REACTIVITY OF ISOQUINOLINE ALKALOIDS WITH BENZYNE

Manuel Paz, Carlos Saá, Enrique Guitián, Luis Castedo,* and José Manuel Saá

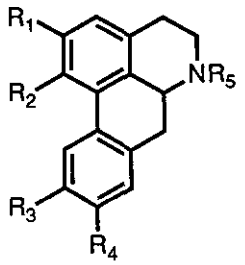
Dpto. Química Orgánica y Sección de Alcaloides del CSIC, E-15706 Santiago de Compostela, Spain
Dpt. Química, Universitat de les Illes Balears, E-07071 Palma de Mallorca, Spain

Abstract.-Benzyne reacts with tertiary aporphines, benzylisoquinolines and cularines by successive β and α eliminations, giving rise to N,N-diphenylarylethylamines. Secondary aporphines (noraporphines) yield N-phenylnoraporphines. Whereas dehydroaporphines undergo α elimination, the corresponding nordehydroaporphines suffer both C and N phenylations by way of an ene reaction followed by N-phenylation of the resulting 7-phenyldehydronoraporphine (aporphine numbering).

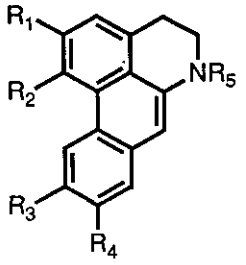
Although there are many references in the literature to the reactivity of simple amines with benzyne,[1,2] very few deal systematically with the corresponding reactivity of heterocyclic amines.[2] No general rules follow from the known data, the course of the reaction depending on the structures of the amine and the aryne, the method of aryne generation, the reaction conditions, etc.

Our interest in the development of methods for the preparation of naturally occurring or synthethically modified isoquinoline alkaloids[3] has led us to study the reactivity of a number of isoquinoline alkaloids with benzyne. We hoped that this would provide us with both a series of novel alkaloid derivatives for future testing and, more importantly, with an understanding of the reactivity of benzyne with secondary and tertiary amines and the corresponding enamines.

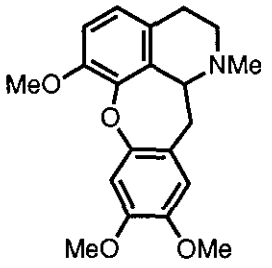
Here we report the results of this study for two naturally occurring aporphines,[4] tertiary amines nuciferine (**1a**)[4a,b] and glaucine (**1b**),[4a,b] and the corresponding dehydroaporphines (**2a** and **2b**);[4a,b] a secondary amine, nornuciferine (**1c**)[4a,c] and the corresponding dehydronoraporphine (**2c**)[4d] (Figure 1); and two tertiary amines, cularine (**3**),[4a] and the simple benzylisoquinoline laudanosine (**4**).[4a] We generated benzyne either by "in situ" preparation of benzenediazonium-2-carboxylate from anthranillic acid and isoamyl nitrite and thermal decomposition[5] or by isolation and subsequent thermal decomposition of this salt.[6]



1a R_1= R_2= OMe, R_3= R_4= H, R_5= Me
1b R_1= R_2= R_3= R_4= OMe, R_5= Me
1c R_1= R_2= OMe, R_3= R_4= R_5= H
1d R_1=R_2= OMe, R_3= R_4= H, R_5= Ph



2a R_1= R_2= OMe, R_3= R_4= H, R_5= Me
2b R_1= R_2= R_3= R_4= OMe, R_5= Me
2c R_1= R_2= OMe, R_3= R_4= R_5= H



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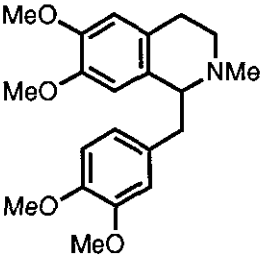

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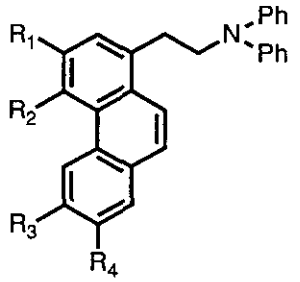
Figure 1

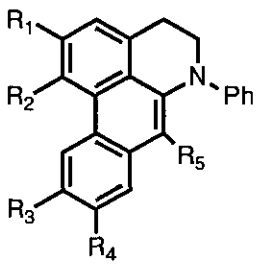
When treated with excess benzyne-generated as mentioned above[6] in a refluxing solution of 1,2-dimethoxyethane-compounds (**1a**, **1b**, **3** and **4**) behaved similarly: all suffered both loss of the *N*-Me group and opening of the isoquinoline B ring by β elimination, thus giving rise in fair yields to the corresponding novel *N*,*N*-diphenylarylethylamines **5a**, **5b**, **7** and **8** (Figure 2). The experimental results of these reactions are summarized in Table 1.

