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Received February 26, 1996

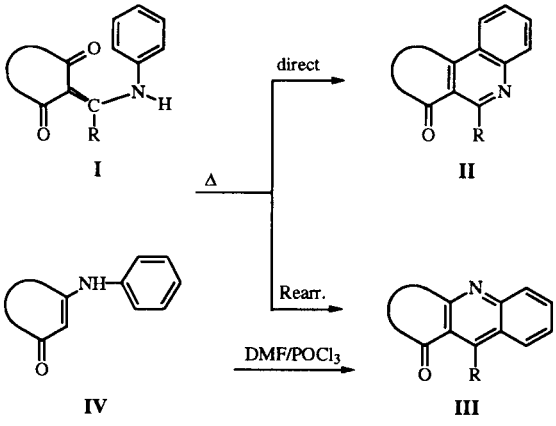
**Dedicated to the memory of Professor Nicholas Alexandrou**

5-Arylaminomethylene compounds such as 5-arylaminomethylenepyrimidine-2,4,6-triones **2** or 2-phenylaminomethylenephenalene-1,3-dione **13** cyclize by thermolysis *via* migration of the arylamino group to pyrimido[4,5-*b*]quinoline-2,4-diones **6** or 7-oxo-7*H*-naphtho[1,8-*bc*]acridine **15**, respectively. 2-Phenylaminomethylenecyclohexane-1,3-dione **8** cyclizes to 9,9-dimethyl-9,10-dihydrophenanthridin-7(8*H*)-one **11** without rearrangement.

*J. Heterocyclic Chem.*, **33**, 905 (1996).

Arylaminomethylene compounds of cyclic 1,3-dicarbonyl compounds such as pyrimidinetriones, quinolinediones, benzopyrandiones or cyclohexandiones have found much interest in the last decade because of their technological and biological properties [1]. Recently we found, that 3-arylaminomethylenequinoline-2,4-diones (a compound of type **I**) cyclize by reaction with phosphoryl chloride but did not give the expected isomeric compounds of type **II** but dibenzo[*b*,*h*][1,6]naphthyridin-6-ones (type **III**) by rearrangement and migration of the arylamino group; the type **III** structure could be confirmed by independent synthesis from phenylamino derivatives (type **IV**) [2]. We observed a similar reaction with 5-chloro-6-formylpyrido[2,3-*d*]pyrimidine-2,4,7-triones and arylamines which yielded also a type **III** product, benzo[*b*]pyrimido-[4,5-*h*][1,6]naphthyridine-1,3,6-triones [3].

