THE SYNTHESIS OF SOME MONOMETHYLANTHRACENAMINES

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Dedicated to Dr Miroslav Protiva on the occasion of his 70th birthday.

The synthesis of 2-methyl-1-anthracenamine (**2**), 3-methyl-1-anthracenamine (**7**), 4-methyl-1-anthracenamine (**14**), 1-methyl-2-anthracenamine (**20**), 3-methyl-2-anthracenamine (**26**), and 1-methyl-3-anthracenamine (**30**) from the corresponding 9,10-anthraquinones in order to confirm their presence in coal-derived products is reported.

A number of polycyclic aromatic amines have been detected in coal liquids, coal--derived products, and shale oils[1]. A number of other polycyclic amines have been shown to have mutagenic activity and therefore, they may be carcinogenic[1]. We now describe the synthesis of six monomethylanthracenamines which occur or are suspected of occurring in coal liquids, shale oils or other coal-derived products.

2-Methyl-1-anthracenamine (**2**) and 3-methyl-1-anthracenamine (**7**) were prepared from the commercially available 1-amino-2-methyl-9,10-anthraquinone (**1**). When **1** was allowed to react with Zn and NaOH, 2-methyl-1-anthracenamine (**2**) was obtained in 58% yield. Bromination of **1** gave 1-amino-4-bromo-2-methyl-9,10--anthraquinone (**3**) in 13% yield. Diazotization of **3** followed by treatment with H_3PO_2 produced 1-bromo-3-methyl-9,10-anthraquinone (**4**) in 82% yield. When **4** was allowed to react with *p*-toluenesulfonamide, 3-methyl-1-(4'-toluenesulfonamido)--9,10-anthraquinone (**5**) was obtained. Sulfuric acid hydrolysis of **5** gave 1-amino--3-methyl-9,10-anthraquinone[2] (**6**) in 85% yield. Treatment of **6** with Zn and NaOH produced the required 3-methyl-1-anthracenamine (**7**) in 59% yield (Scheme 1).

4-Methyl-1-anthracenamine (**14**) was prepared in five steps from phthalic anhydride and *p*-chlorotoluene. The Friedel–Crafts reaction of *p*-chlorotoluene and phthalic anhydride (**8**) in the presence of $AlCl_3$ (anhydrous) gave an inseparable mixture of 2-(2'-chloro-5'-methylbenzoyl)benzoic acid (**9**) and 2-(5'-chloro-2'--methylbenzoyl)benzoic acid (**10**) in a combined yield of 66%. When the mixture of **9** and **10** was allowed to react with fuming H_2SO_4, only one product, 1-chloro-4-

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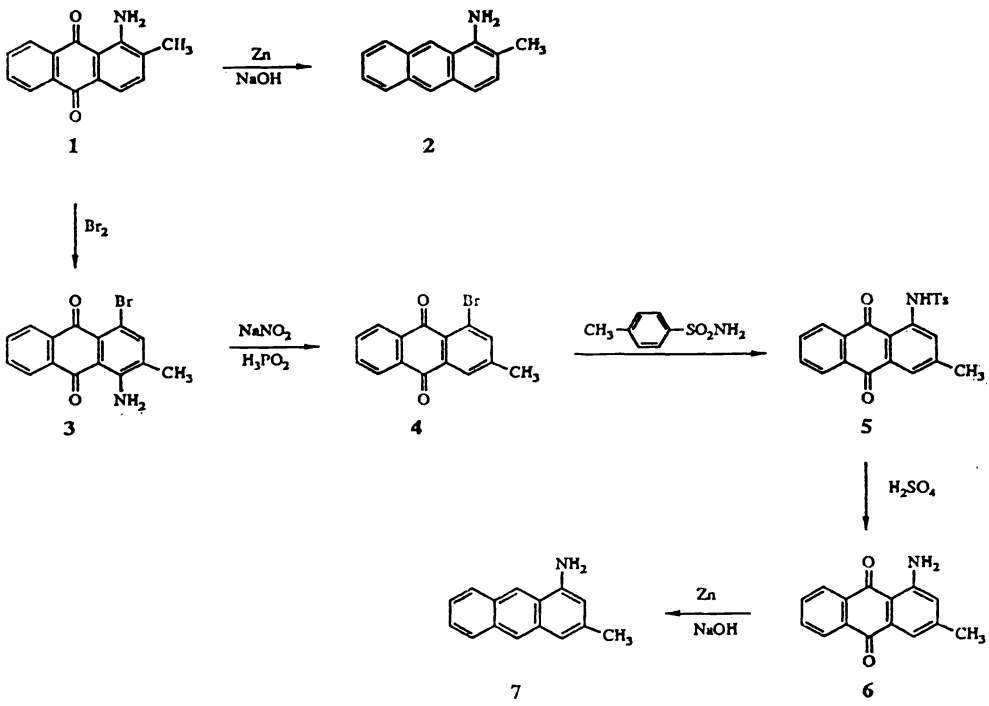


