

139. Carcinogenic Nitrogen Compounds. Part XXXIX.¹ A New Synthesis of γ -Carbolines and of 2,10-Diaza-anthracenes.

By N. P. BUU-HOÏ, ODETTE ROUSSEL, and P. JACQUIGNON.

1-Benzyl-4-piperidone is a convenient intermediate in the synthesis of γ -carbolines, followed by simultaneous dehydrogenation and debenzylation, and for the synthesis of 2,10-diaza-anthracenes by Pfitzinger reactions and subsequent decarboxylation, debenzylation, and dehydrogenation.

SEVERAL derivatives of carbazoles possess carcinogenic activity,² but carbolines, which are isosteres of carbazoles, have not been investigated in this respect, save for some derivatives of β -carboline recently examined for sarcoma-inducing activity in mice and found to be inactive.³ It seemed of interest to investigate the chemical and biological properties of γ -carboline derivatives. γ -Carboline itself was first prepared by Robinson and Thornley⁴ by a three-step synthesis using 4-chloropyridine and *o*-phenylenediamine, but this method can be readily extended only to the symmetrical *o*-diamines (*i.e.*, those which give a single reaction-product with 4-chloropyridine). As 1-benzyl-4-piperidone is now a readily available intermediate, we studied the possibility of using this ketone for γ -carboline syntheses by means of Fischer indolisation of its arylhydrazones, and subsequent dehydrogenation and debenzylation of the intermediate 1,2,3,4-tetrahydro-compounds.

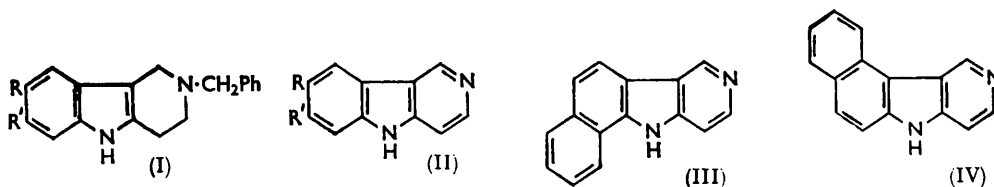
¹ Part XXXVIII, Buu-Hoï, Hoeffinger, and Jacquignon, *J.*, 1963, 5383.

² Boyland and Brues, *Proc. Roy. Soc.*, 1957, *B*, **122**, 429; Boyland and Mawson, *Biochem. J.*, 1938, **32**, 1460; Lacassagne, Buu-Hoï, Zajdela, and Xuong, *Bull. Cancer*, 1955, **42**, 3; Miller, Sandin, Miller, and Rusch, *Cancer Res.*, 1955, **15**, 188.

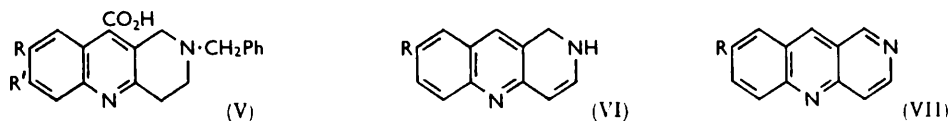
³ Lacassagne, Buu-Hoï, Zajdela, Jacquignon, and Périn, *Compt. rend.*, 1963, **257**, 818.

⁴ Robinson and Thornley, *J.*, 1924, **125**, 2169.

1-Benzyl-4-piperidone phenylhydrazone was readily cyclised to 2-benzyl-1,2,3,4-tetrahydro- γ -carboline (I; R = R' = H) by means of hydrogen chloride in acetic acid, and this compound underwent simultaneous dehydrogenation and debenzylation when heated



with palladium-charcoal; γ -carboline was thus obtained in two steps from 1-benzyl-4-piperidone, in an overall yield of 30%. This simple synthesis was successfully extended to 8-methyl- (II; R = Me, R' = H) and 7,8-dimethyl- γ -carboline (II; R = R' = Me), and to 6,7- (III) and 8,9-benzo- γ -carboline (IV), with comparable yields.