Table 1

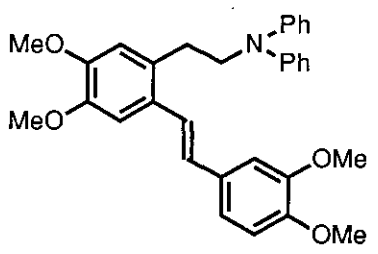
Entry	Substrate	Product	Yield (%)
1	**1a**	**5a**	48
2	**1b**	**5b**	74
3	**1c**	**1d**	55
4	**2a**	**6a**	68
5	**2b**	**6b**	49
6	**2c**	**6c**	30
7	**3**	**7**	38
8	**4**	**8**	30



5a R_1= R_2= OMe, R_3= R_4= H
5b R_1= R_2= R_3= R_4= OMe



6a R_1= R_2= OMe, R_3= R_4=R_5= H
6b R_1= R_2= R_3= R_4=OMe, R_5= H
6c R_1= R_2= OMe, R_3= R_4= H, R_5=Ph



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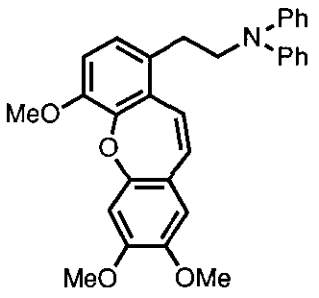

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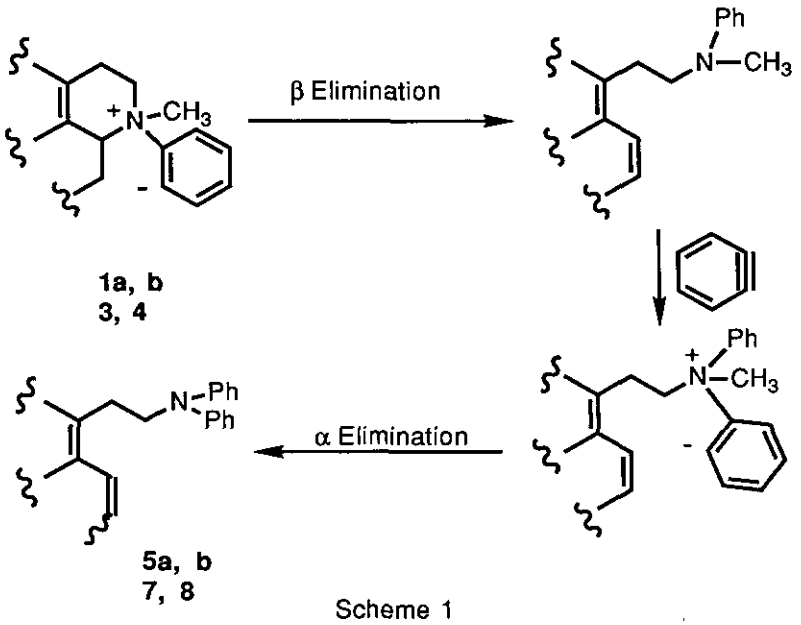
Figure 2

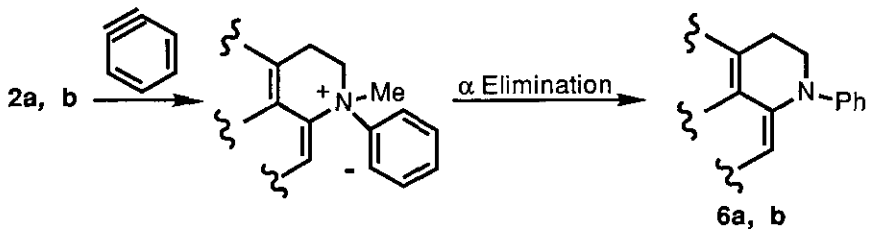
On the other hand, treatment of nornuciferine (**1c**) with excess benzyne yielded *N*-phenylnornuciferine (**1d**) as expected from the well-known tendency of secondary amines to undergo *N*-phenylation,[2] but no further *N*-phenylation involving β elimination took place. The lack of reactivity between benzyne and this kind of tertiary amine is possibly a consequence of steric constraints preventing attack on a phenyl-substituted tertiary nitrogen atom.