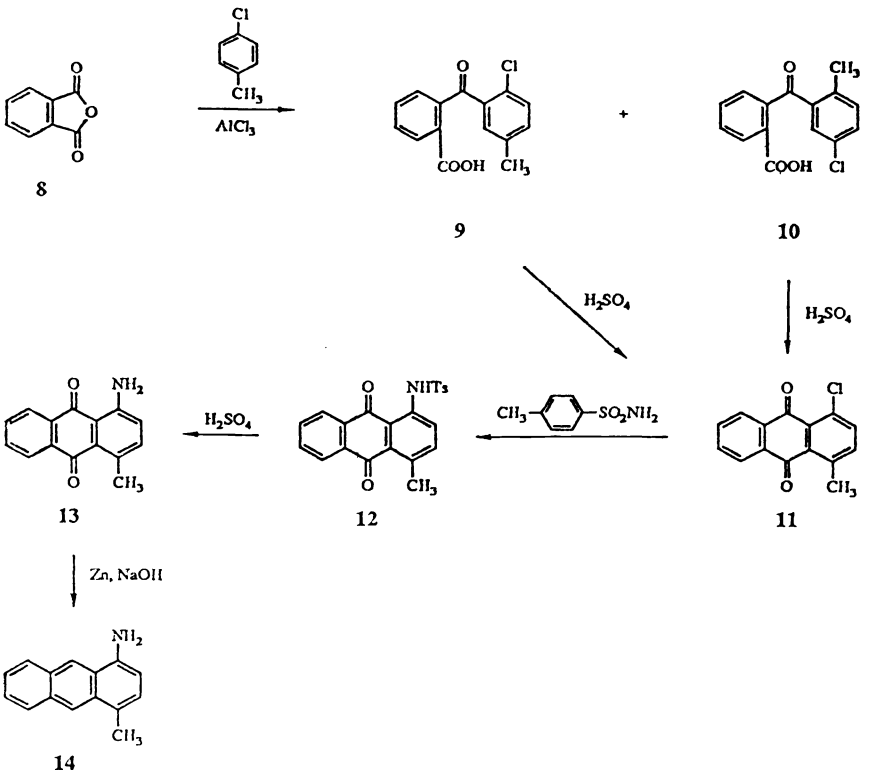
SCHEME 1

-methyl-9,10-anthraquinone[3] (**11**) was obtained in 86% yield. Treatment of **11** with *p*-toluenesulfonamide produced 4-methyl-1-(4′-toluenesulfonamido)-9,10-anthraquinone (**12**). Hydrolysis (H_2SO_4) of **12** gave 1-amino-4-methyl-9,10-anthraquinone[2] (**13**) in 84% yield. The reaction of **13** with Zn and NaOH afforded the required 4-methyl-1-anthracenamine (**14**) in 60% yield (Scheme 2).

1-Methyl-2-anthracenamine (**20**) was prepared in five steps. The Friedel–Crafts reaction of phthalic anhydride and 4-bromotoluene (anhydrous $AlCl_3$) gave an inseparable mixture of 2-(2′-bromo-5′-methylbenzoyl)benzoic acid (**15**) and 2-(5′--bromo-2′-methylbenzoyl)benzoic acid (**16**) in a combined yield of 80%. Treatment of the mixture of **15** and **16** with fuming H_2SO_4 gave 1-bromo-4-methyl-9,10--anthraquinone (**17**) in 75% yield. Nitration of **17** produced 1-bromo-4-methyl-3--nitro-9,10-anthraquinone (**18**) in 73% yield. The reductive debromination of **18** was accomplished with aqueous Na_2S giving 2-amino-1-methyl-9,10-anthraquinone*

* Cadogen and Molina[4] claim to have reported 2-amino-1-methyl-9,10-anthraquinone (**19**) in their Table but they are in error. They actually had in hand the commercially available 1-amino-2-methyl-9,10-anthraquinone (**1**) and not (**19**).

