Carcinogenic Nitrogen Compounds. Part LXXXI.[1] Steric Control in Heterocyclic Cyclisations with 6-Substituted Chrysenes

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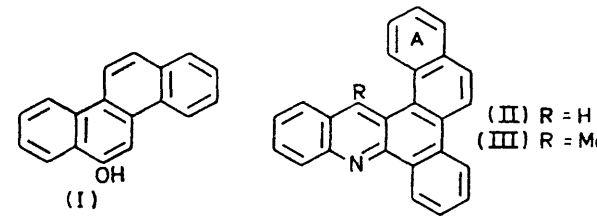
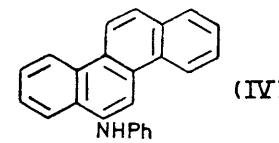
It is shown that heterocyclic cyclisations with 6-substituted chrysenes, and involving position 5 are under the strict control of steric factors. Thus 6-hydroxychrysene readily afforded chryseno[6,5-*b*]furan, benzo[*a*]naphth[2,1-*c*]-acridine, and polycyclic indoles, but failed to undergo a von Pechmann condensation with ethyl acetoacetate; *N*-phenyl-6-aminochrysene resisted Bernthsen acridine and phenothiazine syntheses and the Wieland–Rheinheimer reaction.

BARRETT and BUU-HOÏ [2] have shown that 6-aminochrysene and some of its derivatives fail to undergo several cyclisation reactions normally exhibited by aromatic amines with a free *ortho*-position; they attributed this to unfavourable steric conditions near position 5. The present work, which is concerned with the use of 6-hydroxychrysene (I) and 6-anilino-chrysene (IV) in diverse heterocyclic syntheses, confirms this point.

Compound (I) readily underwent an Ullmann–Fetvadjian reaction [3] with aniline and paraformaldehyde to give benzo[*a*]naphth[2,1-*c*]acridine (II), but the 16-methyl derivative (III), in the molecule of which the methyl group would strongly interfere with the neighbouring angular benzene ring A, could not be prepared by a Bernthsen reaction of 6-anilinochrysene (IV) [obtained from (I) with aniline in the presence of iodine [4]]; the reaction stopped at the formation of the *N*-acetyl derivative of (IV). The same resistance to heterocyclic cyclisations which would introduce a bulky heteroatom in position 5 was illustrated when compound (IV) was recovered unchanged both after treatment with



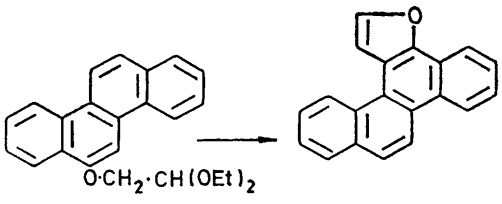


arsenic trichloride under the conditions of the Wieland–Rheinheimer phenarsazine synthesis,[5] and after treat-

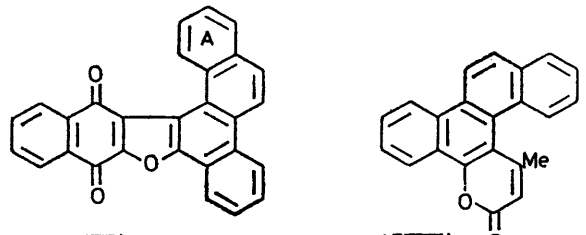
[1] Part LXXX, N. P. Buu-Hoï, A. Croisy, P. Jacquignon, D.-P. Hien, A. Martani, and A. Ricci, *J.C.S. Perkin I*, 1972, 1266.
[2] G. C. Barrett and N. P. Buu-Hoï, *J. Chem. Soc.*, 1958, 2946.
[3] F. Ullmann and A. Fetvadjian, *Ber.*, 1903, **36**, 1027; N. P. Buu-Hoï, *J. Chem. Soc.*, 1949, 670; 1950, 1146, 2096.
[4] E. Knoevenagel, *J. prakt. Chem.*, 1914, **89**, 17.
[5] H. Wieland and W. Rheinheimer, *Annalen*, 1921, **423**, 1.