From a mechanistic viewpoint, the above results are consistent with the co-occurrence of benzyne-promoted α and β eliminations. We assume that nitrogen attack on benzyne provides a zwitterionic intermediate with an equatorial phenyl ring capable of undergoing a thermodynamically driven β-elimination. The resulting tertiary amines (*N*-methyl-*N*-phenylarylethylamines), on further *N*-phenylation (involving an α-elimination[2] process), could provide the final *N*,*N*-diphenylarylethylamines (Scheme 1).



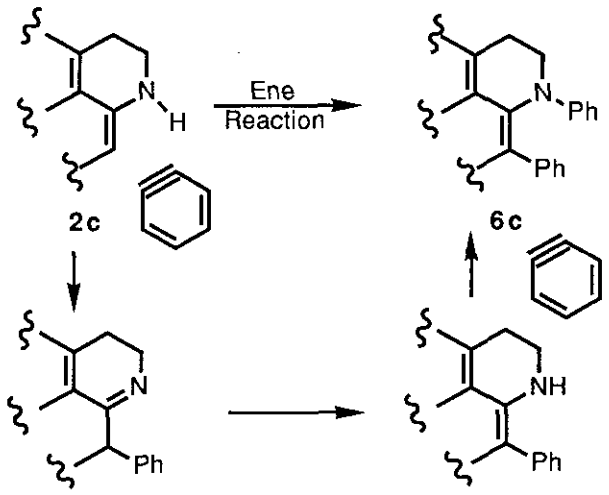
Scheme 1

Finally, reaction of excess benzyne with dehydroaporphines (**2a** and **2b**) and dehydronoraporphine (**2c**) gave somewhat unexpected results. Whereas dehydronuciferine and dehydroglaucine (**2a** and **2b**) yielded the corresponding *N*-phenyl derivatives (**6a** and **6b**) in a moderate yield (presumably by α elimination, Scheme 2), dehydronornuciferine (**2c**) provided the corresponding 6,7-diphenyl derivative (**6c**) (Figure 2).



Scheme 2

In our view, this last result can only be understood as a consequence of a benzyne promoted ene[7] reaction giving rise to an intermediate 7-phenyl-6a,7-dehydronornuciferine capable of undergoing further reaction with benzyne (*N*-phenylation of a secondary amine) to yield 6,7-diphenylnornuciferine (**6c**)(Scheme 3).



Scheme 3

In conclusion, the complex reactivity of benzyne with amines involving α and β eliminations, *N*-phenylations and ene reactions, can be grasped comprehensively from the above observations regarding its reaction with several isoquinolines. We hope that this may in future help towards a rational use of benzyne in synthetic endeavours, e.g., allowing control of the relative intensity of secondary reactions.

ACKNOWLEDGEMENTS

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EXPERIMENTAL SECTION

General Procedures. All melting points were determined on a Büchi apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Bruker (250 MHz) spectrometer using $CDCl_3$ as solvent and Me_4Si as internal standard. Infrared spectra were taken in KBr pellets with either a Pye-Unicam 1100 or a Perkin Elmer 1420 apparatus. Ultraviolet-visible spectra were run either on a Pye-Unicam 1700 or a Kontron 820 apparatus. Low resolution mass spectra were recorded on Hewlett-Packard 84524A and MS-50 instruments. High resolution mass spectra were recorded on a Kratos MS-50 instrument operating at 70 eV.

Reaction of glaucine (1b), cularine (3), laudanosine (4) and dehydroglaucine (2b) with benzyne generated by the *in situ* method. General procedure. A three necked flask provided with a reflux condenser and two addition funnels (with drying tubes) was loaded with **1b**, **3**, **4** or **2b** (typically 0.2 mmol) dissolved in dry DME (15 ml), and heated to reflux. At this point, dropwise addition of DME solutions of anthranilic acid (5 ml, 4 molar equivalents) and isoamyl nitrite (5 ml, 5 molar equivalents) from each of the addition funnels was started. The addition was discontinued when starting material was no longer detected (tlc) in the reaction mixture (90 min, approx). The resulting solution was evaporated to dryness. The residue, taken in methylene chloride, was then washed with 5% HCl solution, 5% NaOH solution and water, and

finally dried over anhydrous sodium sulphate. After solvent removal in a rotary evaporator, the residue was chromatographed on preparative silica gel plates using methylene chloride as eluant.

