, W., Kiehne, H., Juehling, L.: Derivatives of 2-amino-1,4-naphthoquinone as caroinostatic agents. *Z. Krebsforsch* **72**, 162 (1969).
3. Silver, R. F., Holmes, H. L.: Synthesis of some 1,4-naphthoquinones and reaction relating to their use in the study of baoterial growth inhibition. *Canadian J. Chem.* **46**. 1859 (1968).
4. Janos B.: *CRC Handbook of antibiotic compounds 3*, CRC press, Inc., p. 229 (1981).
5. Omura, S., Nakagawa, A., Yamada, H. and Hata, T.: Structure and biological properties of kinamycin A, B, C and D. *Chem. Pharm. Bull.* **21**, 932 (1973).
6. Shin, S. and Suh, M.: Synthesis of benz[f] indole-4,9-dione derivatives *via* intramolecular cyclization. *Yakhak Hoeji*, **35**, 231 (1991).