ment with sulphur in presence of iodine in an attempt to perform a Bernthsen phenothiazine synthesis.[6]

These steric considerations are also consistent with the ready synthesis of chryseno[6,5-*b*]furan (VI) by cyclisation (with polyphosphoric acid) of 2-chrysen-6-yloxyacetaldehyde diethyl acetal (V), and with the successful preparation of chryseno[6,5-*b*]naphtho[2,3-*d*]furan-12,17-quinone (VII) by reaction of compound (I) with 2,3-dichloro-1,4-naphthoquinone;[7] in this latter synthesis, although three rings are annellated to the chrysene skeleton, the resulting molecule does not have a sterically crowded ring A. Further, compound (I) resisted a von Pechmann condensation with ethyl acetoacetate, probably because the resulting coumarin (VIII) would show overcrowding in that same area.

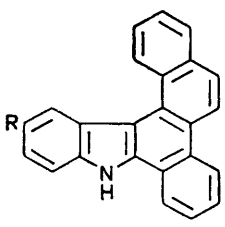


(V) (VI)

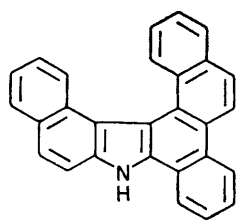


(VII) (VIII)

Similar steric influences were found to govern the reaction of 6-hydroxychrysene with arylhydrazines in the presence of their hydrochlorides (*i.e.* under the conditions of the Japp–Maitland indole synthesis[8]), which was applied successfully with phenylhydrazine, *p*-tolylhydrazine, and β-naphthylhydrazine, giving the three relatively uncrowded polycyclic indoles (IX)—(XI);



(IX) R = H
(X) R = Me



(XI)

this reaction, which occurs the more easily the greater the tendency of the hydroxy-compounds to display keto-enol tautomerism (*e.g.* it is totally unsuccessful with phenol, is less so with the naphthols, and works well with 9-hydroxyphenanthrene[8]), gave high yields in these three cases.

Compound (VI) is the furan analogue of the strongly carcinogenic benzo[*g*]chrysene[9] and chryseno[6,5-*b*]-pyridine,[10] and is undergoing carcinogenicity tests.

[6] A. Bernthsen, *Ber.*, 1883, **16**, 2897; N. P. Buu-Hoï and J. Lecocq, *Compt. rend.*, 1944, **218**, 648; *Rev. sci.*, 1944, **82**, 39.
[7] B. Eistert, *Ber.*, 1947, **80**, 52; N. P. Buu-Hoï, *J. Chem. Soc.*, 1952, 489; N. P. Buu-Hoï and P. Demerseman, *ibid.*, p. 4699.
[8] F. R. Japp and W. Maitland, *J. Chem. Soc.*, 1903, **83**, 270; N. P. Buu-Hoï, P. Jacquignon, and C. T. Long, *ibid.*, 1957, 4994.
[9] G. M. Badger, J. W. Cook, C. L. Hewett, E. L. Kennaway, N. M. Kennaway, R. H. Martin, and A. M. Robinson, *Proc. Roy. Soc.*, 1940, **129** [*B*], 439, 453.

EXPERIMENTAL

Benzo[a]*naphth*[2,1-c]*acridine* (II).—6-Hydroxychrysene (I), m.p. 250°, was best prepared by hydrolysis of 6-aminochrysene with aqueous sulphuric acid.[11] To a boiling mixture of compound (I) (2·4 g) and aniline (1·8 g), paraformaldehyde (2·7 g) was added in small portions, and the product of the vigorous reaction was fractionated *in vacuo*; the fraction of b.p. 240—250° at 0·7 mmHg (2·2 g) was dissolved in benzene and treated with picric acid in ethanol. *Benzo*[a]*naphth*[2,1-c]*acridine picrate* formed orange microprisms, m.p. 227° (decomp.) (from benzene) (Found: N, 10·2. $C_{31}H_{18}N_4O_7$ requires N, 10·0%). The free *base*, obtained on treatment of this with aqueous ammonia, formed yellow prisms (1·7 g), m.p. 174° (from ethanol), giving yellow solutions in sulphuric acid (Found: C, 91·2; H, 4·8; N, 4·2. $C_{25}H_{15}N$ requires C, 91·2; H, 4·6; N, 4·3%); $\lambda_{max.}$ 221 (ε 44,700), 263 (59,000), 273 (60,900), 290 (58,300), 303 (37,200), 317 (41,600), 356 (8070), 375 (9930), and 395 nm (8690).

