1000. *Synthesis of 2-Nitroanthracene and N-Hydroxy-2-anthrylamine*

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2-Nitroanthracene, unavailable by the usual routes, has been synthesised *via* nitration of 1,1α,2,3,4,4α-hexahydroanthrone, followed by selective reduction of the carbonyl function, dehydration, and dehydrogenation. *N*-Hydroxy-2-anthrylamine, desired for studies on the dermal carcinogenicity of 2-anthrylamine, was prepared by ammonium hydrosulphide reduction of 2-nitroanthracene.

PREVIOUS studies have shown that the *N*-hydroxy-derivatives of the carcinogens 2-acetaminofluorene, 2-fluorenylamine, 7-fluoro-2-acetaminofluorene, 4-acetaminobiphenyl, 4-acetaminostilbene, 2-acetaminophenanthrene, and 2-naphthylamine are metabolites of these amides and amines in the rat and are more carcinogenic than the parent compounds in this species.[1] These *N*-hydroxy-metabolites thus appear to be important intermediates in the carcinogenic processes induced by these compounds. Extension of these studies to 2-anthrylamine, which is unique among aromatic amines and amides in that it induces a high incidence of a variety of skin tumours in rats and mice,[2] required the synthesis of *N*-hydroxy-2-anthrylamine.

The *N*-hydroxy-derivatives noted above were prepared by partial reduction of nitro-compounds,[3] and 2-nitroanthracene was desired for a similar reaction. However, several attempts in our laboratory and by Bader [4] failed to reproduce the Sandmeyer-like synthesis of 2-nitroanthracene reported by Battegay and Boehler.[5] In our hands reduction of 2-nitro-9,10-anthraquinone with BF_3–$NaBH_4$ in di-2-methoxyethyl ether [6] gave no detectable nitroanthracene. Direct oxidation of 2-anthrylamine with pertrifluoroacetic acid was not attempted on noting the discouraging results obtained by Emmons [7] using this reagent and 2-naphthylamine. The following synthesis of 2-nitroanthracene depends on direct nitration of a single aromatic ring to give a nitro-derivative which could be completely aromatised (Figure 1).

Friedel–Crafts reaction of cyclohexane-1,2-dicarboxylic anhydride with benzene,[8] followed by base-catalysed isomerisation, gave *trans*-2-benzoylcyclohexanecarboxylic acid (I).[9] Reduction of the keto-function in compound (I) with zinc and hydrochloric acid in ethanol gave only a neutral oil, while the yield of acidic reduction product by the Wolff-Kishner procedure [10] was only 12%. An attempt was made to cyclise the keto-acid before reduction. However, heating compound (I) with sulphuric acid gave a 65% yield of a neutral oil which was identified as the enol-lactone (II) of compound (I). This reaction has been found with *p*-bromobenzoylcyclohexanecarboxylic acid.[11] Reduction of compound (I) by the Clemmensen method with toluene as the upper-phase solvent [12] gave a

[1] J. W. Cramer, J. A. Miller, and E. C. Miller, *J. Biol. Chem.*, 1960, **235**, 885; E. C. Miller, J. A. Miller, and H. A. Hartmann, *Cancer Res.*, 1961, **21**, 815; J. A. Miller, C. S. Wyatt, E. C. Miller, and H. A. Hartmann, *ibid.*, p. 1465; R. A. Andersen, M. Enomoto, E. C. Miller, and J. A. Miller, *ibid.*, 1964, **24**, 128; J. A. Miller, E. C. Miller, and P. D. Lotlikar, unpublished work on 7-fluoro-2-acetaminofluorene and 2-acetaminophenanthrene; E. Boyland, D. Manson, and R. Nery, *Rep. Brit. Emp. Cancer Campaign*, 1960, **38**, 52; E. Boyland, C. E. Dukes, and P. L. Grover, *Brit. J. Cancer*, 1963, **17**, 79.

[2] F. Bielschowsky, *Brit. J. Exp. Path.*, 1946, **27**, 54; B. Lennox, *Brit. J. Cancer*, 1955, **9**, 631; H. S. Zackheim, W. L. Simpson, and L. Langs, *J. Invest. Dermatol.*, 1959, **33**, 385; R. L. Dobson, *J. Nat. Cancer Inst.*, 1963, **31**, 841, 861.

