A New Phenazine Synthesis. The Synthesis of Griseoluteic Acid, Griseolutein A, and Methyl Diacetylgriseolutein B

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Summary 2-Nitrodiphenylamines are reductively cyclized to phenazines by sodium borohydride in ethanolic sodium ethoxide solution: the method has been used to provide the first synthesis of griseoluteic acid and thence of griseolutein A, confirming the allotted structures, and of methyl diacetylgriseolutein B, modifying the suggested structure.

FOLLOWING the observation that some 4′-amino-2-nitrodiphenylamine-6-carboxylic acids heated in aqueous alkali gave low yields of 7-aminophenazine-1-carboxylic acids and the belief that the necessary reduction arose from the *p*-phenylenediamine system,[1] we sought to develop a practical phenazine synthesis by the addition of other reducing agents. With sodium borohydride (2 molecular proportions) in 5N-ethanolic sodium ethoxide solution under reflux, yields have been improved to 60—80%.

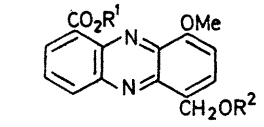
A limited survey of the scope of the reaction gave the results in the Table. It is clear that the reductive cyclisation is general for 2-nitrodiphenylamines and, in particular, is not dependent on a 4′-amino, or any substituent, in the ring on to which cyclisation is taking place. On the other hand, the highest yields are obtained with 6-nitrodiphenylamine-2-carboxylic acids; when the carboxyl group is in another position or when it is absent, lower yields result and/or longer reaction times are necessary.

The behaviour of aromatic nitro-compounds towards borohydride is variable depending on structure and reaction conditions: they may be inert, reduced at the nitro-group or, in the case of polynitro-compounds, reduced in the aromatic ring.[2] It has recently been reported that sodium borohydride in alkali reduces aromatic nitro-compounds *via* radical-anions.[3] Our reaction may proceed *via* 2-nitrosodiphenylamines which may cyclise to phenazines[4] or be

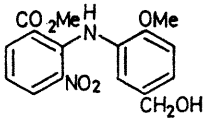
Conversion of 2-nitrodiphenylamines into phenazine

Diphenylamine	Time of reaction (h)	Phenazine	Yield (%)	M.p. (°)
2-Nitro	20	unsubstituted	32	170—171
6-Carboxy-2-nitro	15	1-carboxy	78	239—240
6-Methyl-2-nitro	30	1-methyl	36	107—108
4′-Amino-4-methoxy-2-nitro	18	8-amino-2-methoxy	38	215—217
4′-Amino-6-carboxy-2-nitro	4	7-amino-1-carboxy	75	>300
4′-Amino-4-carboxy-2-nitro	4	7-amino-3-carboxy	37	>300
6-Carboxy-4′-methoxy-2-nitro	10	1-carboxy-7-methoxy	80	256—258
6-Carboxy-3′-methoxy-2-nitro	20	1-carboxy-6-methoxy	40	282—284
		1-carboxy-8-methoxy	32	187—189
6-Carboxy-2′-methoxy-2-nitro	18	1-carboxy-9-methoxy	35	258—260
4′-Amino-2-nitro-4-sulphamoyl	15	2-amino-8-sulphamoyl	67	>300
4′-Amino-6-carboxy-2-nitro-4-sulphamoyl	3	2-amino-6-carboxy-8-sulphamoyl	69	>300
6-Carboxy-4′-methoxy-2-nitro-4-sulphamoyl	10	6-carboxy-2-methoxy-8-sulphamoyl	52	295—299 (decomp.)

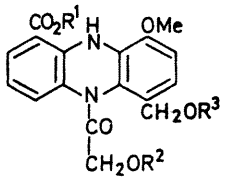
further reduced in competitive reactions. Reduction of 2-nitrodiphenylamine under the conditions described gives only a moderate yield of phenazine, the other main product being 2-aminodiphenylamine; when a trace of fluorenone is added as a hydride-transfer catalyst,[5] 2-aminodiphenylamine is the only product. The advantage of a carboxyl group in the other position *ortho* to the diphenylamine system is then to provide, by hydrogen bonding, a conformation favouring cyclisation over further reduction.