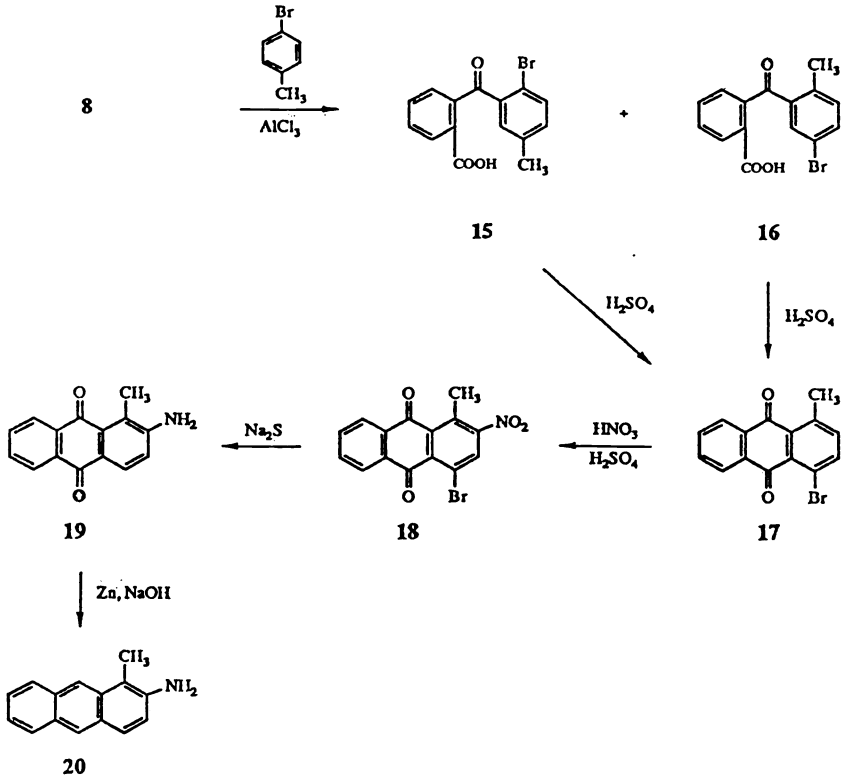
(**19**) in 30% yield. The reaction of **19** with Zn and NaOH afforded the required 1-methyl-2-anthracenamine (**20**) in 28% yield (Scheme 3).



SCHEME 2

3-Methyl-2-anthracenamine (**26**) was obtained in six steps. The Friedel–Crafts reaction of phthalic anhydride (**8**) with toluene (anhydrous $AlCl_3$) produced 2-(4′-methylbenzoyl)benzoic acid (**21**) in 98% yield. Nitration of **21** gave 2-(4′-methyl-3′-nitrobenzoyl)benzoic acid (**22**) in 87% yield. Reduction ($FeSO_4$, NH_4OH) of **22** gave 2-(3′-amino-4′-methylbenzoyl)benzoic acid (**23**) in 95% yield. Treatment of **23** with Ac_2O gave 2-(3′-bisacetylamino-4′-methylbenzoyl)benzoic acid (**24**) in 96% yield. The cyclization of **24** with concentrated H_2SO_4 provided a separable mixture of 2-amino-3-methyl-9,10-anthraquinone[5] (**25**) (24% yield) and 1-amino-2-methyl-9,10-anthraquinone (**1**) (6% yield). Compound **1** is commercially available. When Zn and NaOH were allowed to react with **25** the required 3-methyl-2-anthracenamine (**26**) was obtained in 65% yield (Scheme 4). When phthalic anhydride (**8**) was allowed

to react with *m*-methylacetanilide (anhydrous $AlCl_3$), a separable mixture of two products was obtained. These were 2-(2′-amino-4′-methylbenzoyl)benzoic acid[6] (**27**) in 4% yield and 2-(4′-acetylamino-2′-methylbenzoyl)benzoic acid[6] (**28**) in 20% yield.