6-*Anilinochrysene* (IV).—A mixture of compound (I) (5 g), aniline (8 g), and iodine (0·5 g) was heated at 180° for 30 h, and the brown mass obtained on cooling was taken up in benzene; the benzene solution was washed with aqueous 20% sodium hydroxide, then with water and dried ($CaCl_2$). The solvent was distilled off, and the residue recrystallised thrice from benzene, to give *leaflets* (3·5 g), m.p. 230° (Found: C, 90·0; H, 5·4; N, 4·2. $C_{24}H_{17}N$ requires C, 90·3; H, 5·4; N, 4·4%), $\lambda_{max.}$ 221 (ε 32,600), 264 (55,800), and 354 nm (13,050). The following cyclisations were attempted with this amine.

(*a*) A mixture of the amine (IV) (2·7 g), acetic anhydride (7 g), and freshly fused anhydrous zinc chloride (3·5 g) was heated under reflux for 24 h (modified Bernthsen synthesis[12]). The cooled product was triturated with aqueous 20% sodium hydroxide in the presence of hot toluene, the toluene layer was washed with water and dried ($CaCl_2$), and the solvent was distilled off *in vacuo*. The solid residue was recrystallised twice from ethanol to give 6-N-*phenylacetamidochrysene* as prisms (1·5 g), m.p. 216° (Found: N, 3·8; O, 4·4. $C_{26}H_{19}NO$ requires N, 3·9; O, 4·4%).

(*b*) A mixture of the amine (IV) (0·1 g), sulphur (0·2 g), and iodine (0·01 g) was heated at *ca.* 200—220° for 2 h, during which time no evolution of hydrogen sulphide occurred (*i.e.* no formation of a phenothiazine system); the cooled mixture, on recrystallisation from benzene, gave only the starting compound (IV).

(*c*) A solution of the amine (IV) (0·5 g) and arsenic trichloride (1 ml) in anhydrous *o*-dichlorobenzene (10 ml)

[10] A. Lacassagne, N. P. Buu-Hoï, F. Zajdela, and Ph. Mabille, Compt. rend., 1964, **258**, 3387.
[11] M. Newman, *J. Amer. Chem. Soc.*, 1938, **60**, 2947; D. C. Thang, C. X. Can, N. P. Buu-Hoï, and P. Jacquignon, *Compt. rend.*, 1971, **272** *C*, 1570.
[12] N. P. Buu-Hoï and J. Lecocq, *Compt. rend.*, 1944, **218**, 792.

was heated under reflux for 24 h, during which time no evolution of hydrogen chloride was observed (*i.e.* no formation of a 5,10-dihydro-10-chlorophenarsazine system); concentration of the solution *in vacuo* to 2 ml afforded only unchanged (IV) (95%).

2-*Chrysen*-6-*yloxyacetaldehyde Diethyl Acetal* (V).—6-Hydroxychrysene (12 g) was converted into its sodio-derivative with a solution of sodium (1·5 g) in absolute ethanol (50 ml); bromoacetaldehyde diethyl acetal (10 g) was then added and the mixture was heated under reflux for 48 h. The precipitate which formed on cooling was collected, washed with water, dried, and recrystallised from ethanol to give the *acetal* (V), leaflets (9·5 g), m.p. 140° (Found: C, 79·7; H, 6·9. $C_{24}H_{24}O_3$ requires C, 80·0; H, 6·7%).