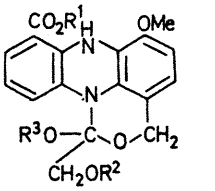
(1) $R^1=R^2=H$
(2) $R^1=H, R^2=CO\cdot CH_2OH$
(3) $R^1=Me, R^2=CO\cdot Me$



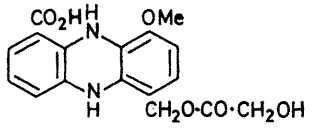
(4)



(5) $R^1=Me, R^2=R^3=CO\cdot Me$
(6) $R^1=R^2=R^3=H$



(7) $R^1=Me, R^2=R^3=CO\cdot Me$
(8) $R^1=R^2=R^3=H$



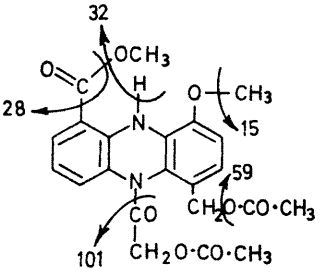
(9)

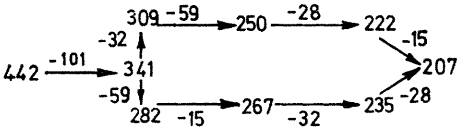
The structure of griseoluteic acid (**1**), a degradation product of the *Streptomyces griseoluteus* metabolites griseoleutein A (**2**) and B,[6] is ideally suited to synthesis by the new method. 4-Methoxy-3-nitrobenzoic acid[7] was converted into its mixed ethoxycarbonic anhydride which was then reduced with sodium borohydride[8] to 4-methoxy-3-nitrobenzyl alcohol[9] then further reduced, on the addition of 10% Pd–C,[10] to 3-amino-4-methoxybenzyl alcohol.[9] The latter was condensed with methyl 2-bromo-3-nitrobenzoate[11] to give methyl 3′-hydroxymethyl-6′-methoxy-2-nitrodiphenylamine-1-carboxylate (**4**) which, by the reductive cyclisation, gave griseoluteic acid (64% after 20 h). The methyl ester had m.p., mixed m.p., spectral, and chromatographic properties identical with those of the methyl ester prepared from authentic acid supplied by Professor S. Nakamura.

Griseoluteic acid (**1**) with t-butoxyacetic acid[12] in the presence of dicyclohexylcarbodi-imide and pyridine gave a product which was cleaved by dry hydrogen chloride in dichloromethane to give griseolutein A (**2**) with m.p., mixed m.p., spectral, and chromatographic properties identical with those described for the natural product.[6b]

Methyl acetylgriseoluteate[6a] (**3**) was hydrogenated in dichloromethane solution with rhodium as catalyst[13] to minimise the ready hydrogenolysis of the acetoxymethyl group. The dichloromethane solution of the dihydro-derivative was treated with acetoxyacetyl chloride in the presence of 1,4-diaza[2,2,2]bicyclo-octane. From this reaction a 31% yield of a yellow, highly fluorescent, crystalline compound was isolated which proved identical in all respects with a sample of the diacetyl derivative of methyl griseolutein B,[6a] supplied by Professor S. Nakamura.

This synthesis does not distinguish between positions 5 and 10 for the acetoxyacetyl group, although the 5





SCHEME. The fragmentations shown are substantiated by metastable peaks at the appropriate *m/e* values.

position, preferred on steric grounds, is supported by other evidence. As already noted,[14] the downfield position of the N–*H* signal in the ^1H n.m.r. spectrum [($CHCl_3$) τ 0·12 br s] is indicative of strong hydrogen bonding with the ester carbonyl. The spatial relationship of the NH with the ester group is also shown in the mass spectrum. After the initial fragmentation of the molecular ion (*m/e* 442) with loss of the acetoxyacetyl group (101 mass units) to give the base peak (*m/e* 341), two pathways are followed which involve the loss of methanol (32 mass units), acetate (59 mass units), carbon monoxide (28 mass units), and methyl (15 mass units) in different sequences (Scheme) which can only be accommodated if the methanol originates in the methoxyl of the ester group and the hydrogen at the 10 position. Further, a fragmentation involving the loss of 31 mass units, normally associated with the methoxycarbonyl group, is not observed. Thus the structure of methyl diacetylgriseolutein B must be (**5**) rather than (**7**).[14]

Although griseolutein B has been given[14] and has been accepted as[15] the cyclol structure (**8**), it is now clear that at least, under some conditions, (**8**) must be in equilibrium with (**6**). The latter structure was apparently not considered by Nakamura *et al.* but none of their evidence[6a,14] excludes it; indeed, the published ^1H n.m.r. spectrum of griseolutein B[14] does not show the AB quartet which might be expected for the ring methylene group in (**8**). Although the reported conversion of griseolutein B into griseolutein A above pH 4[16] presumably does involve the equilibrium (**6**) ⇌ (**8**) ⇌ (**9**), this equilibrium is displaced by the very

rapid atmospheric oxidation of (**9**) to griseolutein A. Under conditions when griseolutein B is stable, therefore, it is probably the *N*-acyl compound (**6**), a conclusion which is strengthened by other arguments to be presented in the full paper.

(*Received, August 19th*, 1970; *Com.* 1409.)

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