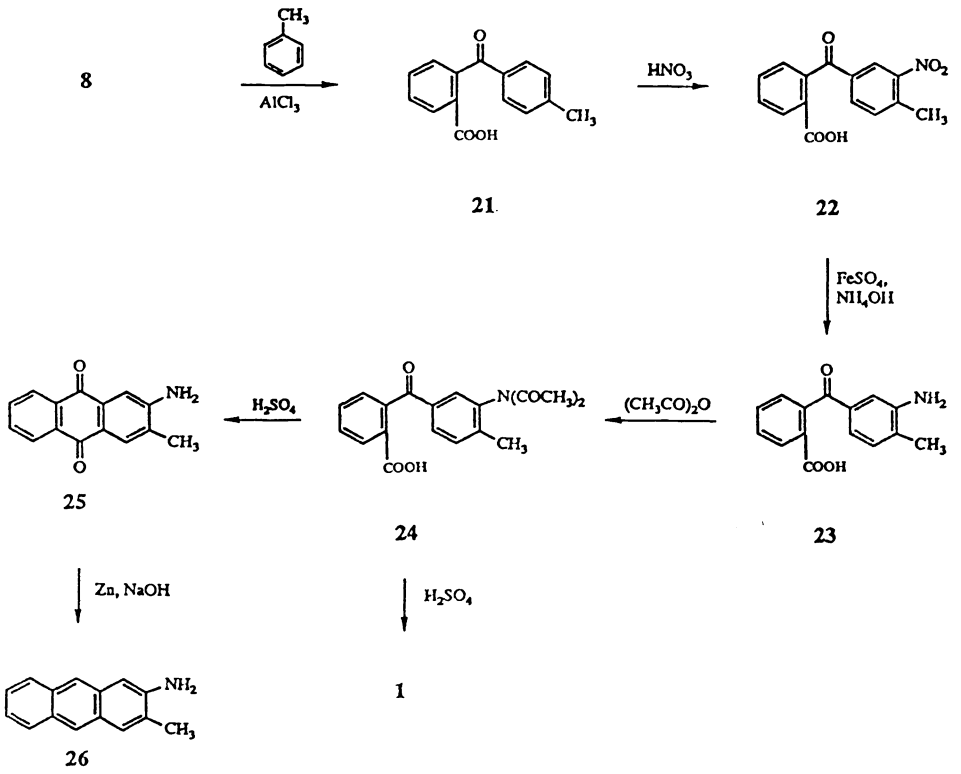
SCHEME 3

Cyclization of **28** in H_2SO_4 solution produced 3-amino-1-methyl-9,10-anthraquinone[6] (**29**) in 75% yield. The reduction of **29** with Zn and NaOH gave the required 1-methyl-3-anthracenamine (**30**) in 59% yield (Scheme 5).

The amines will be screened for mutagenic activity in the Ames test.

EXPERIMENTAL

Melting points were determined on a Thomas–Hoover melting point apparatus and are uncorrected. The IR spectra ($\tilde{\nu}$, cm^{-1}) were obtained on a Beckman Acculab 2 spectrometer and the ^1H NMR (δ, ppm; J, Hz) spectra were obtained on a Varian EM 360 spectrometer in the solvent indicated with TMS as the internal standard. Mass spectra were obtained on a Hewlett

