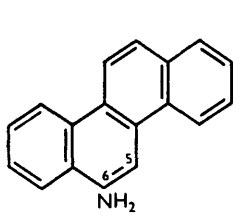
## 600. *Carcinogenic Nitrogen Compounds. Part XXV.* Steric Hindrance to Cyclisation of 6-Aminochrysene and its Derivatives.*

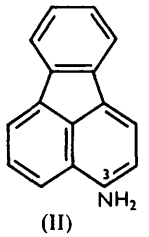
By G. C. Barrett and Ng. Ph. Buu-Hoï.

6-Aminochrysene failed to undergo further cyclisation in three standard reactions, probably on account of steric hindrance at position 5. Another anomaly was that 4′-hydroxy-6′-methylpyridino(2′ : 3′-6 : 5)chrysene, on zinc dust distillation, gave not the expected methylchrysenopyridine, but the corresponding compound with an oxygen bridge in the 4 : 4′-position. The less sterically hindered 3-aminofluoranthene gave an isatin derivative normally.

In view of the antitumour and leukopænia-producing effects of 6-aminochrysene [1] (I), we have investigated some properties of this amine and prepared some substitution products for biological examination. The present work records unsuccessful attempts to cause cyclisation at position 5.



(I)



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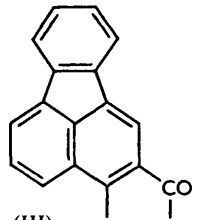

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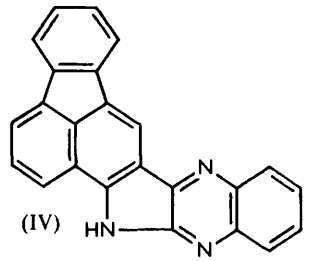
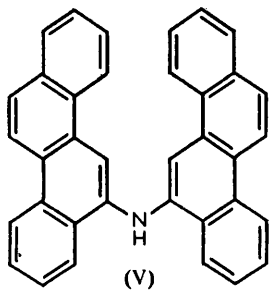


(IV)

6-Aminochrysene and diethyl mesoxalonate, under the conditions of the Martinet isatin synthesis,[2] failed to give the expected isatin derivative, although another tetracyclic arylamine, 3-aminofluoranthene (II), readily gave the dioxo-compound (III). With *o*-phenylenediamine, the last compound gave the heptacyclic compound (IV). Another failure was encountered in an attempt to synthesise phenarsazines by the Wieland–Rheinheimer reaction [3] of arsenic trichloride with di-6-chrysenylamine (V) and 6-2′-



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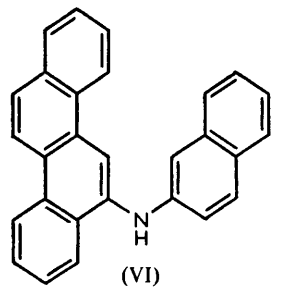


(VI)

naphthylaminochrysene (VI). Both these arylamines were obtained when 6-aminochrysene was condensed with β-naphthol in the presence of iodine, under the conditions of the Knoevenagel reaction,[4] even when β-naphthol was used in great excess. The analogous

* Part XXIV, *J.*, 1958, 738.

[1] Rudali, Buu-Hoï, and Lacassagne, *Compt. rend.*, 1953, **236**, 2020; Rudali and Buu-Hoï, *Le Sang*, 1955, **10**, 28.

[2] Martinet, *Ann. Chim.*, 1919, **11**, 15; Buu-Hoï and Hiong-Ki-Wei, *Rev. sci.*, 1944, **82**, 168, 306, 370.

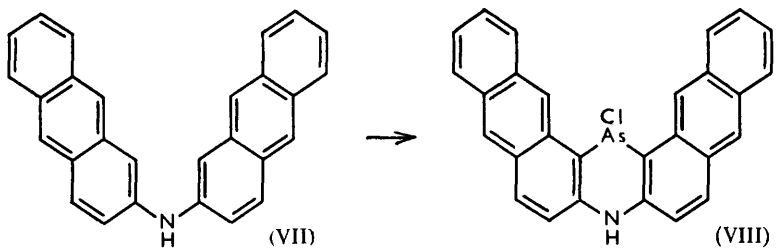
[3] Wieland and Rheinheimer, *Annalen*, 1921, **423**, 1; Burton and Gibson, *J.*, 1926, 2243; Buu-Hoï *et al.*, *Rev. sci.*, 1944, **82**, 453; 1945, **83**, 41.

