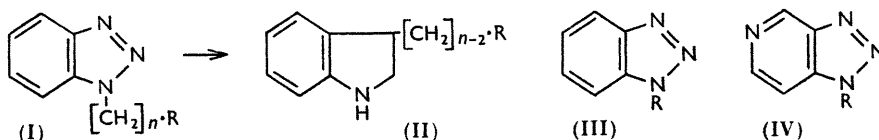


916. The Graebe-Ullmann Carbazole Synthesis.

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Some benzo- (III) and pyridino(3' : 4'-4 : 5)-1 : 2 : 3-triazoles (IV) with 1-alkyl, 1-alkylaryl and 1-cyclohexyl substituents have been pyrolysed to see whether the Graebe-Ullmann carbazole synthesis could be extended to intramolecular arylation of alkyl CH groups. These thermal decompositions generally lead to secondary amines. The preparative value of this synthesis is, therefore, limited to triazoles with 1-aromatic or 1-heteroaromatic substituents.

THE Graebe-Ullmann synthesis has been successfully applied to the preparation of carbazoles¹ and carbolines,² but the thermal decomposition of benzo- (III) or pyridino-(3' : 4'-4 : 5)-1 : 2 : 3-triazoles (IV) with 1-alkyl, 1-alkylaryl, or 1-cycloalkyl substituents has not been reported. We have now sought to extend this synthesis to such compounds which by analogy were expected to lose nitrogen when heated and to cyclise by arylation of an alkyl CH group. This extension could provide a route (I) \rightarrow (II) to 3-substituted indolines (II).



For the preparation of triazoles *o*-chloronitrobenzene or 4-chloro-3-nitropyridine was condensed with the requisite amine, the nitro-compound obtained being reduced with sodium dithionite to a diamine which was then treated with nitrous acid. Pyrolyses were usually carried out in sealed tubes, as most triazoles proved very stable when heated in a liquid medium such as syrupy phosphoric acid, liquid paraffin, or "Silicone Oil." A small amount of inflammable gas, together with ammonia, was generally noticed on opening the tubes, and liquid hydrocarbons could often be separated from the mixture. Nitrogen-containing products were usually identified as picrates. The results of the decompositions are summarised in Table I.

TABLE I.

Substituent	1-Substituted benzo-1 : 2 : 3-triazoles Products	Yield (%)
H	Aniline	40
<i>cyclo</i> Hexyl	Diphenylamine	5
	Carbazole	15
Benzyl	<i>N</i> -Benzylaniline	4
	Phenanthridine	4
Phenethyl	<i>N</i> -Phenethylaniline	7
Butyl	<i>N</i> -Butylaniline	18
Allyl	<i>N</i> -Allylaniline	14
	Aniline	5
	Quinoline	5
	1-Substituted pyridino(3' : 4'-4 : 5)-1 : 2 : 3-triazoles	
<i>cyclo</i> Hexyl	4- <i>cyclo</i> Hexylaminopyridine	6
Benzyl	4-Benzylaminopyridine	8
Phenethyl	4-Aminopyridine	6
	1 : 1'-Substituted benzobis-1 : 2 : 3-triazole	
Hexamethylene	Aniline	10

We isolated phenanthridine from the decomposition products of 1-benzylbenzo-1 : 2 : 3-triazole (III; R = Ph-CH₂), as reported by Gibson,³ and also some *N*-benzylaniline.

¹ Ullmann, *Annalen*, 1904, **332**, 82; Coker, Plant, and Turner, *J.*, 1951, 111.

² Späth and Eiter, *Ber.*, 1940, **73**, 719; Bremer, *Annalen*, 1934, **514**, 279.

³ Gibson, *J.*, 1956, 1076.

Benzylpyridino(3' : 4'-4 : 5)-1 : 2 : 3-triazole (IV; R = Ph-CH₂), however, did not cyclise and gave only 4-benzylaminopyridine.