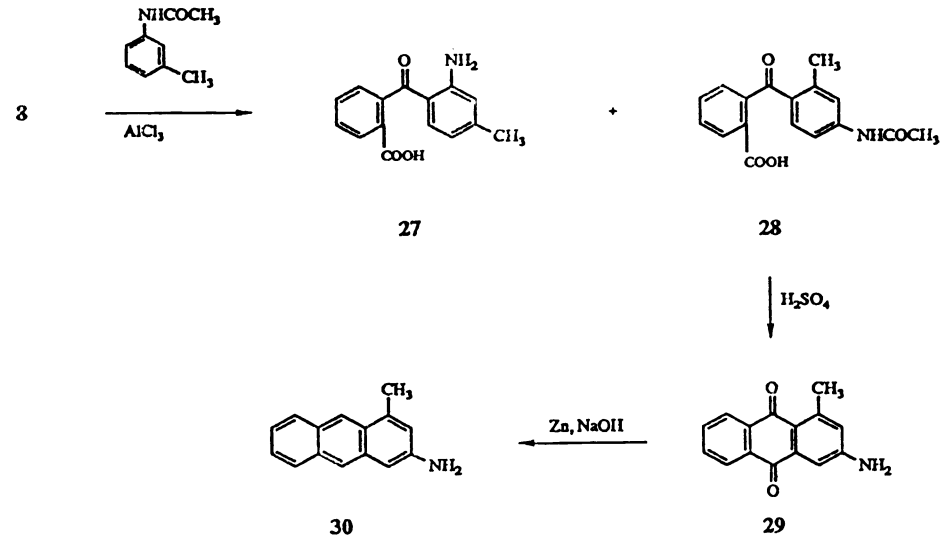


SCHEME 4

Packard Model 5980A mass spectrometer. Elemental analyses were performed by M–H–W Laboratories, Phoenix, Arizona.

2-Methyl-1-anthracenamine (**2**)

Compound **1** (4·7 g, 0·02 mol) was stirred with 200 ml of 1% aqueous NaOH and fresh Zn dust (5 g) at room temperature for 30 min. It was slowly heated and the temperature of the reaction mixture was maintained at 85—90°C in an oil bath. Zn dust (5 g) was then introduced into the reaction mixture in two equal batches at 30 min intervals. Heating and stirring were continued for 24 h at 90°C. The solid from the reaction mixture was collected and washed several times with water. Soxhlet extraction with acetone removed **2** (deep green fluorescence in acetone). Silica gel chromatography using hexane–benzene as the eluent gave 2·4 g (58%) of yellow leaflets, m.p. 142—143°C. IR spectrum (KBr): 1 640, 1 325 (NH_2). ^1H NMR ($CDCl_3$): 2·32 (s, CH_3, 3 H); 4·18 (bs, NH_2, 2 H); 7·11—7·52 (m, 6-H, 7-H, 2 H, ArH); 7·21 (d, $J = 4$, 3-H, 1 H, ArH); 7·41 (d, $J = 4$, 4-H, 1 H, ArH); 7·74—8·08 (m, 5-H, 8-H, 2 H, ArH); 8·29 (s, 9-H, 10-H, 2 H, ArH). Mass spectrum (m/z, %): 208 ($M^+ + 1$, 16), 207 (M^+, 100), 206 ($M^+ - 1$, 42), 178 (21). For $C_{15}H_{13}N$ (207·3) calculated: 86·92% C, 6·32% H, 6·76% N; found: 86·98% C, 6·21% H, 6·53% N.



SCHEME 5

1-Amino-4-bromo-2-methyl-9,10-anthraquinone (**3**)

Compound **3** was obtained in 13% yield from **1** by the method of Naiki and Noguchi[2], m.p. 239°C (ref.[2] 239°C).

1-Bromo-3-methyl-9,10-anthraquinone (**4**)

Compound **4** was obtained in 82% yield from **3** as described[2], m.p. 201°C dec., (ref.[2] 196 to 199°C).

1-Amino-3-methyl-9,10-anthraquinone (**6**)

Compound **6** was obtained from **4** in 85% yield via **5** as described[2], m.p. 194°C (ref.[2] 194°C). Mass spectrum (*m/z*, %): 238 (17), 237 (M^+, 100), 236 (11), 180 (25).