Scheme 1



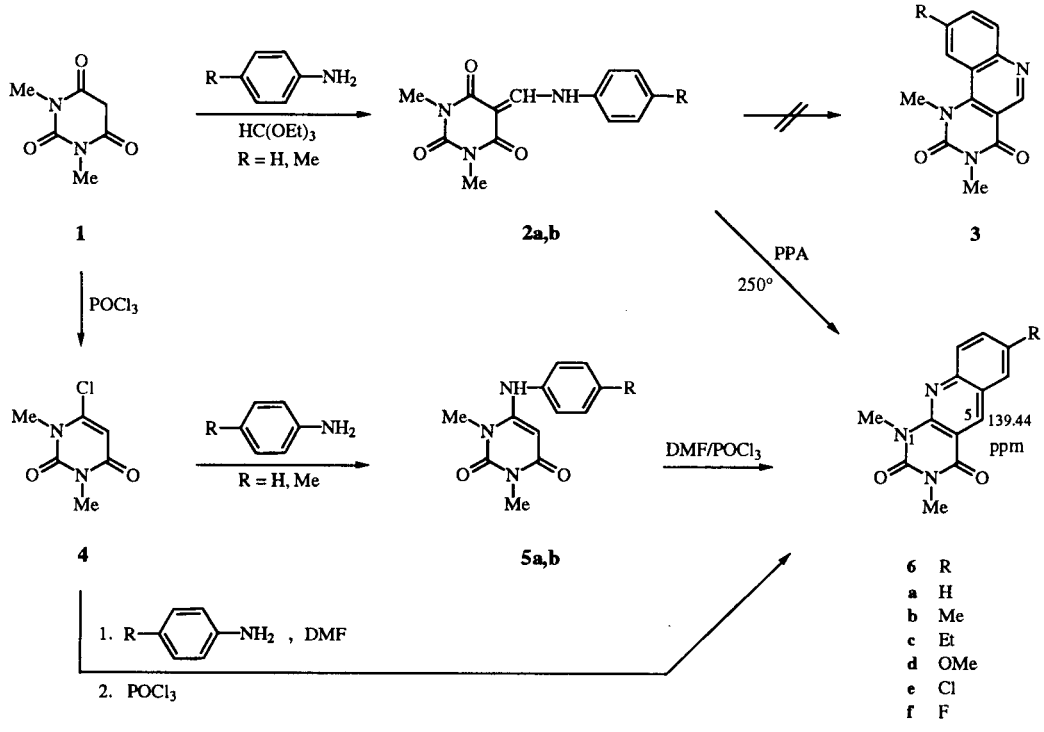

In the cyclohexanedione series a number of publications deal with ring closure reactions of similar arylaminomethylene derivatives (type **I**), which were in some cases not isolated but could be assumed as intermediates in a three component reaction of cyclohexandiones, arylamines and aromatic aldehydes [4-6]. It was revealed by X-ray structure analysis [5], that the compounds obtained in ref [4] have not the structures of type **II** but gave *via* a rearrangement compounds of type **III**. In the indanedione series also ring closure reactions of 2-arylaminomethylene compounds of type **I** were described, and the structures were assigned to compounds of type **II**, but no attention was focused to exclude structures of type **III** [7,8].

In this paper we wish to report our studies of ring closure reactions of arylaminomethylenepyrimidinetriones, -cyclohexandiones and -phenalenediones. One of our aims was to answer the question if the rearrangement reaction to compounds of type **III** can be generalized or if it depends on the particular structure or reaction conditions.

5-Arylaminomethylenepyrimidine-2,4,6-triones **2** were obtained from 1,3-dimethylbarbituric acid (**1**) using the method described in ref [9]. Cyclization attempts with phosphoryl chloride at reflux temperature similar to our reactions in the quinoline series [2] were unsuccessful because only decomposition products could be obtained. When arylaminomethylene compounds **2** were reacted in polyphosphoric acid for 3 hours at temperatures of about 250°, however, a cyclization product could be isolated in about 30% yield, the structure of which was assigned to a pyrimido[4,5-*b*]quinoline **6** (a type **III** product) by comparison with identical compounds obtained by independent syntheses and by spectroscopic structure elucidation.

The independent synthesis was carried out by conversion of 1,3-dimethylbarbituric acid (**1**) with phosphoryl chloride to the 4-chlorouracil **4** [15] and amination with the appropriate aniline to the corresponding arylaminouracil **5**. Vilsmeier formylation of **5** with dimethylformamide and phosphoryl chloride gave in about 90% yield without isolation of an intermediate aminoaldehyde, pyrimido[4,5-*b*]quinoline-2,4-diones **6**, which were identical in all aspects with the compounds obtained by cyclization of the arylaminomethylenepyrimidinetriones **2** with polyphosphoric acid. Amination, formylation and cyclization of the 4-chlorouracil **4** could be achieved also in a one-pot synthesis with a 60% overall yield by heating **4** first with the corresponding aniline in dimethylformamide and then heating the reaction mixture with phosphoryl chloride. Spectral analysis revealed that the $^{13}C$ nmr signal of C-5 (the former arylaminomethylene-car-

Scheme 2

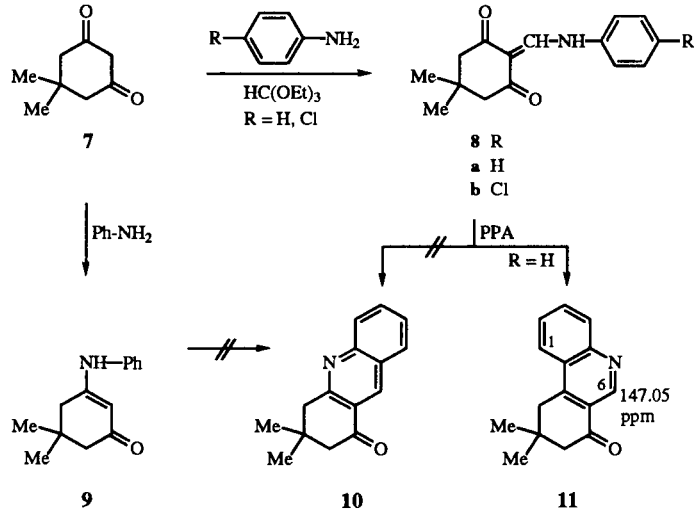



bon) could be observed at 139.4 ppm, which is in good agreement with literature values of γ-quinoline carbons at 136-139 ppm [10] and could be used as an indicator for structural elucidation. Chemical and physical data of **6a,d,e** are also in in agreement with compounds described in the literature obtained by other routes [11].

