Carcinogenic Nitrogen Compounds. Part LXXV.[1] Skraup Reactions with Some Polycyclic Amines, and Two Cases of Anti-Marckwald Orientation

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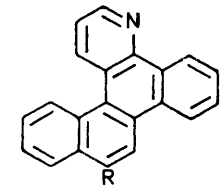
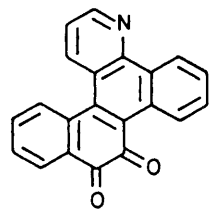
12-Halogeno-6-hexanoylaminochrysenes undergo Skraup reactions to give the corresponding 10-substituted benzo[*h*]naphtho[1,2-*f*]quinolines, but 6-hexanoylamino-12-nitrochrysene gives benzo[*h*]benzo[7,8]quino-[6,5-*f*]quinoline. Benzo[*h*]naphtho[1,2-*f*]quinoline undergoes oxidation to an *o*-quinone, from which several benzo[*c*]benzo[7,8]quino[6,5-*a*]phenazines have been prepared. Phenanthro[9,10-*g*]quinoline and benzo[*h*]-quino[6,7-*f*]quinoline were obtained from 2-aminotriphenylene and 3-acetamido-9-aminophenanthrene respectively, in two rare examples of anti-Marckwald Skraup cyclisations.

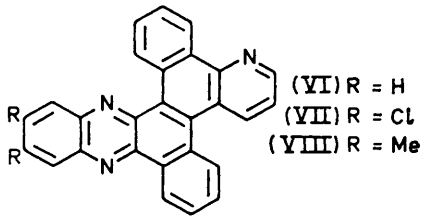
BENZO[*h*]NAPHTHO[1,2-*f*]QUINOLINE (I) possesses carcinogenic [2] and enzyme-inducing [3] activities. Its 10-fluoro- (II), 10-chloro- (III), and 10-bromo- (IV) derivatives have been prepared by Skraup cyclisations of the appropriate 12-halogeno-6-aminochrysenes or their *N*-hexanoyl derivatives. An attempt to prepare the 10-nitro-derivative from 6-hexanoylamino-12-nitrochrysene failed, however; benzo[*h*]benzo[7,8]quino-[6,5-*f*]quinoline was obtained instead, in relatively high yield. The K-region in compound (I) was readily



(I) R = H
(II) R = F
(III) R = Cl
(IV) R = Br



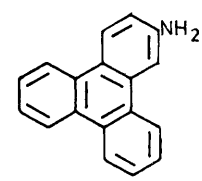
(V)



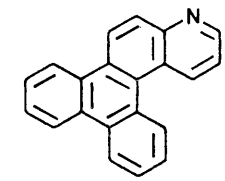
(VI) R = H
(VII) R = Cl
(VIII) R = Me

oxidised by sodium dichromate in acetic acid and the dark red quinone (V) thus obtained gave, on condensation with *o*-phenylenediamine, benzo[*c*]benzo[7,8]-quino[6,5-*a*]phenazine (VI); this compound and its derivatives (VII) and (VIII) are of potential biological interest as several polyaza-hydrocarbons are known to be carcinogenic.[4]

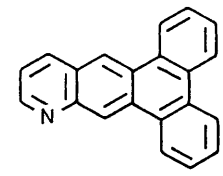
The Skraup reaction with 2-aminotriphenylene (IX) was found not to conform to the Marckwald rule [*i.e.* preferential *angular* cyclisation whenever possible,[5] which in the present case would give phenanthro-[9,10-*f*]quinoline (X)] but to involve linear cyclisation,



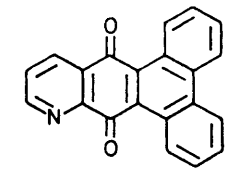
(IX)



(X)



(XI)



(XII)