3-Methyl-1-anthracenamine (**7**)

This compound was prepared from **6** (2 g, 8·4 mmol) similar to the preparation of **2**; 1 g (59%) of **7** was obtained as yellow needles, m.p. 107—108°C. IR spectrum (KBr): 1 630 (NH_2). ^{1}H NMR spectrum ($CDCl_3$): 2·41 (s, CH_3, 3 H); 4·21 (bs, NH_2, 2 H); 6·08 (s, 4-H, 1 H, ArH); 7·19—7·60 (m, 2-H, 6-H, 7-H, 3 H, ArH); 7·70—8·18 (m, 5-H, 8-H, 2 H, ArH); 8·22 (s, 10-H, 1 H, ArH); 8·31 (s, 9-H, 1 H, ArH). Mass spectrum (*m/z*, %): 208 ($M^+ + 1$, 17), 207 (M^+, 100), 206 ($M^+ - 1$, 23), 178 (12). For $C_{15}H_{13}N$ (207·3) calculated: 86·92% C, 6·32% H, 6·76% N; found: 87·14% C, 6·52% H, 6·82% N.

1-Chloro-4-methyl-9,10-anthraquinone (**11**)

Compound **11** was prepared by the method of Heller and Schülke[3] from phthalic anhydride (**8**)

and *p*-chlorotoluene. The mixture of ketoacids **9** and **10** (66% yield) was cyclized to **11**, m.p. 164°C (ref.[3] 164°C).

1-Amino-4-methyl-9,10-anthraquinone (**13**)

By the method of Naiki and Noguchi[2] **11** gave **13** via **12** (m.p. 185—186°C) in 84% yield, m.p. 180—182°C (ref.[2] 180—182°C).

4-Methyl-1-anthracenamine (**14**)

This compound was prepared form **13** (2·3 g, 9·7 mmol) in a manner similar to the preparation of **2**; 1·2 g (60%) of **14** was obtained as yellow needles, m.p. 114—115°C. IR spectrum (KBr): 1 640 (NH_2). ^{1}H NMR spectrum ($CDCl_3$): 2·72 (s, CH_3, 3 H); 4·18 (bs, NH_2, 2 H); 6·62 to 6·75 (m, J = 8, 2-H, 1 H, ArH); 7·05—7·20 (m, J = 8, 3-H, 1 H, ArH); 7·19—7·64 (m, 6-H, 7-H, 2 H, ArH); 7·84—8·20 (m, 5-H, 8-H, 2 H, ArH); 8·40 (s, 10-H, 1 H, ArH), 8·45 (s, 9-H, 1 H, ArH). Mass spectrum (*m/z*, %): 208 ($M^+ + 1$, 16), 207 (M^+, 100), 206 ($M^+ - 1$, 55), 178 (13). For $C_{15}H_{13}N$ (207·3) calculated: 86·92% C, 6·32% H, 6·76% N; found: 87·11% C, 6·26% H, 6·72% N.

2-(2′-Bromo-5′-methylbenzoyl)benzoic Acid (**15**) and 2-(5′-Bromo-2′-methylbenzoyl)benzoic Acid (**16**)

A mixture of **8** (25 g, 0·17 mol), *p*-bromotoluene (31 g, 0·17 mol), anhydrous $AlCl_3$ (75 g, 0·56 mol), and 1,1,2,2-tetrachloroethane (150 ml) was heated at 100°C for 2 h. After cooling a large excess of water and dilute HCl were added to the mixture. The tetrachloroethane layer was separated from the aqueous solution and neutralized with dilute alkali. The alkaline solution was acidified, the precipitate was collected and recrystallized from benzene to give 43 g (80%) of a mixture of **15** and **16** as white prisms. IR spectrum (KBr): 1 650 (C=O), 1 280 (COOH). ^{1}H NMR ($CDCl_3$): 2·37 (s, 2′-CH_3, 3 H); 2·51 (s, 5′-CH_3, 3 H); 6·89—7·69 (m, 4′-H, 6′-H, 3-H, 4-H, 4 H, ArH); 7·79—8·69 (m, 3′-H, 2-H, 5-H, 3 H, ArH). Mass spectrum (*m/z*, %): 320 (M^+, ^{81}Br, 12), 318 (M^+, ^{79}Br, 11), 305 (15), 303 (15), 223 (78), 199 (98), 197 (100). For $C_{15}H_{11}BrO_3.H_2O$ (337·2) calculated: 53·44% C, 3·89% H; found: 53·73% C, 3·78% H.