1-(N,N-Diphenyl-2-ethylamino)-3,4,6,7-tetramethoxyphenanthrene (5b). This compound was obtained as pale yellow crystals in 74% yield, mp 122-124° C (MeOH). Ir (KBr): 1635, 1550, 1530, 1450, 1130 cm^{-1}. Uv (MeOH) λ_{max}: 266, 284 (sh), 310, 324 (sh) 348, 366 nm. ^1H Nmr: 3.41 (t, J= 6 Hz, 2H), 3.91 (s, 3H), 4.04 (s, 3H), 4.08 (s, 3H), 4.04-4.10 (m, 2H), 6.93-7.01 (m, 6H), 7.20-7.30 (m, 6H), 7.50 (d, J= 9.1 Hz, 1H), 7.63 (d, J= 9.1 Hz, 1H), 9.29 (s, 1H). MS, m/z (%) 493 (M^+, 23), 182 (100). HRms for $C_{32}H_{31}NO_4$. Calcd : 493.22529. Found: 493.2250.

Dibenzoxepine 7 (38% yield). Pale yellow crystals, mp 65-66° C (MeOH). Ir (KBr): 1640, 1600, 1500, 1270, 1110 cm^{-1}. Uv (EtOH) λ_{max}: 222 (log ε: 4.46), 252 (sh, 4.25), 292 (4.16) nm. ^1H Nmr: 2.96 (m, 2H), 3.85 (s, 3H), 3.90 (s, 3H), 3.91 (s, 3H), 3.85-3.91 (m, 2H), 6.65-7.25 (m, 16H). MS m/z (%): 479 (M^+, 8), 182 (100).

1-(N,N-Diphenyl-2-ethylamino)-3,3',4,4'-tetramethoxystilbene (8). (30% yield). White crystals, mp. 109-110° C. Ir (KBr): 1600, 1520, 1250, 1140, 1100 cm^{-1}. Uv (EtOH) λ_{max}: 246 (sh, log ε: 4.42), 298 (4.49), 336 (4.41) nm. ^1H Nmr : 3.10 (t, J= 8.2 Hz, 2H), 3.86 (s, 3H), 3.91-3.94 (m, 11H), 6.63 (s, 1H), 6.81-7.01 (m, 11 H), 7.09 (s, 1H), 7.16-7.25 (m, 4H). MS m/z (%): 495 (M^+, 9), 182 (100), 104 (59), 77 (69). HRms for $C_{32}H_{33}NO_4$. Calcd : 495.24094. Found: 495.2418.

6,7-Diphenyldehydronorglaucine (6b). This compound was obtained as a yellowish crystalline material in 49% yield, mp. 72-74° C. Ir (KBr): 1610, 1590, 1460, 1250, 1220, 1120 cm^{-1}. Uv (EtOH) λ_{max}: 220, 260 (log ε: 4.62), 340 (4.03) nm. ^1H Nmr: 3.33 (t, J= 5.9 Hz, 2H), 3.82 (t, J= 5.9 Hz, 2H), 3.92 (s, 6H), 4.02 (s, 3H), 4.03 (s, 3H), 6.65 (s, 1H), 6.82 (s, 1H), 7.04 (s, 1H), 7.15-7.47 (m, 5H), 9.12 (s, 1H). MS m/z (%): 415 (M^+, 100), 342 (24), 77 (25).

Reaction of nuciferine (1a), nornuciferine (1c), dehydronuciferine (2a) and dehydronornuciferine (2c) with benzyne generated by heating of the preformed benzenediazonium-2-carboxylate salt. General procedure. To a cooled (0° C), stirred solution of anthranillic acid (typically, 0.14 g, 1 mmol) in dry DME (10 ml) containing a catalytic amount of trichloroacetic acid, a solution of isoamyl nitrite (0.16 g, 1.4 mmol) was added in 1-2 min. Stirring was continued at 0° C for 15 min, and then at room temperature for 90 min. The resulting heterogeneous mixture was diluted with DME and then the supernatant was discarded (the use of a syringe with teflon tubing instead of a metallic needle is recommended). The resulting brownish precipitate, which should always be soaked with solvent, was aspirated with the aid of a syringe with teflon tubing (never use a metallic needle!) and added slowly to a refluxing DME solution of **1a**, **1c**, **2a** or **2c** (typically, 0.1-0.2 mmol in 10 ml of DME). The reaction was monitored by tlc until the disappearance of starting material. The solvent was removed under vacuum and the residue was chromatographed on preparative silica gel plates using hexanes-ethyl acetate (8:2) as eluant.