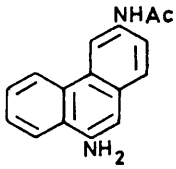
furnishing phenanthro[9,10-*g*]quinoline (XI). This last compound was identified by oxidation with sodium dichromate to a yellow quinone (XII) which failed to react with *o*-phenylenediamine; had the Skraup reaction led to the expected angular compound (X), this oxidation would have given an *o*-quinone reactive towards *o*-phenylenediamine and probably having a deeper colour, as is the case with the isosteric red benzo[*g*]chrysene-quinone.[6] The preferential linear cyclisation of (IX) is to our knowledge the first instance of an anti-Marckwald orientation in a Skraup reaction where no substituent is present in the starting amine to prevent the alternative angular cyclisation.† This anomaly probably arises from the extreme steric hindrance obtaining

† Several successful Skraup linear cyclisations have been reported [7] with amines in which the site for angular cyclisation is blocked.

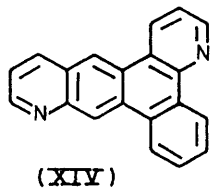
[1] Part LXXIV, J.-C. Perche, C. Saint-Ruf, and N. P. Buu-Hoï, preceding paper.
[2] N. P. Buu-Hoï, *J. Org. Chem.*, 1954, **19**, 721; A. Lacassagne, N. P. Buu-Hoï, F. Zajdela, and Ph. Mabille, *Compt. rend.*, 1964, **258**, 3387.
[3] N. P. Buu-Hoï, D.-P. Hien, and Ph. Mabille, in: *Japan Cancer Assoc. Gann Monograph, 2*: Cancer Chemotherapy, Maruzen Co. Ltd., Tokyo, 1967, p. 71.
[4] R. W. Baldwin, G. J. Cunningham, and M. W. Partridge, *Brit. J. Cancer*, 1959, **13**, 94.
[5] W. Marckwald, *Annalen*, 1893, **274**, 331; E. Mosettig and J. W. Kreuger, *J. Amer. Chem. Soc.*, 1936, **58**, 1311; *J. Org. Chem.*, 1938, **3**, 317; N. P. Buu-Hoï, M. Dufour, and P. Jacquignon, *J. Chem. Soc.*, (*C*) 1968, 2070.
[6] C. L. Hewett, *J. Chem. Soc.*, 1938, 193.
[7] R. Huisgen, *Annalen*, 1948, **559**, 101.

at the *peri*-positions in triphenylene, as is shown, for instance, by the resistance to demethylation of 1-methoxytriphenylene.[8]

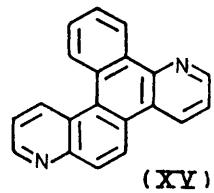
A second example of an anti-Marckwald Skraup cyclisation was encountered in the behaviour of 3-acetamido-9-aminophenanthrene (XIII),[9] which gave benzo[*h*]quino[6,7-*f*]quinoline (XIV) instead of the expected benzo[*h*]quino[6,5-*f*]quinoline (XV). Structure (XIV) was confirmed by its n.m.r. spectrum ($CDCl_3$; Me_4Si as internal reference), which showed two characteristic singlets, one corresponding to the strongly deshielded 9-proton (τ 2·4) and the other to the 14-proton (τ 2·56). Here again, the alternative angular Skraup cyclisation would suffer extreme steric hindrance.



(XIII)



(XIV)



(XV)

In preliminary biological screenings, compounds (II), (III), (IV), and (XI), like the unsubstituted heterocycle (I),[3] proved to be strong inducers of the microsomal enzyme zoxazolamine hydroxylase and are therefore being tested for carcinogenic activity.[10]