Chryseno[6,5-b]*furan* (VI). A mixture of the acetal (V) (7 g), anhydrous benzene (100 ml), and polyphosphoric acid (50 ml) was heated under reflux and with vigorous stirring for 7 h. After cooling, the benzene layer was collected and the lower layer was extracted with boiling benzene (with stirring). The total benzene solution was washed with aqueous hydrogen sodium carbonate, then with water, and dried (Na_2SO_4); the solvent was distilled off, and the solid residue was recrystallised thrice from propanol. The *furan* (VI) formed pale yellow prisms (4 g), m.p. 155° (Found: C, 89·7; H, 4·6. $C_{20}H_{12}O$ requires C, 89·5; H, 4·5%), $\lambda_{max.}$ 232 (ε 28,500), 275 (96,300), 298 (14,200), 310 (11,300), 323 (10,500), 352 (2500), and 370 nm (3350).

Chryseno[6,5-b]*naphtho*[2,3-d]*furan*-12,17-*quinone* (VII).—A solution of compound (I) (1·2 g) in anhydrous pyridine (25 ml) was heated under reflux with 2,3-dichloro-1,4-naphthoquinone (1·2 g) for 9 h. The precipitate which formed on cooling was washed with methanol, dried, and recrystallised from xylene to give the *quinone* (VII), as deep red prisms (1·5 g), m.p. 346—347° (Found: C, 84·6; H, 3·4. $C_{28}H_{14}O_3$ requires C, 84·4; H, 3·5%).

Attempted von Pechmann Reaction with 6-*Hydroxychrysene* (I).—A warm suspension of compound (I) (2·4 g) in glacial acetic acid (100 ml) was treated with ethyl acetoacetate (2 g); the mixture was saturated with hydrogen chloride and maintained at room temperature for 7 days. The precipitate obtained on dilution with water afforded, on recrystallisation from acetic acid, unchanged (I) (90%). A negative result was also recorded when the reaction was attempted in propan-2-ol.

11H-*Benzo*[a]*naphtho*[2,1-c]*carbazole* (IX).—An intimate mixture of compound (I) (4·8 g), phenylhydrazine (4 g), and phenylhydrazine hydrochloride (5 g) was heated at *ca.* 150°; a vigorous reaction set in, and the mixture was then heated at 180° for 2 h. The cooled product was treated with dilute hydrochloric acid in the presence of toluene, the toluene solution was washed with water and dried ($CaCl_2$), the solvent was distilled off *in vacuo*, and the residue was recrystallised thrice from benzene, to give the *carbazole* (IX) as greenish yellow platelets (2·5 g), m.p. 256°, solutions of which in sulphuric acid were orange-red (Found: C, 90·8; H, 4·8; N, 4·5. $C_{24}H_{15}N$ requires C, 90·8; H, 4·8; N, 4·4%). This compound gave a brown complex with picric acid, m.p. 215°, which could not be recrystallised without decomposition; the brick red addition complex with tetrachlorophthalic anhydride, m.p. 225° (decomp.), was also unstable. 14-*Methyl*-11H-*benzo*[a]*naphtho*[2,1-c]-*carbazole* (X), similarly prepared from compound (I), *p*-tolylhydrazine, and *p*-tolylhydrazine hydrochloride, formed yellow prisms (30%), m.p. 275° (from benzene) (Found: C, 90·5; H, 5·3; N, 4·1. $C_{25}H_{17}N$ requires C, 90·6; H, 5·2; N, 4·2%).

11H-*Dibenzo*[a,g]*naphtho*[2,1-c]*carbazole* (XI).—An intimate mixture of compound (I) (4·8 g), β-naphthylhydrazine (5 g), and β-naphthylhydrazine hydrochloride (6 g) was heated at 185—190° for 1·5 h, and the cooled product was treated with dilute hydrochloric acid and toluene as before. The *carbazole* (XI) formed fluorescent yellow microprisms (3·9 g), m.p. 335—336° (from toluene), solutions of which in sulphuric acid were deep yellow (Found: C, 91·4; H, 4·7; N, 3·8. $C_{28}H_{17}N$ requires C, 91·5; H, 4·7; N, 3·8%), $\lambda_{max.}$ 230 (ε 43,300), 249 (51,200), 277 (28,800), 306 (35,600), 361 (16,400), 380 (7900), and 401 nm (9200).

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