Synthesis of a Variety of Polycyclic Heteroaromatic Compounds *via* Quinone Methide Intermediates

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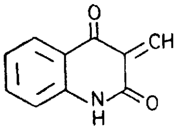
Summary A useful method of preparing polycyclic heteroaromatic compounds by heating the precursors (**4**) and (**9**) with a variety of aromatic amines is reported.

DURING an investigation of a well known synthesis of 3-dimethylallyl-4-hydroxy-2-quinolones we discovered that the reaction afforded low yields of substituted dibenzo[*b*,*h*]-[1,6]naphthyridin-6(5*H*)-ones (**2**) in addition to the expected products.[1] An explanation[1] for the production of these compounds invoked a quinone methide intermediate (**1**) which might react with aniline to afford the final product (**2**) of well proven structure.[1,2] One way to improve the method would be to seek a more direct route to the putative quinone methide (**1**),[3] and so the Mannich base (**3**) was prepared and pyrolysed in the presence of various anilines with results as summarised in the Table. Yields of the desired products from the Mannich base (**3**) were but moderate (see Table), and were especially low when the electron deficient 2- and 3-aminopyridines were used. Since the major byproduct in the reaction, 3,3′-methylenebis-4-hydroxy-2-quinolone, was presumably for-

TABLE. Pyrolysis of compounds (**3**) and (**4**) in the presence of various anilines

		% Yield	
Aniline	Product	From (**3**)	From (**4**)
Aniline	(**2**)	36	77[a], 76[b]
Aniline	5-Me-(**2**)	—	80[c]
o-Phenylenediamine	11-NH_2-(**2**)	29	71,[a] 66[b]
o-Anisidine	11-MeO-(**2**)	26	64[b]
o-Anisidine	5-Me,11-MeO-(**2**)	—	60[c]
m-Phenylenediamine	10-NH_2-+8-NH_2-(**2**)	20	—
m-Anisidine	10-MeO-+8-MeO-(**2**)	—	48[b]
m-Anisidine	5-Me,10-MeO-+ 5-Me,8-MeO-(**2**)	—	56[c]
2-Aminopyridine	11-Aza-(**2**)	5	—
3-Aminopyridine	8-Aza-(**2**)	1	—
3-Aminopyrazole	(**5**)	—	84[c]
5-Aminoisoquinoline	(**6**)	—	51[c]
5-Aminoindole	(**8**)	—	73[c]
5-Aminoindazole	(**7**)	—	71[c]
9-Aminophenanthrene	8,9; 10,11-Dibenzo-(**2**)	—	29[c]

[a] (**4**; $R^1 = H$, $R^2 = Me$). [b] (**4**; $R^1 = H$, $R^2 = OH$). [c] (**4**; $R^1 = Me$, $R^2 = OH$).



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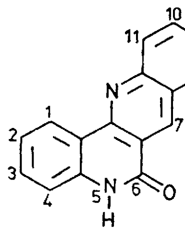

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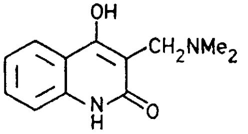

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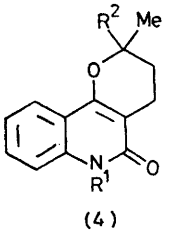

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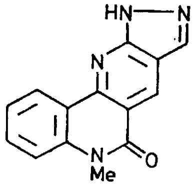

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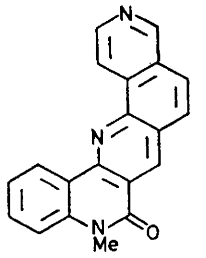

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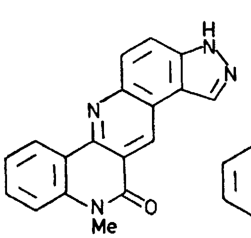

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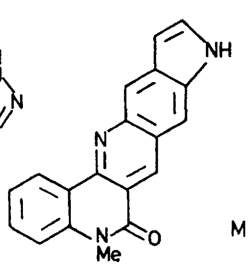

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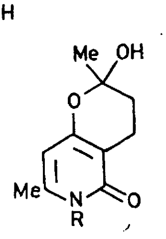

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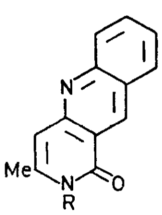

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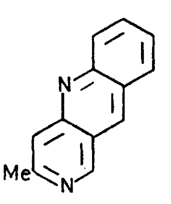

(11)

med by reaction of the quinone methide (**1**) with 4-hydroxy-2-quinolone, and this latter compound was formed from the base (**3**) by a retro-Mannich reaction, it seemed that the synthesis might be improved if this latter process could be obviated. We therefore investigated generation of the quinone methide from cyclic precursors of the general structure (**4**) by a retro-Diels–Alder process.