A literature survey of ring closure reactions of carbocyclic 1,3-dicarbonyl-2-arylaminomethylene compounds (or their predecessors) showed that the reaction of aromatic aldehydes and aminonaphthalenes with dimedone as cyclic 1,3-dicarbonyl compound led to structures of type **III** [5,6], and not to structures of type **II** [4]. Ring closure reaction of arylaminomethylene dimedones with activating groups such as methoxy substituents in the meta-position to the NH-group, is reported to form structures of type **II** by thermolysis at 140-180° in polyphosphoric acid, but no structural distinction was performed to exclude a rearrangement to type **III** products [13]. When we thermolyzed the unsubstituted derivative **8a** in polyphosphoric acid at 190-220° we obtained in about 40% yield a ring closure product with an elemental analysis in agreement with both structures **10** or **11**. The arylaminomethylene compound **8b** with the desactivating chloro substituent gave no reaction product. Attempts to prove the structure of **10/11** by an independent synthesis *via* the enamine **9** [19] was not successful.

Comparison of the data of our cyclization product with literature data of **10** [12] synthesized by an unambigous method, showed differences in mp, ir and nmr data (although some nmr signals were missing in the reference) which indicated the structure of **11** for our cyclization product. This assumption was confirmed by $^{13}C$ nmr spectral data which revealed that the signal of C-6 (the former arylaminomethylene carbon) could be observed at 147.1 ppm, which is in good agreement with literature values of α-pyridine and α-quinoline carbons at about 150 ppm [10].

Scheme 3




This result means that in the cyclization reaction of arylaminomethylenecyclohexandiones - as proposed in ref [13] and in opposition to observations in similar reactions obtained in ref [5] - no rearrangement took place and the direct cyclization product of type **II** could be obtained.

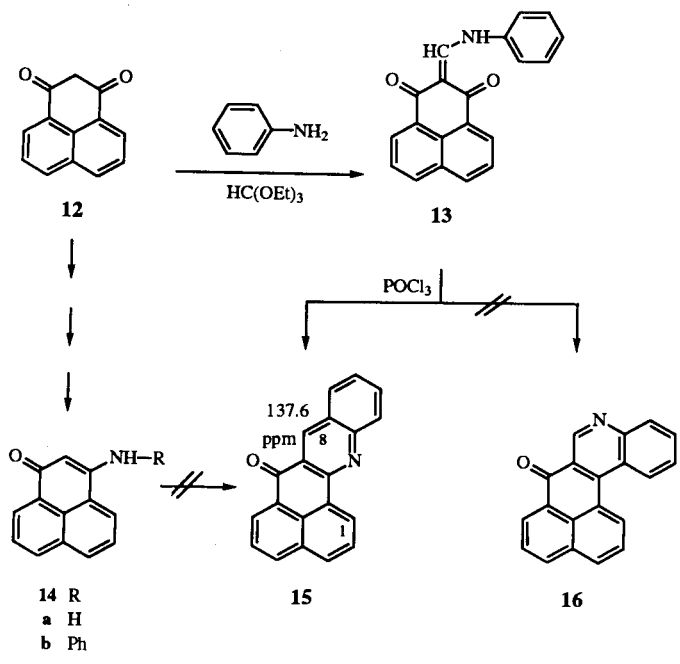
Table 1.

Experimental, Analytical and Spectroscopic Data of 1,3-Dimethyl-7-substituted-pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-diones **6a-f**.