EXPERIMENTAL

10-*Fluorobenzo*[h]*naphtho*[1,2-f]*quinoline* (II).—A mixture of 6-amino-12-fluorochrysene (0·3 g),[11] glycerol (1·5 g), arsenic acid (0·4 g), and sulphuric acid (1·5 g) was stirred at 130—140° for 1 h; after cooling, the product was treated with water and made basic with aqueous ammonia. The solid precipitate obtained was dried and extracted with boiling toluene; the solvent was removed, and the residue was taken up in ethanol and treated with picric acid. The *picrate* of (II) crystallised as yellow microprisms, m.p. 249—250° (decomp. >220° on gradual heating) (from nitrobenzene) (Found: N, 10·6. $C_{27}H_{15}FN_4O_7$ requires N, 10·6%). The *free base* (II), obtained by treatment of the picrate with aqueous ammonia, formed needles (0·1 g), m.p. 157° (from ethanol) (Found: C, 85·0; H, 4·0; N, 4·7. $C_{21}H_{12}FN$ requires C, 84·8; H, 4·1; N, 4·7%). This compound and the analogous bases (III) and (IV) showed yellow halochromism in sulphuric acid.

10-*Chlorobenzo*[h]*naphtho*[1,2-f]*quinoline* (III), similarly prepared from 12-chloro-6-hexanoylaminochrysene (1·2 g),[11] glycerol (4 g), arsenic acid (2 g), and sulphuric acid (3 g), formed prisms (0·3 g), m.p. 194° (from ethanol) (Found: C, 80·2; H, 4·0; N, 4·5. $C_{21}H_{12}ClN$ requires C, 80·4; H, 3·9; N, 4·5%); *picrate*, yellow microneedles, m.p. 241° (decomp. >205°) (from xylene) (Found: N, 10·5. $C_{27}H_{15}ClN_4O_7$ requires N, 10·3%). The 10-*bromo-compound* (IV), similarly obtained from 12-bromo-6-hexanoylaminochrysene, formed faintly yellow needles (0·3 g), m.p. 163° (from ethanol) (Found: C, 70·2; H, 3·5; N, 3·9. $C_{21}H_{12}BrN$ requires C, 70·4; H, 3·4; N, 3·9%); orange-yellow *picrate*, m.p. 248° (decomp. >225°) (from xylene) (Found: N, 9·5. $C_{27}H_{15}BrN_4O_7$ requires N, 9·5%).

A similar reaction with 6-hexanoylamino-12-nitrochrysene afforded benzo[*h*]benzo[7,8]quino[6,5-*f*]quinoline (35%), m.p. and mixed m.p.[12] 293—294° (Found: C, 87·0; H, 4·2; N, 8·3. Calc. for $C_{24}H_{14}N_2$: C, 87·3; H, 4·3; N, 8·5%).

Benzo[h]*naphtho*[1,2-f]*quinoline*-9,10-*quinone* (V).—A solution of benzo[*h*]naphtho[1,2-*f*]quinoline [2] (0·5 g) in acetic acid (25 ml) was heated under reflux for 30 min with sodium dichromate (2·3 g); after cooling and dilution with water, the precipitate was washed with water, dried, and recrystallised from acetic acid to give deep red needles (0·4 g), m.p. 267—268°; solutions of this material in sulphuric acid were violet, turning brown-red (Found: C, 81·4; H, 3·5; N, 4·3. $C_{21}H_{11}NO_2$ requires C, 81·6; H, 3·6; N, 4·5%).

Benzo[c]*benzo*[7,8]*quino*[6,5-a]*phenazine* (VI).—A solution of the preceding quinone (0·25 g) and *o*-phenylenediamine (0·1 g) in ethanol (100 ml) was heated under reflux for 2 h and the precipitate which formed on cooling was recrystallised from benzene to afford yellow prisms (0·3 g), m.p. 271°, showing deep red halochromism in sulphuric acid (Found: C, 85·2; H, 4·0; N, 10·8. $C_{27}H_{15}N_3$ requires C, 85·0; H, 4·0; N, 11·0%). The 15,16-*dichloro-derivative* (VII) formed yellow needles, melting first at 299°, then resolidifying to melt again at 320° (from toluene), giving violet solutions in sulphuric acid (Found: C, 72·2; H, 2·9; N, 9·1. $C_{27}H_{13}Cl_2N_3$ requires C, 72·0; H, 2·9; N, 9·3%); the 15,16-*dimethyl compound* (VIII) formed yellow needles, m.p. 257° (from benzene) (Found: C, 85·0; H, 4·5; N, 10·0. $C_{29}H_{19}N_3$ requires C, 85·1; H, 4·7; N, 10·3%).