1-(N,N-Diphenyl-2-ethylamino)-3,4-dimethoxyphenanthrene (5a). This compound was obtained as pale yellow crystals in 48% yield, mp 68-70° C (EtOH). Ir (KBr): 1580, 1490, 1445, 1275, 1115 cm^{-1}. Uv (MeOH) λ_{max}: 238 (sh, log ε :4.37), 252 (4.64), 280 (4.17), 302 (4.22), 347 (3.30), 364 (3.25) nm. ^1H Nmr: 3.43 (t, J= 7.5 Hz, 2H), 3.91 (s, 3H), 3.97 (s, 3H), 4.09 (t, J= 7.5 Hz, 2H), 6.93-7.00 (m, 6H), 7.14 (s, 1H), 7.22-7.32 (m, 5H), 7.55-7.85 (m, 5H). MS, m/z (%): 433 (M^+, 6), 251 (4), 182 (100), 165 (7), 77 (13). HRms for $C_{30}H_{27}NO_2$. Calcd : 433.20417. Found: 433.2021.

N-Phenylnornuciferine (1d). This compound was obtained as white crystals in 55% yield, mp 116-118° C (MeOH). Ir (KBr): 1590, 1495, 1250 cm^{-1}. Uv (MeOH) λ_{max}: 263 nm. ^1H Nmr: 2.69 (t, J= 13.9 Hz, 1H), 2.88-2.98 (m, 3H), 3.29-3.35 (m, 1H), 3.61 (m, 1H), 3.67 (s, 3H), 3.92 (s, 3H), 4.38 (d, J= 12.1 Hz and J= 3.46 Hz, 1H), 6.71 (s, 1H), 6.92 (t, J= 7.3 Hz, 1H), 7.02 (s, 1H), 7.06 (s, 1H), 7.17-7.36 (m, 5H), 8.42 (d, J= 8.0 Hz, 1H). Ms m/z (%): 357 (M^+, 98), 356 (100), 342 (57), 326 (27), 252 (21), 106 (32). HRms for $C_{24}H_{22}NO_2$. Calcd : 356.16504 Found: 356.1648.

N-Phenyldehydronornuciferine (6a). This compound was obtained as pale yellow crystals in 68% yield, mp 176-178° C (MeOH). Ir (KBr): 1615, 1590, 1495, 1445, 1410, 1390, 1330, 1225, 1170, 1015 cm^{-1}. Uv (MeOH) λ_{max}: 258 (log ε : 4.39), 342 (3.77) nm. ^1H Nmr: 3.36 (t, J= 6.0 Hz, 2H), 3.85 (t, J= 6.0 Hz, 2H), 3.92 (s, 3H), 4.05 (s, 3H), 6.68 (s, 1H), 7.10 (s, 1H), 7.21 (t, J= 7.2 Hz, 1H), 7.33-7.48 (m, 7H), 9.48 (d, J= 8.5 Hz, 1H). Ms, m/z (%): 355 (M^+, 100), 340 (25), 296 (22), 267 (12). HRms for $C_{24}H_{21}NO_2$. Calcd : 355.1572. Found: 355.1528.

6,7-Diphenyldehydronornuciferine (6c). This compound was obtained as white crystals in 30% yield, mp 158-160° C (MeOH). Ir (KBr): 1590, 1490, 1370, 1300, 1110, 1010 cm^{-1}. Uv (MeOH) λ_{max}: 261 (log ε: 4.34), 342 (3.43) nm. ^1H Nmr: 3.07 (t, J= 5.6 Hz, 2H), 3.86 (t, J= 5.6 Hz, 2H), 3.99 (s, 3H), 4.05 (s, 3H), 6.54 (s, 1H), 6.57 (s, 1H), 6.71 (t, J= 7.3 Hz, 1H), 6.91 (m, 2H), 7.03-7.16 (m, 6H), 7.38-7.56 (m, 3H), 9.75 (d, J= 8.4 Hz, 1H). Ms, m/z (%): 431 (M^+, 50), 105 (49), 77 (100). HRms for $C_{30}H_{25}NO_2$. Calcd : 431.18852. Found: 431.1877.

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