[3] R. Willstätter and H. Kubli, *Ber.*, 1908, **41**, 1936; L. A. Poirier, J. A. Miller, and E. C. Miller, *Cancer Res.*, 1963, **23**, 790.

[4] A. Bader, Aldrich Chemical Co., private communication.

[5] M. Battegay and P. Boehler, *Compt. rend.*, 1936, **203**, 333.

[6] D. S. Bapat, B. C. SubbaRao, M. K. Unni, and K. Venkataraman, *Tetrahedron Letters*, 1960, no. **5**, 15.

[7] W. D. Emmons, *J. Amer. Chem. Soc.*, 1954, **76**, 3470.

[8] L. F. Fieser and F. C. Novello, *J. Amer. Chem. Soc.*, 1942, **64**, 805.

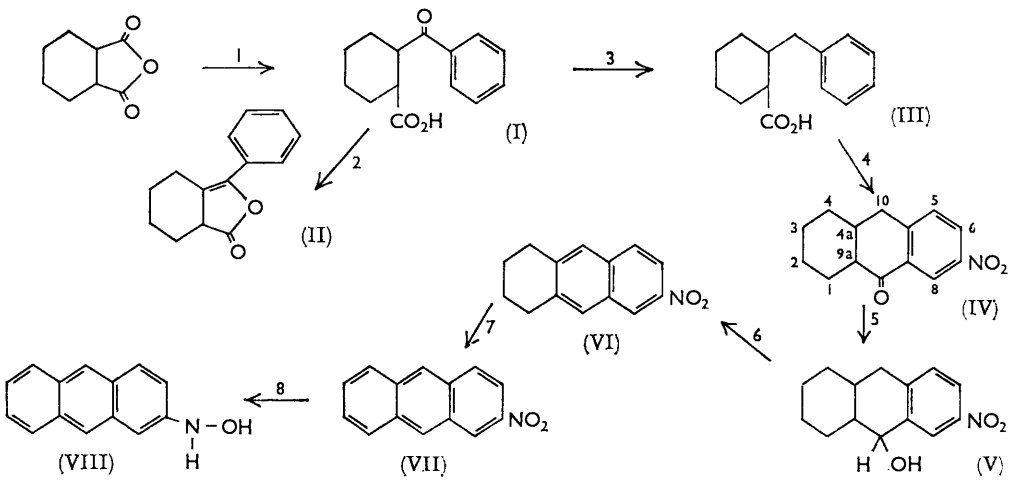
[9] E. Jucker and R. Süss, *Helv. Chim. Acta*, 1959, **42**, 2506.

[10] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.

[11] E. P. Kohler and J. E. Jansen, *J. Amer. Chem. Soc.*, 1938, **60**, 2142.

[12] E. L. Martin, *J. Amer. Chem. Soc.*, 1936, **58**, 1438.

70% yield of the desired benzyl acid (III) previously prepared [13] by a different route. The acid, on dehydration [13] and nitration [14] in sulphuric acid, gave 1,2,3,4,4a,9,9a,10-octahydro-7-nitroanthracene-9-one (IV). The alcohol (V) was obtained by reducing compound (IV) with sodium borohydride. When the alcohol (V) was dissolved in sulphuric



Reagents: 1, C_6H_6–$AlCl_3$; 2, H_2SO_4, 85°; 3, Zn–HCl; 4, Cold H_2SO_4, followed by HNO_3; 5, $NaBH_4$; 6, Cold H_2SO_4 (O_2?); 7, Pd–C; 8, NH_4SH.

acid diluted with methanol it was dehydrated and oxidised to 1,2,3,4-tetrahydro-7-nitroanthracene (VI) in 78% yield (approximately 15% yield from cyclohexane-1,2-dicarboxylic anhydride). Compound (VI) was heated with palladised charcoal *in vacuo*, and the mixture of sublimed starting material and product was separated by chromatography on alumina. 2-Nitroanthracene (VII) was obtained in 15—20% yield from compound (VI); approximately 50% of the starting material was recovered. Reduction of compound (VII) gave the known 2-aminoanthracene.