1-Benzyl-4-piperidone is also useful in the synthesis of other little-known nitrogen heterocycles. 2,10-Diaza-anthracene (VII; R = H) was recently prepared by Goscia and Dickermann⁵ from 1-acetyl-3-ethoxycarbonyl-4-piperidone by a six-step synthesis, but no homologue of this nucleus has yet been reported. Our preliminary observation,⁶ that the cinchoninic acid (V; R = R' = H) (obtained from 1-benzyl-4-piperidone and isatin by means of a Pfitzinger reaction) underwent simultaneous decarboxylation, debenzylation, and dehydrogenation to give 1,2-dihydro-2,10-diaza-anthracene (VI; R = H), provides a shorter, three-step route to 2,10-diaza-anthracene, and we have applied this method to the preparation of 7-methyl-2,10-diaza-anthracene, although with 7-halogenated 2,10-diaza-anthracenes we were unsuccessful because the corresponding cinchoninic acids underwent extensive decomposition on pyrolysis.

EXPERIMENTAL

Melting points were taken on a Maquenne block.

2-Benzyl-1,2,3,4-tetrahydro- γ -carboline (I; R = R' = H).—1-Benzyl-4-piperidone phenylhydrazone was prepared according to Cook and Reed's procedure for 1-methyl-4-piperidone.⁷ A mixture of 1-benzyl-4-piperidone (3.8 g.), phenylhydrazine hydrochloride (3 g.), and water (6 c.c.) was shaken at room temperature for 24 hr., and the product then basified with potassium carbonate; the oil obtained readily solidified, and gave the *phenylhydrazone* as straw-coloured needles (4.5 g.), m. p. 78–79° (from hexane) (Found: C, 77.4; H, 8.0; N, 14.9. C₁₈H₂₁N₃ requires C, 77.4; H, 7.6; N, 15.0%). A solution of this hydrazone (3 g.) in acetic acid saturated with hydrogen chloride (15 c.c.) was boiled for a few seconds, and the mixture then basified with aqueous sodium carbonate; the precipitate that formed gave the *tetrahydro-compound* as shiny needles (2 g.), m. p. 161° (from ethanol) (Found: C, 82.4; H, 7.1; N, 10.5. C₁₈H₁₈N₂ requires C, 82.4; H, 6.9; N, 10.7%). The *picrate* formed orange-yellow microcrystals, m. p. 183° (decomp. > 160°) (Found: N, 14.2. C₂₄H₂₁N₅O₇ requires N, 14.2%).

γ -Carboline (II; R = R' = H).—An intimate mixture of the foregoing compound (1 g.) with 5% palladium-charcoal (0.5 g.) was slowly heated above 200° in a sublimation apparatus until sublimation had ceased; the sublimate (0.35 g.) was recrystallised from water, giving γ -carboline as needles, m. p. 225° (lit.,⁴ m. p. 225°) (Found: N, 16.8. Calc. for C₁₁H₈N₂: N,

⁵ Goscia and Dickermann, *J. Amer. Chem. Soc.*, 1959, **81**, 3098.

⁶ Buu-Hoi, Roussel, and Jacquignon, *Bull. Soc. chim. France*, 1963, 1125.

⁷ Cook and Reed, *J.*, 1945, 399.

16.7%). The *picrate* formed golden-yellow needles, m. p. 242° (from nitrobenzene) (lit.,⁴ m. p. 250°) (Found: N, 17.3. C₁₇H₁₁N₅O₇ requires N, 17.6%).