| No. | Method Yield (%) | Mp (°C) Recrystallization solvent | Molecular Formula Molecular mass | Analysis, % Calcd./Found C | H | N | IR [cm$^{-1}$] $^1$H nmr (δ ppm) [a] |
|---|---|---|---|---|---|---|---|
| **6a** | A: 30<br>B: 88<br>C: 63 | 209<br>DMF<br>213 [11] | $C_{13}H_{11}N_3O_2$<br>(241.3) | 64.72<br>64.69 | 4.60<br>4.56 | 17.42<br>17.49 | 1710 s, 1655 s, 1620 s<br>3.33 (s, N-Me), 3.64 (s, N-Me), 7.52-8.15 (m, 4 Ar-H), 9.06 (s, H-5) |
| **6b** | A: 32<br>B: 91<br>C: 60 | 232<br>DMF | $C_{14}H_{13}N_3O_2$<br>(255.3) | 65.87<br>65.90 | 5.13<br>5.16 | 16.46<br>16.47 | 1705 s, 1660 s, 1610 m<br>2.54 (s, Me), 3.51 (s, N-Me), 3.80 (s, N-Me), 7.64 (d, J = 9 Hz, H-8), 7.67 (s, H-6), 7.85 (d, J = 9 Hz, H-9), 8.89 (s, H-5) |
| **6c** | C: 55 | 215<br>DMF | $C_{15}H_{15}N_3O_2$<br>(269.3) | 66.90<br>66.72 | 5.61<br>5.50 | 15.60<br>15.57 | 2960 w, 1710 s, 1660 m, 1610 s<br>1.33 (t, J = 7 Hz, Me), 2.79 (q, J = 7 Hz, $CH_2$), 3.52 (s, N-Me), 3.79 (s, N-Me), 7.66 (d, J = 9 Hz, H-8), 7.69 (s, H-6), 7.89 (d, J = 9 Hz, H-9), 8.9 (s, H-5) |
| **6d** | C: 56 | 272<br>DMF<br>274 [11] | $C_{14}H_{13}N_3O_3$<br>(271.3) | 61.99<br>62.04 | 4.83<br>4.70 | 15.49<br>15.51 | 1705 s, 1655 s, 1610 s<br>[b] 3.60 (s, N-Me), 3.95 (s, N-Me), 4.04 (s, O-Me), 7.60 (s, H-6), 7.85 (d, J = 9 Hz, H-8), 8.16 (d, J = 9 Hz, H-9), 9.65 (s, H-5) |
| **6e** | C: 51 | 271<br>DMF<br>270 [11] | $C_{13}H_{10}ClN_3O_2$<br>(275.7) | 56.64<br>56.59 | 3.66<br>3.66 | 15.24<br>15.24 | 1720 s, 1660 s, 1620 s<br>[b] 3.64 (s, N-Me), 4.02 (s, N-Me), 8.21 (d, J = 9 Hz, H-8), 8.27 (s, H-6), 8.32 (d, J = 9 Hz, H-9), 9.71 (s, H-5) |
| **6f** | C:52 | 242<br>DMF | $C_{13}H_{10}FN_3O_2$<br>(259.2) | 60.23<br>60.04 | 3.89<br>3.89 | 16.21<br>16.25 | 1720 s, 1660 s, 1620 s<br>3.51 (s, N-Me), 3.79 (s, N-Me), 7.50-7.63 (m, 2 ArH), 7.98-8.05 (m, 1 ArH), 8.92 (s, H-5) |

[a] $^{13}$C nmr of **6a**: δ 28.1 (Me), 29.2 (Me), 111.1 (C-4a), 124.3 (C-5a), 125.5 (C-7), 127.2 (C-6), 129.6 (C-8), 133.2 (C-9), 139.4 (C-5), 148.4 (C-2), 148.7 (C-9a), 151.1 (C-4), 160.7 (C-10a). [b] Trifluoroacetic acid was used as the solvent.

Scheme 4




When we extended the cyclization reaction to other carbocyclic arylaminomethylenediones, we obtained in the indanedione series only decomposition products. 2-Phenylaminomethylenephenalene-1,3-dione **13** which was prepared from 1,3-phenalenedione **12** [20], aniline and orthoformate, gave decomposition products with polyphosphoric acid but cyclized in boiling phosphoryl chloride to give a compound, which could be shown to have the structure of **15**, a type **III** product obtained by rearrangement. Results of 2D $^1$H nmr data and NOE difference spectra indicate the spatial neighborhood of the proton, H-9 and H-8, and the $^{13}$C nmr spectrum confirmed the structure of **15** with a signal of 137.6 ppm for C-8, which is in agreement with literature values of γ-quinoline carbons at 136-139 ppm [10]. Attempts to obtain **15** by an independent synthesis *via* 3-amino-1-phenalenone **14a** [21] or 3-phenylamino-1-phenalenone **14b** were not successful.