Small amounts of carbazole and diphenylamine were obtained on pyrolysis of 1-cyclohexylbenzo-1 : 2 : 3-triazole (III; R = C₆H₁₁). The formation of carbazole, however, is probably not caused by ring closure of Graebe-Ullmann type between the aromatic nucleus and cyclohexane (followed by dehydrogenation), because we found that *N*-cyclohexylaniline under similar conditions also gives a mixture of the two amines. The primary reaction product is probably *N*-cyclohexylaniline, yielding by dehydrogenation diphenylamine which is known to cyclise to carbazole when strongly heated.⁴ In some decompositions loss of nitrogen and dealkylation occurred.

From the pyrolysis products of 1-allylbenzo-1 : 2 : 3-triazole small quantities of quinoline and *N*-allylaniline were isolated. Since, however, one of the compounds produced by a sealed-tube reaction with *N*-allylaniline⁵ is quinoline, its presence is probably not accounted for by the Graebe-Ullmann reaction.

Apart from the triazoles listed above, 5-chloro- and 5-methyl-1-2'-pyridylbenzo-1 : 2 : 3-triazole were heated in syrupy phosphoric acid and gave in good yield the corresponding α -carbolines needed for another research. In an unsuccessful attempt to improve the overall yield of α -carboline previously made by a Graebe-Ullmann synthesis,⁶ we prepared the intermediate 2-amino-*N*-2'-pyridylaniline by condensation of 2-aminopyridine and 1-chloro-2-nitrobenzene, followed by reduction.

As the Graebe-Ullmann synthesis has a superficial resemblance to the Pschorr type reaction, a suggestion by Hey and Mulley,⁷ which relates the ease of formation of five-membered rings by internal cyclisation to the internuclear distances in the unstrained molecules, was applied to our problem. From an inspection of Courtauld models and from calculations based on diagrams, the distances between the relevant aryl- and alkyl-carbon atoms in our structures are found to be 2.0 Å. Since this value is close to that found for molecules undergoing Graebe-Ullmann reactions, the distance involved in these cyclisations cannot be regarded as decisive for the success of the reaction. Some correlation can, however, be made between the nature of substituents in the benzene ring of benzo-1 : 2 : 3-triazoles and yields obtained on pyrolysis. Electron-supplying substituents lead to generally good results,^{8,9} whereas electron-withdrawing groups (including halogens) lead to negligible yields.^{9,10} On this basis the mechanism of the Graebe-Ullmann reaction appears to be ionic and the failure of benzo- or pyridino-1 : 2 : 3-triazoles with 1-alkyl substituents to cyclise may be explained by the inertness of inactivated alkyl structures towards heterolytic substitution.

TABLE 2. Ultraviolet absorption maxima ($m\mu$) in EtOH.

Substituent	1-Substituted benzo-1 : 2 : 3-triazoles					
	λ_1	ϵ_1	λ_2	ϵ_2	λ_3	ϵ_3
H	250	6560	255	6449	270	5260
cycloHexyl	254	6880	259	6940	275	4690
Benzyl	253	6490	259	6410	275	4170
Phenethyl	254	6770	259	6685	277	4510
1-Substituted pyridino(3' : 4'-4 : 5)-1 : 2 : 3-triazoles						
cycloHexyl	261	5415	—	—	—	—
Benzyl	261	5725	—	—	—	—
Phenethyl	257	6050	—	—	—	—

Absorption spectra of a number of triazoles are given in Table 2. The curves of 1-benzyl- and 1-phenethyl-substituted benzo- and pyridino-triazoles hardly differ from

⁴ Graebe, *Ber.*, 1872, 5, 377.

⁵ Carnahan and Hurd, *J. Amer. Chem. Soc.*, 1930, 52, 4586.

⁶ Lawson, Perkin, and Robinson, *J.*, 1924, 626.

⁷ Hey and Mulley, *J.*, 1952, 2276.

⁸ Allen, *Chem. Listy*, 1954, 48, 1075.

⁹ Preston, Tucker, and Cameron, *J.*, 1942, 500.