8-Methyl- γ -carboline (II; R = Me, R' = H).—1-Benzyl-4-piperidone *p*-tolylhydrazone, prepared from the ketone (3.8 g.) and *p*-tolylhydrazine hydrochloride (3.2 g.) in water, could not be obtained as a solid and was therefore cyclised directly with acetic acid–hydrogen chloride, to give 2-benzyl-1,2,3,4-tetrahydro-8-methyl- γ -carboline (I; R = Me, R' = H) as prisms (4 g.), m. p. 170–171° (from ethanol) (Found: C, 82.7; H, 7.6; N, 9.6. C₁₈H₂₀N₂ requires C, 82.6; H, 7.3; N, 10.1%). Its *picrate* formed ochre-yellow prisms, m. p. 146° (from ethanol). Treatment of the tetrahydro-compound with palladium–charcoal afforded 6-methyl- γ -carboline (40%), as prisms, m. p. 244° (sublim. >195°) (from ethanol) [Found: C, 79.2; H, 6.2; N, 14.8%; *M* (mass spectroscopy), 182. C₁₂H₁₀N₂ requires C, 79.1; H, 5.5; N, 15.4%; *M*, 182]. The *picrate* formed orange needles, m. p. 259–260° (sublim. and decomp. >240°) (from nitrobenzene) (Found: N, 17.2. C₁₈H₁₃N₅O₇ requires N, 17.0%).

7,8-Dimethyl- γ -carboline (II; R = R' = Me).—The 4-*o*-xylylhydrazone of 1-benzyl-4-piperidone, prepared from the ketone (1.9 g.), 4-*o*-xylylhydrazine hydrochloride (1.7 g.), and sodium acetate (1.4 g.), could not be satisfactorily indolised with our usual reagent, but on treatment with acetic acid–sulphuric acid it readily afforded 2-benzyl-1,2,3,4-tetrahydro-7,8-dimethyl- γ -carboline (I; R = R' = Me), as shiny leaflets (1.5 g.), m. p. 187–188° (from ethanol) (Found: C, 82.6; H, 7.4; N, 9.8. C₂₀H₂₂N₂ requires C, 82.7; H, 7.6; N, 9.7%). The *picrate* formed red needles, m. p. 126–127° (from chlorobenzene) (Found: N, 13.4. C₂₆H₂₅N₅O₇ requires N, 13.5%). Treatment with palladium–charcoal furnished 7,8-dimethyl- γ -carboline (40%) as shiny needles, m. p. 245–246° (from ethanol) (Found: C, 79.5; H, 6.2; N, 14.3. C₁₃H₁₂N₂ requires C, 79.6; H, 6.2; N, 14.3%). Its *picrate* formed ochre-yellow prisms, m. p. 278° (decomp. >266°) (from ethanol) (Found: N, 16.5. C₁₉H₁₅N₅O₇ requires N, 16.5%).

6,7-Benzo- γ -carboline (III).—The crude hydrazone obtained from 1-benzyl-4-piperidone (3.8 g.) and 1-naphthylhydrazine hydrochloride (3.9 g.) in water (6 c.c.) gave, on indolisation with acetic acid–hydrogen chloride, 2-benzyl-1,2,3,4-tetrahydro-6,7-benzo- γ -carboline, as shiny prisms (6 g.), m. p. 166–167° (from ethanol) (Found: C, 84.3; H, 6.6; N, 8.6. C₂₂H₂₀N₂ requires C, 84.6; H, 6.5; N, 9.0%). The *picrate* formed brown-yellow needles, m. p. 248° (decomp. >208°) (from *o*-dichlorobenzene) (Found: N, 12.8. C₂₈H₂₃N₅O₇ requires N, 12.9%). Dehydrogenation and debenzylation afforded 6,7-benzo- γ -carboline (40%) as needles, m. p. 309–310° (sublim. >230°) (from ethanol) (Found: C, 82.4; H, 4.6; N, 12.8. C₁₅H₁₀N₂ requires C, 82.5; H, 4.6; N, 12.8%). Its *picrate* formed orange needles, m. p. 296° (sublim. >260°, decomp. >275°) (from nitrobenzene) (Found: N, 15.5. C₂₁H₁₃N₅O₇ requires N, 15.6%).

8,9-Benzo- γ -carboline (IV).—2-Benzyl-1,2,3,4-tetrahydro-8,9-benzo- γ -carboline, prepared as for the above isomer, formed needles, m. p. 168° (from benzene) (Found: C, 84.4; H, 6.5; N, 9.0%). The *picrate* formed ochre-yellow needles, m. p. 259° (decomp. >249°) (from nitrobenzene) (Found: N, 12.9%). Dehydrogenation and debenzylation gave 8,9-benzo- γ -carboline (40%) as shiny needles, m. p. 241° (sublim. >205°) (from ethanol) (Found: N, 12.7%) [*M* (mass spectroscopy), 218. Req'd., 218]. Its *picrate* formed orange needles, m. p. 295–296° (decomp. >280°) (from nitrobenzene) (Found: N, 15.5%).