These results indicate that the rearrangement of arylaminomethylene-1,3-diones (type **I**) to quinoline derivatives of type **III** is not a general reaction pathway but has to be taken into consideration for reactions of this kind. It can be shown that $^{13}$C nmr spectroscopy is a very helpful

tool for this purpose indicating whether or not a rearrangement has taken place by the signal of the α- or γ-quinoline carbon which is formed from the former aryl-aminomethylene carbon.

## EXPERIMENTAL

Melting points were obtained on a Gallenkamp Melting Point Apparatus, Model MFB-595 in open capillary tubes. The $^1H$ nmr spectra were recorded on a Varian Gemini 200 instrument (200 MHz), and the $^{13}C$ nmr spectra on a Bruker AM 360 instrument (90 MHz). Chemical shifts are reported in ppm from internal tetramethylsilane as the standard and are given in δ-units. The solvent for nmr spectra was deuteriodimethyl sulfoxide unless otherwise stated. Infrared spectra were taken in potassium bromide pellets on a Perkin-Elmer 298 spectrophotometer. Elemental analyses were performed on a Carlo Erba 1106 C,H,N-automatic analyzer and are within ±0.4 of the theoretical percentages. All reactions were monitored by thin layer chromatography, carried out on 0.2 mm silica gel F-254 (Merck) plates using uv light (254 and 366 nm) for detection. Common reagent-grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures.

1,3-Dimethyl-5-phenylaminomethylenepyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (**2a**).

A mixture of 1,3-dimethylbarbituric acid (**1**) (15.6 g, 100 mmoles), triethyl orthoformate (14.8 g, 100 mmoles) and aniline (9.3 g, 100 mmoles) in 1,2-dihydroxyethane (30 ml) was heated with stirring. At about 110° formation of ethanol started. During 30 minutes the temperature was increased to 190°, and ethanol was distilled from the solution. Then the reaction mixture was cooled to 110° and diluted with ethanol (100 ml). The resulting precipitate was filtered with suction and washed with ethanol, yield 24.0 g (93%), yellow prisms, mp 202-204° (ethanol), (lit mp 198-203° [14]).

1,3-Dimethyl-5-(4-tolueneaminomethylene)pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (**2b**).

From **1** (15.6 g, 100 mmoles), triethylorthoformate (14.8 g, 100 mmoles) and 4-methylaniline (10.7 g, 100 mmoles) according to the method described for **2a**, yield 23.0 g (84%), yellow prisms, mp 194-196° (ethanol); ir: 1710 m, 1660 s, 1620 s $cm^{-1}$; $^1H$ nmr: δ 2.37 (s, Ar-Me), 3.37 (s, 2 N-Me), 7.17-7.26 (m, 4 ArH), 8.63 (d, J = 13 Hz, = CH), 12.05 (d, J = 13 Hz, NH).

*Anal.* Calcd. for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.67, H, 5.34, N, 15.52.

1,3-Dimethyl-4-phenylaminopyrimidine-2,6(1*H*,3*H*)-dione (**5a**).

A mixture of **4** [15] (17.5 g, 100 mmoles), aniline (23.3 g, 250 mmoles) and ethanol (50 ml) was heated under reflux for 12 hours. The warm reaction mixture was poured into ice/water (500 ml) and brought to *p*H = 1 with concentrated hydrochloric acid. The precipitate was filtered, washed with water and dried. The residue was recrystallized from ethanol, yield 18.5 g (80%), colorless prisms, mp 185° (ethanol), (lit mp 181-182° [16]).

1,3-Dimethyl-4-(4-methylphenylamino)pyrimidine-2,6(1*H*,3*H*)-dione (**5b**).

From **4** [15] (17.5 g, 100 mmoles), *p*-toluidine (26.8 g, 250 mmoles) and ethanol (50 ml) according to the method described for **5a**, **5b** was obtained in 75% yield (18.4 g), colorless prisms, mp 235-238° (ethanol), (lit mp 240-241° [17]).

General Method for the Preparation of 1,3-Dimethyl-7-substituted-pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-diones **6a-f**.

Method A.

A mixture of the appropriate 1,3-dimethyl-5-(4-substituted phenylaminomethylene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**2a,b**) (10 mmoles) with polyphosphoric acid (20 g) was heated to 250° for 3 hours. The warm reaction mixture was poured into ice/water (300 ml), then brought to *p*H = 6-7 with aqueous 10% sodium hydroxide solution and the formed precipitate filtered by suction and dried. The residue was recrystallized from dimethylformamide to yield colorless prisms. Experimental and spectroscopic data in Table 1.