¹⁰ Allen and Suschitzky, *J.*, 1953, 3845.

those of their respective 1-cyclohexyl derivatives, undoubtedly owing to the presence of the CH_2 and $\text{CH}_2\cdot\text{CH}_2$ groups whose insulating effects prevent conjugation of the benzene ring with the triazole systems.

EXPERIMENTAL

Condensations.—(a) *o*-Chloronitrobenzene (1 mol.) and the appropriate amine (2.5 mol.) were heated for 5–10 hr. on a water-bath. The resulting oil was extracted with water and then with concentrated hydrochloric acid. Basification of the acid extract with aqueous ammonia was followed by recrystallisation of the nitro-amine from ethanol.

(b) To a 10% solution of the amine (2.5 mol.) in benzene was slowly added a similar solution of 4-chloro-3-nitropyridine¹¹ (1 mol.) and the mixture refluxed for 5 hr. The precipitated amine hydrochloride was filtered off and a crude product was obtained by removing the solvent from the filtrate by distillation. Recrystallisation occurred from ethanol. The compounds thus prepared are recorded in Table 3.

TABLE 3.
N-Substituted *o*-nitroanilines

Substituent	M. p.	Found (%)			Formula	Required (%)			Yield (%)
		C	H	N		C	H	N	
<i>cyclo</i> Hexyl	105.5	65.5	7.3	13.0	$\text{C}_{12}\text{H}_{16}\text{O}_2\text{N}_2$	65.5	7.3	12.7	87
Benzyl	75 ^a	—	—	—	—	—	—	—	80
Phenethyl	72	69.2	5.6	11.9	$\text{C}_{14}\text{H}_{14}\text{O}_2\text{N}_2$	69.4	5.8	11.6	75
Butyl	^b	62.0	7.6	14.1	$\text{C}_{10}\text{H}_{14}\text{O}_2\text{N}_2$	61.8	7.2	14.4	70
Allyl	^c	60.3	5.8	16.0	$\text{C}_9\text{H}_{10}\text{O}_2\text{N}_2$	60.7	5.6	15.7	54
2'-Pyridyl	66–67	61.8	4.2	19.9	$\text{C}_{11}\text{H}_8\text{O}_2\text{N}_3$	61.4	4.2	19.5	9
4-Chloro-2'-pyridyl	108	53.2	3.4	17.1	$\text{C}_{11}\text{H}_8\text{O}_2\text{N}_3\text{Cl}$	52.9	3.2	16.9	10
4-Methyl-2'-pyridyl ...	97	62.9	4.8	—	$\text{C}_{12}\text{H}_{11}\text{O}_2\text{N}_3$	62.9	4.8	—	9
4-N-Substituted 4-amino-3-nitropyridine									
<i>cyclo</i> Hexyl	102–103	60.0	6.8	18.7	$\text{C}_{11}\text{H}_{15}\text{O}_2\text{N}_3$	59.7	6.8	19.0	90
Benzyl	100–101	63.1	4.9	18.0	$\text{C}_{12}\text{H}_{11}\text{O}_2\text{N}_3$	62.9	4.8	18.3	70
Phenethyl	83	63.8	5.4	17.1	$\text{C}_{13}\text{H}_{13}\text{O}_2\text{N}_3$	64.2	5.3	17.3	78
<i>o</i> -Ethoxyphenyl	100	59.8	5.0	15.8	$\text{C}_{13}\text{H}_{13}\text{O}_3\text{N}_3$	60.3	5.0	16.2	86
Di- <i>o</i> -nitroanilinohexane	110	60.4	5.9	16.0	$\text{C}_{18}\text{H}_{22}\text{O}_4\text{N}_4$	60.3	6.1	15.6	48

^a Gibson, *J.*, 1956, 1076, gives m. p. 74–75°. ^b B. p. 161°/8 mm. ^c B. p. 260°/76 mm.