[4] Knoevenagel, *J. prakt. Chem.*, 1914, **89**, 17; Buu-Hoï, *J.*, 1952, 4346.

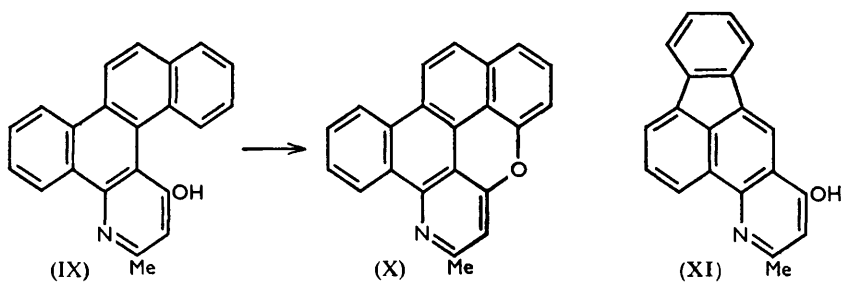
dichrysenylamine was also obtained when α-naphthol was used in place of β-naphthol. In contrast, di-2-anthrylamine (VII) gave 10-chloro-5 : 10-dihydrodinaphtho[2′ : 3′-1 : 2]-[2″ : 3″-8 : 9]phenarsazine (VIII) rapidly and in good yield.

The above failures are assumed to be caused by steric hindrance at position 5, which is seen when the formulæ (V) and (VI) are contrasted with (VII). The last amine, but not di-6-chrysenylamine, also gives a phenothiazine derivative on treatment with sulphur.

6-Aminochrysene did not react with ethyl acetoacetate in the presence of piperidine at room temperature, although 1-aminopyrene gives the imino-derivative in these conditions.[5] A more drastic procedure, use of boiling ethyl acetoacetate, resulted in direct




condensation [6] to 4-hydroxy-6-methylchryseno(6′ : 5′-2 : 3)pyridine (IX). A further anomaly was observed when the last compound was distilled with zinc dust, the oxygen-bridged compound (X) being obtained instead of the expected oxygen-free compound. A similar failure to eliminate an oxygen atom was experienced in the 1 : 2-benzanthracene series by Rădulescu and Bărbulescu [7] and could be explained by the high temperature of the reaction and the dehydrogenating action of zinc.




The direct Conrad–Limpach cyclisation, applied to 3-aminofluoranthene, readily gave the fluoranthenopyridine (XI); condensation of the same amine with acetonylacetone [8] yielded 3-(2 : 5-dimethyl-1-pyrryl)fluoranthene. Both the amines (I) and (II) gave monoanils with acetylacetone in excellent yields.

## Experimental

*Preparation of Intermediates.*—6-Aminochrysene was prepared by reduction of 6-nitrochrysene,[9] and 3-aminofluoranthene, b. p. 280—290°/40 mm., by reduction of 3-nitrofluoranthene with powdered tin and hydrochloric acid; nitration of fluoranthene was effected at 75—80° in acetic acid.[10] 2-Anthrylamine was prepared by reduction of 2-aminoanthraquinone.[11]

6-(1-*Methyl*-3-*oxobutylimino*)*chrysene.*—A solution of 6-aminochrysene (10 g.) in acetylacetone (25 g.) was refluxed for 40 hr., the excess of acetylacetone was distilled off, and the