Phenanthro[9,10-g]*quinoline* (XI).—A mixture of 2-aminotriphenylene [13] (0·6 g), glycerol (4 g), arsenic acid (1·8 g), and sulphuric acid (5 ml) was stirred at 160° for 1 h; after cooling, the product was diluted with water and made basic with aqueous ammonia. The solid precipitate was extracted into benzene, and the solution was concentrated and treated with ethanolic picric acid. The *picrate* of (XI) crystallised as yellow microprisms, m.p. 241° (from xylene) (Found: N, 11·0. $C_{27}H_{16}N_4O_7$ requires N, 11·0%). The *free base* formed prisms (0·1 g), m.p. 204° (from ethanol) (Found: C, 90·0; H, 4·7; N, 4·9. $C_{21}H_{13}N$ requires C, 90·3; H, 4·7; N, 5·0%). A solution of compound (XI) (0·1 g) in acetic acid (5 ml) was heated under reflux for 15 min with sodium dichromate (0·5 g); after dilution with water, the precipitate was recrystallised from ethanol to give *phenanthro*[9,10-g]*quinoline*-9,14-*quinone* (XII), yellow prisms (0·05 g), m.p. 256—257° (Found: C, 81·3; H, 3·5; N, 4·2. $C_{21}H_{11}NO_2$ requires C, 81·6; H, 3·6; N, 4·5%). This quinone did not react with *o*-phenylenediamine in boiling ethanol.

Benzo[h]*quino*[6,7-f]*quinoline* (XIV).—A mixture of 3-acetamido-9-aminophenanthrene (1 g), glycerol (8 g), arsenic acid (6·5 g), sulphuric acid (40 ml), and water (7 ml) was stirred for 1 h at 135—140°; when cool, the

[8] W. S. Rapson, *J. Chem. Soc.*, 1941, 15.
[9] D. C. Thang, N. P. Buu-Hoï, and N. D. Xuong, *J. Chem. Soc.*, 1965, 4585.
[10] For correlation between carcinogenicity and induction of zoxazolamine hydroxylase, see N. P. Buu-Hoï and D.-P. Hien, *Biochem. Pharmacol.*, 1968, **17**, 1227; 1969, **19**, 741.
[11] D. C. Thang, N. P. Buu-Hoï, and P. Jacquignon, *Chimie Thérapeutique*, 1971, **6**, 6.
[12] M. Dufour, N. P. Buu-Hoï, and P. Jacquignon, *J. Chem. Soc.* (*C*), 1967, 1415.
[13] N. P. Buu-Hoï and P. Jacquignon, *J. Chem. Soc.*, 1953, 941.

product was diluted with water and filtered. The solid residue was washed with aqueous ammonia, dried, and extracted with toluene in a Kumagawa apparatus. The solution was concentrated and treated with picric acid in ethanol. The *picrate* of (XIV) crystallised as yellow microprisms, m.p. 253° (decomp. >230°) (from chlorobenzene) (Found: N, 13·7. $C_{26}H_{15}N_5O_7$ requires N, 13·8%). The *free base* (XIV) formed needles (0·2 g), m.p. 208° (from ethanol) (Found: C, 85·4; H, 4·1; N, 9·7. $C_{20}H_{12}N_2$ requires C, 85·7; H, 4·3; N, 10·0%). No pure quinone could be obtained on chromic acid oxidation of this product. The m.p.s of compounds (XIV) and (XI) are both close to that of the corresponding hydrocarbon (m.p. 205°).[14]

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[1/1547 *Received, August 24th*, 1971]

[14] *Cf.* N. P. Buu-Hoï, D. Lavit, and J. Lamy, *J. Chem. Soc.*, 1960, 2845.