1-Bromo-4-methyl-9,10-anthraquinone (**17**)

A solution of the mixture of **15** and **16** (30 g, 0·094 mol) and fuming H_2SO_4 (20%, 150 ml) was heated on a steam bath for 2 h. After cooling the solution was poured into ice-water and the precipitated solid was collected giving 21 g (75%) of **17** as pale yellow prisms. An analytical sample was recrystallized from benzene, m.p. 217—218°C. IR spectrum (KBr): 1 660, 1 560, 1 325, 1 300, 1 275 (C=O). ^{1}H NMR ($CDCl_3$): 2·54 (s, CH_3, 3 H); 7·61—7·78 (m, 3-H, 6-H, 7-H, 3 H, ArH); 7·98—9·62 (m, 2-H, 5-H, 8-H, 3 H, ArH). Mass spectrum (*m/z*, %): 302 (M^+, ^{81}Br, 99), 300 (M^+, ^{79}Br, 100), 193 (33), 165 (39). For $C_{15}H_9BrO_2$ (301·1) calculated: 59·83% C, 3·01% H; found 60·00% C, 3·21% H.

4-Bromo-1-methyl-2-nitro-9,10-anthraquinone (**18**)

To a warmed (50—60°C) mixture of **17** (6 g, 0·02 mol) and concentrated H_2SO_4 (60 ml) was added with stirring a mixture of HNO_3 (70%, *d* 1·4, 1·5 ml, 0·023 mol) and concentrated H_2SO_4 (15 ml) during a period of 30 min. After the resulting solution was allowed to stand at room temperature for 30 min, it was poured into crushed ice (200 g). The solid was filtered and washed with water. The crude material was used in the next reaction.

2-Amino-1-methyl-9,10-anthraquinone (**19**)

A solution of **18** (10 g, 0·03 mol) and 300 ml of a 5% Na_2S solution was refluxed for 1 h. After cooling, the solid was filtered and the residue was washed with water (3×). Benzene (100 ml) was added to the solid (7 g) and the extraneous precipitate removed by filtration. Dry HCl gas was bubbled gently through the benzene solution. The resulting precipitate (amine hydrochloride) was removed by filtration and neutralized with dilute NH_4OH solution. After filtration the product was chromatographed on a silica gel column using hexane–benzene as the eluent affording 2·1 g (30%) of red prisms m.p. 157—158°C, IR spectrum (KBr): 1 690 (C=O), 1 625 (NH_2). ^1H NMR ($CDCl_3$): 2·21 (s, CH_3, 3 H); 3·82 (bs, NH_2, 2 H); 7·21—7·83 (m, 5-H, 6-H, 7-H, 3 H, ArH); 8·03—8·35 (m, 4-H, 5-H, 8-H, 3 H, ArH). Mass spectrum (*m/z*, %): 238 ($M^+ + 1$, 17), 237 (M^+, 100), 236 ($M^+ - 1$, 39), 208 (17), 180 (32). For $C_{15}H_{11}NO_2$ (237·7) calculated: 75·93% C, 4·67% H, 5·90% N; found: 75·65% C, 4·83% H, 5·72% N.

1-Methyl-2-anthracenamine (**20**)

Compound **20** was prepared from **19** (5 g, 0·02 mol) in a manner similar to the preparation of **2** and 1·2 g (28%) was obtained as yellow-green prisms, m.p. 124—125°C. IR spectrum (KBr): 1 620 (NH_2). ^1H NMR ($CDCl_3$): 2·53 (s, CH_3, 3 H); 3·51 (bs, NH_2, 2 H); 7·12—7·52 (m, 3-H, 6 H, 7-H, 3 H, ArH); 7·60—8·13 (m, 4-H, 5-H, 8-H, 3 H, ArH); 8·29 (m, 10-H, 1 H, ArH), 8·33 (m, 9-H, 1 H, ArH). Mass spectrum (*m/z*, %): 208 ($M^+ + 1$, 17), 207 (M^+, 100), 206 (43), 178 (18). For $C_{15}H_{13}N$ (207·3) calculated: 86·92% C, 6·32% H, 6·76% N; found: 87·17% C, 6·36% H, 6·54% N.