[5] Weizman and Bograchov, *J.*, 1942, 377.
[6] Conrad and Limpach, *Ber.*, 1891, **24**, 2990.
[7] Rădulescu and Bărbulescu, *Bull. Soc. chim. România*, 1939, **1**, III, 7; *Chem. Abs.*,1943, **37**, 4070.
[8] Cf. Buu-Hoï, *J.*, 1949, 2882.
[9] Newman and Cathcart, *J. Org. Chem.*, 1940, **5**, 618.
[10] Garascia, Fries, and Ching, *ibid.*, 1952, **17**, 227.
[11] Ruggli and Henze, *Helv. Chim. Acta*, 1930, **13**, 409; Bollert, *Ber.*, 1883, **16**, 1635.

solid formed on cooling was collected, washed with acetone, and recrystallised from that solvent; the *anil* formed beige prisms (10·2 g.), m. p. 165° (Found: C, 85·0; H, 5·8; O, 5·1. $C_{23}H_{19}ON$ requires C, 84·9; H, 5·9; O, 4·9%).

3-(1-*Methyl*-3-*oxobutylimino*)*fluoranthene*.—A solution of 3-aminofluoranthene (2·3 g.) in acetonylacetone (10 g.) was treated as above, giving the *anil*, which crystallised as large yellow prisms (1·8 g.), m. p. 152°, from benzene (Found: C, 84·5; H, 5·8; N, 4·8. $C_{21}H_{17}ON$ requires C, 84·3; H, 5·7; N, 4·7%).

4 : 5-*Dihydro*-4 : 5-*dioxofluoroantheno*(3′ : 2′-2 : 3)*pyrrole* (III).—Diethyl mesoxalonate (2 g.) was refluxed with 3-aminofluoranthene (1 g.) in acetic acid (20 c.c.) for 1 hr.; the solution was concentrated *in vacuo*, the residue diluted with water, and the solid obtained was recrystallised from ethanol, giving an intermediate ester, as orange-tinged prisms, m. p. 229—231° (decomp.). A suspension of this (1 g.) in 4% aqueous potassium hydroxide (50 c.c.) was refluxed for 1 hr., and air was bubbled through the solution which was then filtered and acidified. The precipitate recrystallised from acetic acid, giving the *isatin derivative*, violet-black prisms (0·7 g.), decomp. >320°, dissolving in sulphuric acid with brown halochromy (Found: C, 79·4; H, 3·4; N, 5·1. $C_{18}H_9O_2N$ requires C, 79·7; H, 3·3; N, 5·2%). The derived *quinoxaline* (IV) was prepared by refluxing the foregoing compound (0·5 g.) and *o*-phenylenediamine (0·5 g.) in acetic acid (40 c.c.) for 15 min.; the solid which separated from solution after concentration crystallised from pyridine as yellow needles, m. p. >320°, giving a greenish-yellow halochromy in sulphuric acid (Found: N, 12·0. $C_{23}H_{13}N_3$ requires N, 12·2%).

*Condensation of* 6-*Aminochrysene*.—(a) *With* β-*naphthol*. A mixture of 6-aminochrysene (10 g.), β-naphthol (15 g.), and iodine (0·1 g.) was heated at 180—200° for 5 hr., steam being evolved. The product was poured into 10% aqueous sodium hydroxide (100 c.c.), and the insoluble portion was collected, washed with water, and treated with acetone. The acetone solution gave, on evaporation, 6-2′-*naphthylaminochrysene* (VI), crystallizing from benzene as greyish prisms (5 g.), m. p. 188° (Found: C, 90·7; H, 5·3; N, 3·8. $C_{28}H_{19}N$ requires C, 91·0; H, 5·2; N, 3·8%). The portion insoluble in acetone (4·2 g.) was recrystallised from benzene (blue fluorescent solution), giving *di*-6-*chrysenylamine* (V), yellowish prisms, m. p. 314° (Found: C, 91·8; H, 5·0; N, 2·8. $C_{36}H_{23}N$ requires C, 92·1; H, 4·9; N, 3·0%). The proportion of compound (VI) was not substantially enhanced by using a greater excess of β-naphthol.

(b) *With* α-*naphthol*. A mixture of 6-aminochrysene (5 g.), α-naphthol (20 g.) and iodine (0·1 g.) was heated at 200—230° for 3 hr., and the product was worked up as in (a). The portion insoluble in acetone (3·8 g.) was di-6-chrysenylamine (m. p. and mixed m. p.). The acetone-soluble portion gave a greyish compound, giving on recrystallisation from ethanol 6-1′-*naphthylaminochrysene*, cream-coloured needles, m. p. 208—209° (Found: C, 91·3; H, 5·5%).