Experimental

All melting points were determined on a Fisher–Johns apparatus and are corrected. Ultraviolet spectra were taken in 95% ethanol on a Beckman DB recording spectrophotometer; infrared spectra were obtained with a Perkin-Elmer 137B spectrophotometer.

trans-2-*Benzoylcyclohexanecarboxylic Acid* (I).—*cis*-2-Benzoylcyclohexanecarboxylic acid was prepared by Fieser's method,[8] and converted into compound (I) by heating in 10% aqueous sodium hydroxide on a steam-bath for 1 hr.[9] The *product* had m. p. 153·5—154° (Found: C, 72·2; H, 6·85. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·95%).

1,4,5,6,7,7a-*Hexahydro*-3-*phenylisobenzofuran*-1-*one* (II).—Compound (I) (15 g.) was dissolved in 98% sulphuric acid (250 ml.) and heated for 2 hr. on a steam-bath. The dark solution was poured over cracked ice and the brown-violet mixture extracted with ether. After the ether extract was dried over potassium carbonate, the solvent was removed to give a pale yellow oil (9·5 g.) $\nu_{max.}$ (film) 2960, 1760, 1680, 1490, 1480, 1390, 1300, 1240, 1150, 1110, 1060, 1030, 945, 845, 770, 750, 700 cm.$^{-1}$. Similar systems are reviewed by Bellamy.[15] Compound (II) was hydrolysed by 5% sodium hydroxide in 85% ethanol to give compound (I).

Reduction [12] *of* trans-2-*Benzoylcyclohexanecarboxylic Acid* (I).—Mossy zinc (168 g.), mercuric chloride (10 g.), concentrated hydrochloric acid (10 ml.), and water (170 ml.) were swirled

[13] J. W. Cook, C. L. Hewett, and C. A. Lawrence, *J.*, 1936, 71.
[14] J. von Braun, *Annalen*, 1927, **451**, 40.
[15] L. J. Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen, 1958, p. 186.

together for 5 min. in a 1-litre flask. The liquid was decanted and compound (I) (70 g.), water (105 ml.), toluene (140 ml.), and concentrated hydrochloric acid (245 ml.) were placed in the flask. This mixture was refluxed vigorously for 30 hr. with additions of hydrochloric acid (70 ml.) every 6 hr. After removal of most of the toluene the remainder of the organic phase was poured into hexane (500 ml.). *trans*-2-Benzylcyclohexanecarboxylic acid (III) (46·5 g.) slowly crystallised, m. p. 135·5—137·5° (lit.,[13] 133·5—134°).

trans-1,2,3,4,4a,9,9a,10-*octahydroanthracen*-9-*one* (trans-*Hexahydroanthrone*).[13]—On addition of a solution containing compound (III) (44 g.) and 98% sulphuric acid (250 ml.) to water and ice, hexahydroanthrone (33 g.) precipitated, m. p. 109·5—111° (lit.,[13] 109°).

7-*Nitro*-1,2,3,4,4a,9,9a,10-*octahydro*-7-*nitroanthracen*-9-*one* (IV).—The hexahydroanthrone (3·1 g.) or the corresponding amount of compound (III) was dissolved in 98% sulphuric acid (36 ml.) and cooled in an ice–salt bath. A mixture of 70% nitric acid (1·1 ml.) in 98% sulphuric acid (16 ml.) was added in 1-ml. portions at intervals of 1 min. After the addition was complete, the solution was set aside for 1 hr. in the ice-bath and then poured over cracked ice. The mixture was extracted with ether, and the residue from the ether extract, together with the undissolved precipitate, was extracted with boiling hexane. The material which did not dissolve was recrystallised from the minimal amount of 95% ethanol to give compound (IV) (1·95 g.), m. p. 119—124°. Treatment with charcoal followed by another recrystallisation gave *material* melting at 129·5—130° (Found: C, 68·3; H, 6·15; N, 5·8. $C_{14}H_{15}NO_3$ requires C, 68·55; H, 6·15; N, 5·7%), $\lambda_{max.}$ 234, 269 mμ (log ε 4·43, 4·34). The $\lambda_{max.}$ of 7-nitro-1-tetralone (Aldrich) = 234, 269 mμ (log ε 4·34, 3·92). The $\nu_{max.}$ of compound (IV) (chloroform) = 3020, 2920, 2860, 1700, 1610, 1520, 1340, 1080, 930, 865, 845, 830, 810 cm.$^{-1}$.