Method B.

Phosphoryl chloride (3.0 ml, 33 mmoles) was added in portions to a cold, stirred suspension of the corresponding 1,3-dimethyl-4-(4-substituted phenylamino)pyrimidine-2,6(1*H*,3*H*)-dione (**5a,b**) (10 mmoles) in dimethylformamide (10-15 ml). Then the reaction mixture was stirred for 90-120 minutes at 90-95°. After cooling, the reaction mixture was poured into ice/water (200 ml) and the suspension brought to *p*H = 6-7 with 2 *N* aqueous sodium hydroxide solution. The colorless precipitate obtained was collected by suction, washed with water and recrystallized from the appropriate solvent. Experimental and spectroscopic data are in Table 1.

Method C.

A mixture of 4-chloro-1,3-dimethylpyrimidine-2,6(1*H*,3*H*)-dione (**4**) [15] (1.75 g, 10 mmoles) in dimethylformamide (10 ml) and the appropriate aromatic amine (25 mmoles) was refluxed for 12 hours. After cooling, phosphoryl chloride (2.0 ml, 22 mmoles) was added, which caused a strong exothermic reaction. Then the mixture was stirred at 90° for 1 hour. After cooling, the obtained precipitate was collected by suction, washed with ethanol and recrystallized from the appropriate solvent. Experimental and spectroscopic data are in Table 1.

5,5-Dimethyl-2-phenylaminomethylenecyclohexane-1,3-dione (**8a**).

From 5,5-dimethylcyclohexane-1,3-dione (**7**), aniline and triethyl orthoformate **8a** was prepared as reported in ref [18].

2-(4-Chlorophenylaminomethylene)-5,5-dimethylcyclohexane-1,3-dione (**8b**).

A mixture of 5,5-dimethylcyclohexane-1,3-dione (**7**) (2.8 g, 20 mmoles), 4-chloroaniline (2.5 g, 20 mmoles) and triethyl orthoformate (12 ml, 72 mmoles) was heated at 130° for 5 minutes. Then the mixture was cooled to room temperature, the yellow precipitate filtered by suction and washed with ethanol, yield 5.08 g (92%), colorless prisms, mp 204-205.8° (ethanol); ir: 2960-2940 w, 1660 s, 1605 m, 1590 m, 1575 m, 1500 w $cm^{-1}$.

*Anal.* Calcd. for $C_{15}H_{16}ClNO_2$: C, 64.87; H, 5.81; N, 5.04. Found: C, 64.98; H, 5.77; N, 5.00.

9,9-Dimethyl-9,10-dihydrophenanthridin-7(8*H*)-one (**11**).

5,5-Dimethyl-2-phenylaminomethylenecyclohexane-1,3-dione (**8a**) (1.22 g, 5 mmoles) was heated to 190-220° under stirring in polyphosphoric acid (40 g) for 2 hours. After cooling

the mixture was diluted with ice/water (50 ml) and brought to *p*H = 6 with aqueous 2 *N* sodium hydroxide solution. The mixture was kept for 12 hours at room temperature, then the precipitate was filtered and washed with water, yield 0.42 g (37%), yellow prisms, mp 84.5-85.5° (ethanol/water); ir: 2960 w, 1670 s, 1590 m, 1580 sh $cm^{-1}$; $^1H$ nmr: δ 1.12 (s, 2 $CH_3$), 2.64 (s, $CH_2$), 3.36 (s, $CH_2$), 7.70-7.80 (t, J = 8 Hz, 3-H), 7.94 (t, J = 8 Hz, 2-H), 8.09 (d, J = 8 Hz, 4-H), 8.30 (d, J = 8 Hz, 1-H), 9.25 (s, 6-H); $^{13}C$ nmr: δ 27.9 (Me), 32.8, 37.5, 50.7, 123.1 (C-6a), 125.2, 125.9, 127.4, 129.7, 131.7, 147.1 (C-6), 148.9 (C-10b), 150.1 (C-4a), 197.5 (C-7).

*Anal.* Calcd. for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.76; H, 6.76; N, 6.05.

2-Phenylaminomethylenephenalene-1,3-dione (**13**).