10-*Chloro*-5 : 10-*dihydrodinaphtho*(2′ : 3′-1 : 2)(2″ : 3″-8 : 9)*phenarsazine* (VIII).—A solution of di-2-anthrylamine (1 g.) and arsenic trichloride (0·5 g.) in *o*-dichlorobenzene (10 c.c.) was refluxed for 30 min.; the precipitate formed on cooling was washed with ethanol and recrystallised from nitrobenzene, forming orange leaflets (0·7 g.), m. p. >340° (decomp. from 225°), giving a red halochromy in sulphuric acid (Found: C, 70·6; H, 3·8. $C_{28}H_{17}NAsCl$ requires C, 70·4; H, 3·6%).

*Bernthsen Reaction with Di*-2-*anthrylamine*.—This amine (0·5 g.; prepared from 2-anthrylamine [11]) was heated with sulphur (0·2 g.) and iodine (0·05 g.) at 200° until hydrogen sulphide ceased to be evolved; the product gave with sulphuric acid a deep violet colour characteristic of phenothiazine derivatives.[12] This reaction was negative with amine (V).

4-*Hydroxy*-6-*methylchryseno*(6′ : 5′-2 : 3)*pyridine* (IX).—A solution of 6-aminochrysene (5 g.) in ethyl acetoacetate (20 g.) was refluxed for 24 hr., then the excess of ethyl acetoacetate was distilled off, and the solid (3·5 g.) which separated on cooling was collected and recrystallised from nitrobenzene, giving colourless prisms, m. p. 360—362°, insoluble in ethanol and benzene (Found: C, 85·5; H, 5·1; N, 4·7. $C_{22}H_{15}ON$ requires C, 85·4; H, 4·9; N, 4·5%). An attempt to prepare the uncyclised intermediary imino-derivative by leaving for 4 days at room temperature a solution of 6-aminochrysene and ethyl acetoacetate in dioxan in the presence of piperidine resulted only in recovery of the amine.

2′-*Methyl*-1-*oxa*-3′-*aza*-2 : 3-4 : 5-*dibenzopyrene* (X).—An intimate mixture of the foregoing hydroxy-compound (2 g.) and zinc dust (20 g.) was dry distilled, and the solid distillate was recrystallised from ethanol–benzene, forming yellowish needles (0·7 g.), m. p. 210°, giving an intense yellow halochromy in sulphuric acid (Found: C, 85·9; H, 4·5. $C_{22}H_{13}ON$ requires

[12] Cf. Buu-Hoï, *Rev. sci.*, 1945, **83**, 170.

C, 86·0; H, 4·3%). The *picrate* formed deep yellow prisms, m. p. 207—208°, from xylene (Found: N, 10·1. $C_{28}H_{16}O_8N_4$ requires N, 10·4%).

4-*Hydroxy*-6-*methylfluorantheno*(3′ : 2′-2 : 3)*pyridine* (XI).—A solution of 3-aminofluoranthene (1 g.) in ethyl acetoacetate (5 g.) was refluxed for 30 min.; the solid (1 g.) formed on cooling was collected, washed with acetone, and recrystallised from nitrobenzene, giving yellowish crystals, m. p. >360° (Found: C, 84·5; H, 4·6; N, 5·1. $C_{20}H_{13}ON$ requires C, 84·8; H, 4·6; N, 4·9%).

3-(2 : 5-*Dimethyl*-1-*pyrryl*)*fluoranthene* (XII).—A solution of 3-aminofluoranthene (3 g.) in acetonylacetone (5 g.) was refluxed for 30 min.; the solid (2·9 g.) obtained on cooling formed from acetic acid yellowish prisms, m. p. 169°, which darkened rapidly in air (Found: C, 89·1; H, 6·0; N, 4·7. $C_{22}H_{17}N$ requires C, 89·5; H, 5·8; N, 4·8%).

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