1,2,3,4,4a,9,9a,10-*Octahydro*-7-*nitroanthracen*-9-*ol* (V).—A mixture of compound (IV) (10 g.) and sodium borohydride (1 g.) [16] was added to anhydrous methanol (500 ml.) and set aside for 6 hr. Most of the solvent was removed by flash evaporation, water (200 ml.) was added, and the precipitate removed by filtration. After one crystallisation from methanol, followed by washing with hexane, *compound* (V) (6·6 g.), m. p. 203·5—204°, was obtained (Found: C, 67·8; H, 6·85; N, 5·7. $C_{14}H_{17}NO_3$ requires C, 68·0; H, 6·95; N, 5·65%).

1,2,3,4-*Tetrahydro*-7-*nitroanthracene* (VI).—After methanol (40 ml.) was slowly diluted with 98% sulphuric acid (300 ml.) and cooled in ice, compound (V) (6 g.) was added. The dark solution was poured over 2 litres of cracked ice, the precipitate was dissolved in ether, and the residue from the ether solution was chromatographed with 1 : 1 benzene–hexane on alumina. The first fraction was collected and, after treatment with charcoal and crystallisation from hexane, *compound* (VI) (4·3 g.) was obtained, m. p. 129·5—130° (Found: C, 73·6; H, 5·9; N, 6·35. $C_{14}H_{13}NO_2$ requires C, 74·0; H, 5·75; N, 6·15%), $\lambda_{max.}$ 217, 263, 271, 320 mμ (log ε 4·41, 4·16, 4·16, 3·89). The $\lambda_{max.}$ of 2-nitronaphthalene = 220, 264, 270, 312 mμ (log ε 4·68, 4·38, 4·40, 4·94). When this transformation was attempted on the alcohol derived from 7-nitro-1-tetralone, no 2-nitronaphthalene could be isolated.

2-*Nitroanthracene* (VII).—Compound (VI) (0·2 g.) was mixed intimately with 10% palladised charcoal (0·4 g.) and sublimed for 4 hr. at 200—210°/1 mm. The sublimate (0·16 g.) was chromatographed on alumina with 3% benzene in hexane. Compound (VI) (0·1 g.) emerged first and the nitroanthracene (0·035 g.) was washed out with ether since there were no other visible contaminants. The 2-nitroanthracene gave a brilliant yellow fluorescence in ultraviolet light and had m. p. 180—181° (lit.,[5] 172°) (Found: C, 75·45; H, 4·3; N, 5·9. Calc. for $C_{14}H_9NO_2$: C, 75·35; H, 4·05; N, 6·25%), $\lambda_{max.}$ 236, 265, 302 mμ (log ε 4·67, 4·31, 4·33), $\nu_{max.}$ (chloroform) 3020, 1630, 1540, 1510, 1340, 1080, 920, 890, 875, 850 cm.$^{-1}$. Reduction of compound (VII) with zinc and 1 : 4 hydrochloric acid in ethanol afforded pure 2-anthrylamine (the ultraviolet spectrum of the acid reduction mixture diluted 1 : 10 with ethanol was identical with that of authentic material).

N-*Hydroxy*-2-*anthrylamine* (VIII).—A solution of compound (VII) (54 mg.) in a mixture of dimethylformamide (3 ml.) and 95% ethanol (15 ml.) was cooled in ice and saturated with ammonia, then with hydrogen sulphide.[3] The ammonium hydrosulphide was washed down with ethanol (10 ml.) and the mixture allowed to warm to room temperature over a 6 hr. period. On dilution with water (100 ml.) a tan flocculent material precipitated. Filtration, resuspension, and a second filtration yielded compound (VIII) (23 mg.), which gave a positive test with Tollen's reagent. *Compound* (VIII) exhibited no melting point but slowly decomposed on

[16] S. W. Chaikin and W. G. Brown, *J. Amer. Chem. Soc.*, 1949, **71**, 122.

heating above 100° (Found: C, 80·15; H, 5·1; N, 6·85. $C_{14}H_{11}NO$ requires C, 80·35; H, 5·3; N, 6·7%).

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