A mixture of phenalene-1,3-dione (**12**) [20] (9.81 g, 50 mmoles), triethyl orthoformate (8.31 ml, 50 mmoles), aniline (4.56 ml, 50 mmoles) and 1,2-dihydroxyethane (50 ml) was heated with stirring; at about 140° formation of ethanol started. During 2 hours the temperature was increased to 190°, and ethanol was distilled from the solution until the formation of ethanol was completed. Then the reaction mixture was cooled to room temperature, the precipitate was filtered and washed with cold ethanol, yield 11.37 g (75%), orange-red prisms, mp 204-205° (dimethylformamide); ir: 1650 s, 1570 s $cm^{-1}$; $^1H$ nmr: δ 7.23-7.52 (m, 5 H of phenyl), 7.64-7.75 (t, J = 7 Hz, 5-H and 8-H of phenalene), 8.08-8.16 (d, J = 8 Hz, 6-H and 7-H of phenalene), 8.50-8.64 (d, J = 7 Hz, 4-H and 9-H of phenalene), 9.02-9.12 (d, J = 7 Hz, = CH).

*Anal.* Calcd. for $C_{20}H_{13}NO_2$: C, 80.25; H, 4.38; N, 4.68. Found: C, 80.09; H, 4.72; N, 4.75.

3-Phenylaminophenalen-1-one (**14b**).

A mixture of phenalene-1,3-dione (**12**) (7.0 g, 35.7 mmoles), aniline hydrochloride (4.64 g, 36 mmoles) and aniline (16.26 ml, 178 mmoles) was heated at reflux for 2.5 hours. After cooling to room temperature, the mixture was digested with diethyl ether (50 ml). The precipitate was filtered by suction and washed with methanol to remove the excess of aniline and colored side products, yield 6.13 g (63%), orange-red prisms, mp 268.4° (methanol); ir: 3320 s, 1635 s, 1610 s, 1570 s, 1530 s, 1500 s $cm^{-1}$; $^1H$ nmr: δ 5.93 (s, 2-H), 7.25 (t, J = 8 Hz, 4-H of phenyl), 7.42-7.50 (m, 5-H, 6-H, 7-H and 8-H of phenalene), 7.70-7.84 (m, 3-H and 5-H of phenyl), 8.31 (m, 4-H of phenalene, 2-H and 6-H of phenyl), 8.60 (d, J = 8 Hz, 9-H of phenalene), 9.23 (s, NH).

*Anal.* Calcd. for $C_{19}H_{13}NO$: C, 84.11; H, 4.83; N, 5.16. Found: C, 83.75; H, 4.80; N, 5.16.

7-Oxo-7*H*-naphtho[1,8-*bc*]acridine (**15**).

A suspension of 2-phenylaminomethylenephenalene-1,3-dione (**13**) (3.0 g, 10 mmoles) in phosphoryl chloride (11.6 ml, 127 mmoles) and triethylamine (1.45 ml, 10 mmoles) was heated at reflux for 1 hour and then poured onto crushed ice (220 ml) to give a green precipitate. To this precipitate 6 *N* aqueous sodium hydroxide solution was added until *p*H = 6 was reached. After 1 hour the green precipitate was filtered by suction, washed with water and dried, yield 2.7 g (95%), dark green prisms, mp 219-222.6° (cyclohexane); ir: 1660 s, 1620 m, 1580 s, 1560 w $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 7.57-7.63 (t, J = 2 Hz, 10-H), 7.77-7.83 (m, 2-H and 5-H), 7.83-7.88 (t, J = 7 Hz, 11-H), 8.03-8.07 (d, J = 2 Hz, 9-H), 8.12-8.14 (d, J = 2 Hz, 4-H), 8.23-8.26 (d, J = 2 Hz, 12-H), 8.26-8.32 (d, J = 2 Hz, 3-H), 8.77-8.80 (d, J = 2 Hz, 1-H), 9.27 (s, 8-H), 9.33-9.38 (d, J = 2 Hz, 6-H); $^{13}C$ nmr (deuteriochloroform): δ 125.0, 126.4, 127.0, 127.1, 127.2, 127.5, 128.2, 129.5, 129.7, 129.7, 131.5, 132.2, 133.1, 135.4, 137.6 (C-8), 150.3 (C-13a), 152.2 (C-12a), 183.9 (C-7).

*Anal.* Calcd. for $C_{20}H_{11}NO$: C, 85.39; H, 3.94; N, 4.98. Found C, 85.0; H, 4.14; N, 4.84.

Acknowledgement.

This work was supported by the Austrian Academic Exchange Service (EH-project No. 894/93 of the north south dialog, fellowship for D.V.T.).

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