2-(*p*-Methylbenzoyl)benzoic Acid (**21**)

The Friedel–Crafts reaction of phthalic anhydride (**8**, 50 g), toluene (150 g) and 30 g of anhydrous $AlCl_3$ gave 80 g (99%) of **21**, m.p. 95°C, upon recrystallization from toluene.

2-(4′-Methyl-2′-nitrobenzoyl)benzoic Acid[5] (**22**)

Prepared by the method of Bradley and Nursten[5] in 87% yield, m.p. 188°C, (ref.[5] 188—189·5°C).

2-(3′-Amino-4′-methylbenzoyl)benzoic Acid[5] (**23**)

Prepared as described by Bradley and Nursten[5] in 95% yield, m.p. 198°C dec., (ref.[5] 197·5°C dec.).

2-Amino-3-methyl-9,10-anthraquinone (**25**)

Prepared from **23** through the oily diacetylamide **24** (96%) to provide **25** in 24% yield, m.p. 261°C (ref.[5] 261—262°C). Mass spectrum (*m/z*, %): 238 (16), 237 (M^+, 100), 236 (15), 180 (29). Compound **1** was also obtained in 6% yield and the low yield of **25** was due to losses in the chromatographic separation on alumina (benzene).

3-Methyl-2-anthracenamine (**26**)

Compound **26** was prepared in a manner similar to that described for **20** from **25** (3 g, 0·013 mol), thus 1·7 g (65%) of **26** was obtained after silica gel chromatography using hexane and hexane–benzene as eluents, yellow leaflets, m.p. 255°C dec. ^1H NMR ($CDCl_3$): 2·39 (s, CH_3, 3 H); 3·86 (bs, NH_2, 2 H); 7·02—7·95 (m, 1-H, 4-H, 5-H, 6-H, 7-H, 8-H, 6 H, ArH); 8·04 (s, 10-H,

1 H, ArH); 8·15 (s, 9-H, 1 H, ArH). Mass spectrum (*m/z*, %): 208 (16), 207 (M^+, 100), 206 (12). For $C_{15}H_{13}N$ (207·3) calculated: 86·92% C, 6·32% H, 6·76% N; found: 87·03% C, 6·31% H, 6·69% N.

2-(2'-Amino-4'-methylbenzoyl)benzoic Acid (**27**) and 2-(4'-Acetylamino-2'-methylbenzoyl) benzoic Acid (**28**)

The carboxylic acids **27** and **28** were prepared as described by Kränzlein[6]. Compound **27** had m.p. 184°C (ref.[6] 184°C, 51% yield). Mass spectrum of **27** (*m/z*, %): 297 (47), 255 (58), 236 (100), 209 (43). Compound **28** had m.p. 241°C (ref.[6] 241°C, 27% yield). Mass spectrum of **28** (*m/z*, %): 297 (23), 296 (12), 279 (71), 278 (67), 210 (75), 134 (100).

3-Amino-1-methyl-9,10-anthraquinone (**29**)

Compound **29** was obtained in 21% yield from **28** by the method of Kränzlein[6]. Mass spectrum (*m/z*, %): 237 (M^+, 100), 236 (20), 208 (20), 180 (30).

1-Methyl-3-anthracenamine (**30**)

This compound was prepared from **29** (2 g, 8·4 mmol) in a manner similar to the preparation of **2** and 1 g (59%) of **30** was obtained as yellow prisms, m.p. 131—132°C. IR spectrum (KBr): 1 380 (NH_2). ^{1}H NMR ($CDCl_3$): 2·75 (s, CH_3, 3 H); 3·76 (bs, NH_2, 2 H); 6·80 (m, 1-H, 1 H, ArH); 6·86 (m, 3-H, 1 H, ArH); 7·09—7·58 (m, 6-H, 7-H, 2 H, ArH); 7·63—7·95 (m, 5-H, 8-H, 2 H, ArH); 8·02 (m, 9-H, 1 H, ArH); 8·34 (m, 10-H, 1 H, ArH). Mass spectrum (*m/z*, %): 208 ($M^+ + 1$, 16), 207 (M^+, 100), 206 ($M^+ - 1$, 17), 178 (14). For $C_{15}H_{13}N$ (207·3) calculated: 86·92% C, 6·32% H, 6·76% N; found: 87·04% C, 6·30% H, 6·51% N.

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