Pfitzinger Reactions with 1-Benzyl-4-piperidone.—These were effected as follows. A mixture of 1-benzyl-4-piperidone (6 g.), 5-methylisatin (6.5 g.), and potassium hydroxide (6.8 g.) in ethanol (30 c.c.) was refluxed on a water-bath for 20 hr.; the ethanol was distilled off, the residue dissolved in water, the neutral impurities extracted with ether, and the aqueous layer slightly acidified with aqueous acetic acid. The precipitate was collected, washed with acetone, dried *in vacuo* over potassium hydroxide, and recrystallised from dioxan. Yield of the acid (V; R = Me, R' = H), 75%. The other cinchoninic acids were prepared in the same way and with similar yields.

2-Benzyl-1,2,3,4-tetrahydro-2,10-diaza-anthracene-9-carboxylic acids.

Substituent	M. p.	Found (%)			Formula	Required (%)		
		C	H	N		C	H	N
7-Methyl	275° (decomp. >215°)	75.6	6.1	8.1	C ₂₁ H ₂₀ N ₂ O ₂	75.9	6.0	8.4
7-Fluoro	281–282 (decomp. >225)	71.0	5.2	8.5	C ₂₀ H ₁₇ FN ₂ O ₂	71.4	5.1	8.3
7-Bromo	288 (decomp. >235)	60.4	4.4	7.0	C ₂₀ H ₁₇ BrN ₂ O ₂	60.4	4.3	7.0
6,7-Dimethyl	287–288 (decomp. >225)	75.6	6.2	8.2	C ₂₂ H ₂₂ N ₂ O ₂	76.3	6.4	8.1

1,2-Dihydro-7-methyl-2,10-diaza-anthracene (VI; R = Me).—The cinchoninic acid (V; R = Me, R' = H) (2 g.) was heated above its m. p. in a sublimation apparatus, and the sublimate was recrystallised from benzene, giving shiny *needles* (0.2 g.), m. p. 284° (sublim. >200°) (Found: C, 79.5; H, 6.3; N, 14.4. $C_{13}H_{12}N_2$ requires C, 79.6; H, 6.1; N, 14.3%). The structure postulated for this compound, by analogy with its lower homologue,⁶ was confirmed by nuclear magnetic resonance spectroscopy (singlet at $\tau = 4.05$, characteristic of the two protons in the 1-position, and indicative of a methylene group situated between a nitrogen atom and an aromatic radical). The *picrate* formed saffron-yellow needles, m. p. 253° (decomp. >220°) (from ethanol) (Found: N, 16.2. $C_{19}H_{15}N_5O_7$ requires N, 16.4%).

7-Methyl-2,10-diaza-anthracene (VII; R = Me).—A mixture of the foregoing dihydro-compound (0.1 g.) and 5% palladium-charcoal (0.1 g.) was heated above 165°, and the sublimate was recrystallised from water, giving shiny *leaflets* (0.07 g.), m. p. 179°, with strongly lachrymatory vapours (Found: C, 80.4; H, 5.3; N, 14.3. $C_{13}H_{10}N_2$ requires C, 80.4; H, 5.2; N, 14.4%). The *picrate* formed ochre-yellow prisms, m. p. 217° (decomp. >150°) (from ethanol) (Found: N, 16.3. $C_{19}H_{13}N_5O_7$ requires N, 16.5%).

This investigation was supported in part by a grant from the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service, and we thank the authorities concerned.

INSTITUT DE CHIMIE DES SUBSTANCES NATURELLES DU C.N.R.S.,
GIF-SUR-YVETTE (S.-ET-O.), FRANCE.

[Received, July 31st, 1963.]