Reductions.—To a boiling 5–10% ethanolic solution of the nitro-compound (1 mol.) 40% aqueous potassium hydroxide (10 mol.) was added, followed slowly by a saturated solution of sodium dithionite until the mixture became colourless or straw-yellow. After distillation of ethanol the mixture was poured into water. The precipitated amine was purified from water or ethanol. *N*-Allyl-*o*-nitroaniline gave some unidentified products by this method, but when reduced with stannous chloride and hydrochloric acid, yielded *N*-allyl-2-aminoaniline as a

TABLE 4.
N-Substituted *o*-aminoanilines

Substituent	M. p.	Found (%)			Formula	Required (%)			Yield (%)
		C	H	N		C	H	N	
<i>cyclo</i> Hexyl	51°	75.8	10.0	14.4	$\text{C}_{12}\text{H}_{16}\text{N}_2$	75.8	9.5	14.7	91
Benzyl	78	78.8	7.2	14.4	$\text{C}_{13}\text{H}_{14}\text{N}_2$	78.8	7.0	14.1	74
Phenethyl	55	79.4	7.5	12.9	$\text{C}_{14}\text{H}_{16}\text{N}_2$	79.2	7.5	13.2	66
Butyl	35	73.3	9.8	16.9	$\text{C}_{10}\text{H}_{16}\text{N}_2$	73.2	9.8	17.1	62
Allyl	^a	72.8	8.0	19.2	$\text{C}_9\text{H}_{12}\text{N}_2$	72.9	8.1	18.9	45
4-N-Substituted 3 : 4-diaminopyridines									
<i>cyclo</i> Hexyl	143	68.9	8.8	22.2	$\text{C}_{11}\text{H}_{17}\text{N}_3$	69.1	8.9	21.9	40
Benzyl	119	72.1	6.6	21.0	$\text{C}_{12}\text{H}_{13}\text{N}_3$	72.4	6.5	21.1	84
<i>o</i> -Ethoxyphenyl	232	67.7	7.0	18.0	$\text{C}_{13}\text{H}_{15}\text{ON}_3$	68.1	6.6	18.2	54
Di- <i>o</i> -aminoanilinohexane	121	72.6	9.0	19.0	$\text{C}_{18}\text{H}_{26}\text{N}_4$	72.5	8.7	18.8	64

^a B. p. 120°/10 mm.

light-sensitive, unstable oil, whose *benzoate* had m. p. 140° (Found: C, 76.4; H, 6.6. $\text{C}_{16}\text{H}_{16}\text{ON}_2$ requires C, 76.2; H, 6.3%). 3-Amino-4-phenethylaminopyridine was too unstable for analysis and had to be used immediately for triazole formation. *Compounds* thus prepared are listed in Table 4.

¹¹ Kruger and Mann, *J.*, 1955, 2758.

Triazole Formation.—A cooled solution (2–5%) of the diamine in 2*N*-hydrochloric acid to which a few ml. of ethanol had been added was diazotised at 0–5° with 5% aqueous sodium nitrite, stirring being continued for 1 hr. The mixture, after addition of a few ml. of concentrated hydrochloric acid to dissolve precipitated triazole, was boiled (charcoal), filtered and basified with ammonia (*d* 0.88). The triazole was filtered off and recrystallised from water, aqueous ethanol, or acetone. The triazoles obtained in this way are collected in Table 5.

Pyrolysis of Triazoles.—(a) *In syrupy phosphoric acid.* A solution of the triazole (0.5 g.) in syrupy phosphoric acid (2 ml.) was heated at 200° until evolution of nitrogen had ceased. This was determined by comparison with a blank experiment. The product was obtained by extracting the basified (sodium hydroxide) mixture with ether. 5-Chloro-1-2'-pyridylbenzo-1 : 2 : 3-triazole gave 6-chloro- α -carboline (37%), m. p. 229–230° (Found: C, 65.1; H, 3.6; N,

TABLE 5.