In the reaction of dihydroflindersine (**4**, R^1 = H, R^2 = Me)[4] with aniline or *o*-phenylenediamine, the respective tetracyclic products† were obtained in excellent yields (see Table), but the usefulness of the synthesis was limited since the preparation of dihydroflindersine was a multistep synthesis.[4] This problem was overcome by preparing the hemiacetals† (**4**, R^1 = H, R^2 = OH) and (**4**, R^1 = Me, R^2 = OH) in one step from 4-hydroxy-2-quinolone, diethylaminobutan-3-one, methyl iodide, and base. These hemiacetals provided excellent yields of a variety of interesting polycyclic heteroaromatic compounds† when heated in refluxing diphenyl ether with the appropriate aromatic amine (see Table).

The reaction seemed to be totally regiospecific when 3-aminopyridine, 5-aminoindazole, and 5-aminoindole were used as the bases. The n.m.r. spectra of the products of the former two reactions allowed us to assign structures (**2**, 8-aza) and (**7**) unambiguously to them and this would suggest that the regiospecificity with respect to the aromatic amine component in the reaction was the same as in the Skraup synthesis when anilines substituted in the *meta*-position with an electron-withdrawing group were used.[5] It was not possible to be so certain of the structure of the product from the reaction with 5-aminoindole although we favoured structure (**8**) of the two possibilities. Reaction with *m*-anisidine and *m*-phenylenediamine gave mixtures but the major isomer‡ was the 10-substituted compound in each case. Thus for anilines *meta*-substituted with electron-releasing groups, regiospecificity with respect to the amine component was the same as in the Skraup synthesis.[5]

Preliminary results using the quinone methide precursors (**9**) have shown that the method can be extended to other systems. Reaction of the compounds (**9**, R = H)† and (**9**, R = Me)† with aniline gave the products (**10**, R = H)† and (**10**, R = Me)† in 48% and 47% yield, respectively, whilst reaction of (**9**, R = Me) with 3-aminopyrazole gave the expected product in 56% yield. Reaction of the tricyclic compound (**10**, R = H) with phosphorus oxychloride and subsequent reduction with Raney nickel gave a small amount of the aromatic compound (**11**) which had m.p. and spectral data in accord with literature values.[6]

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† Compounds were characterised by analytical and spectroscopic data. Comparison of features of the spectra of the various compounds with those of the compounds (**2**, 5-Me) and (**10**) which had been structurally related to compounds synthesised by alternative methods proved most helpful.

‡ The isomers were distinguished by assigning the compound with the lower field values for 7-H in the n.m.r. spectrum to the 8-substituted product. This is in accord with expectations for the *peri* effect, G. O. Dudek, *Spectrochim. Acta*, 1963, **19**, 691.

[1] R. Oels, R. Storer, and D. W. Young, *Chem. and Ind.*, 1974, 499; *J.C.S. Perkin I*, in the press.
[2] J. T. Braunholtz and F. G. Mann, *J. Chem. Soc.*, 1955, 381.
[3] A. B. Turner, *Quart. Reviews*, 1964, **18**, 347.
[4] R. F. C. Brown, G. K. Hughes, and E. Ritchie, *Austral. J. Chem.*, 1956, **9**, 277.
[5] L. Bradford, T. J. Elliott, and F. M. Rowe, *J. Chem. Soc.*, 1947, 437.
[6] N. S. Prostakov, L. M. Kirillova, D. Phal'gumani, L. A. Shakhparonova, and V. P. Zvolinskii, *Chem. Heterocyclic Compounds* 1967, **3**, 832.