Substituent	M. p.	1-Substituted benzo-1 : 2 : 3-triazoles			Formula	Required (%)			Yield (%)
		Found (%)				C	H	N	
cycloHexyl	104°	71.6	7.7	21.2	C ₁₂ H ₁₅ N ₃	71.6	7.5	20.9	66.5
Benzyl	115 ^a	—	—	—	—	—	—	—	35
Phenethyl	37	75.0	5.7	18.6	C ₁₄ H ₁₃ N ₃	75.3	5.8	18.8	52
Butyl	^b	68.7	7.2	24.0	C ₁₀ H ₁₃ N ₃	68.6	7.4	24.0	56
Allyl	^c	67.9	5.8	26.6	C ₉ H ₉ N ₃	67.9	5.7	26.4	37
1-Substituted pyridino(3' : 4' : 4 : 5)-1 : 2 : 3-triazoles									
cycloHexyl	97	65.6	6.8	27.6	C ₁₁ H ₁₄ N ₄	65.3	6.9	27.7	69
Benzyl	120 ^d	—	—	—	—	—	—	—	85
Phenethyl	83	69.4	5.3	25.1	C ₁₃ H ₁₂ N ₄	69.6	5.4	25.0	90
<i>o</i> -Ethoxyphenyl	85	64.9	6.2	23.0	C ₁₃ H ₁₆ ON ₄	65.0	5.0	23.3	72
1 : 1'-Substituted bisbenzo-1 : 2 : 3-triazole									
Hexamethylene	107	67.2	6.4	26.6	C ₁₈ H ₂₀ N ₆	67.5	6.3	26.3	54
5-Substituted 1-2'-pyridylbenzo-1 : 2 : 3-triazoles									
5-Methyl	109	63.4	4.7	27.0	C ₁₂ H ₁₀ N ₄	68.5	4.7	26.7	63
5-Chloro	152	57.2	3.0	24.6	C ₁₁ H ₇ N ₄ Cl	57.3	3.0	24.3	90.7

^a Gibson ³ gives m. p. 115–116°. ^b B. p. 176°/18 mm. ^c B. p. 160°/16 mm. ^d Bremer (*Annalen*, 1935, **518**, 274) records m. p. 124°.

14.1; Cl, 17.7. C₁₁H₇N₂ requires C, 65.2; H, 3.5; N, 13.8; Cl, 17.5%). Under similar conditions 5-methyl-1-2'-pyridylbenzo-1 : 2 : 3-triazole yielded 6-methyl- α -carboline (46%), m. p. 220–221° (Found: C, 79.1; H, 5.7. C₁₂H₁₀N₂ requires C, 79.1; H, 5.5%).

(b) *In a sealed tube.* The triazole (0.5–0.8 g.) was heated in a sealed Pyrex tube (2'' × $\frac{3}{8}$ '') at 400° for 0.75 hr. In order to avoid losses due to the ensuing explosion the glass tube was opened by dropping it down a copper tube. Extraction of the mixture (Soxhlet) with light petroleum (b. p. 60–80°) gave usually, after evaporation of the solvent, a syrup. Nitrogenous constituents were extracted from the syrup with hydrochloric acid, the extract basified, and the residue chromatographed on alumina with benzene. From the pyrolysis products of 1-cyclohexylbenzo-1 : 2 : 3-triazole, carbazole was not removed by extraction with hydrochloric acid and thus was separable from diphenylamine. Products were identified by analysis, their picrates, and mixed m. p. determinations. The results of these decompositions are collected in Table 1.

4-cycloHexylaminopyridine.—4-Chloropyridine (7 g.), cyclohexylamine (15 g.), and anhydrous potassium carbonate (2 g.) were refluxed for 15 hr. Distillation of the filtered mixture gave a colourless liquid (b. p. 70–80°/75 mm.) which on sublimation at 2 mm. yielded 4-cyclohexylaminopyridine, m. p. 140° (10%) (Found: C, 74.9; H, 9.0. C₁₁H₁₆N₂ requires C, 75.0; H, 9.1%).

4-Phenethylaminopyridine.—By the above procedure 4-chloropyridine and phenethylamine gave 4-phenethylaminopyridine, m. p. 108–109° (10%) (Found: C, 78.9; H, 6.8. C₁₃H₁₄N₂ requires C, 78.8; H, 7.1%).

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