THE NITRATION OF HETEROCYCLIC NITROGEN COMPOUNDS

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I. Introduction

Our knowledge of aromatic nitration is not entirely unsatisfactory, as shown by the recent comprehensive survey by Gillespie and Millen.[1] Much quantitative work has been done, not only in determining the precise proportions of isomers formed when a given compound is nitrated, but also in establishing the intimate mechanism of substitution. Unfortunately, the same cannot be said of the problem of substitution, particularly nitration, in heterocyclic compounds. Not only are quantitative studies of orientation lacking, but the effect of changes in reaction medium, of great importance with compounds which are almost always basic in nature, has rarely been evaluated. Many compounds are to some extent protonised by sulphuric acid,[1] but this becomes a major consideration with basic substances.

Fortunately, much of our knowledge of the mechanism of nitration of aromatic compounds can be carried over unchanged to heterocyclic substances, but the gaps indicated above place the problem of substitution in heterocyclic compounds in much the same position as was that in the aromatic series before the work of Holleman. It is the purpose of the present Review to collate the known facts, largely qualitative, about the nitration of heterocyclic nitrogen compounds, providing a sort of extended footnote on this topic to Gillespie and Millen's article.

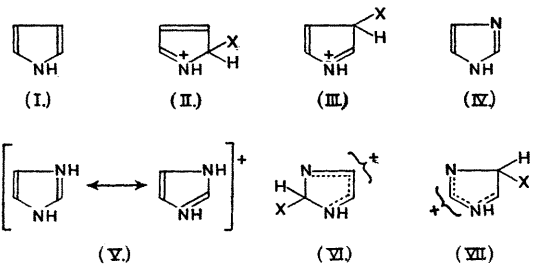
II. Five-membered Monocyclic Compounds

The monocyclic nitrogen compounds present interesting contrasts between pyrrole on the one hand and pyridine on the other, with pyrazole and glyoxaline occupying intermediate positions. As is well known, pyrrole (I) is very feebly basic (Table I), this being attributed to the need for the nitrogen atom to contribute electrons to the aromatic structure, thereby becoming incapable of salt formation. As a result, strong acids, by destroying their aromatic character, cause pyrrole derivatives to polymerise, a fact which renders satisfactory nitration difficult. However, the peculiar structure of pyrrole, besides making it sensitive to acids, renders it very susceptible to electrophilic substitution. Dewar[2] points out that the transition complex (II) involved in such substitution contains the same number of double bonds as pyrrole itself, so the activation energy is small. Further discussion leads to the conclusion that substitution will occur preferentially at the α-carbon atom.

[1] *Quart. Reviews*, 1948, **2**, 277.

[2] "The Electronic Theory of Organic Chemistry", Oxford Univ. Press, 1949. This monograph will frequently be referred to because it is the only one on the subject which contains a reasonably extensive discussion of heterocyclic compounds. Some of Dewar's views are also to be found in *Research*, 1950, **3**, 154.

The results of nitration experiments in the pyrrole series fit into this description satisfactorily, so far as they go. Early workers had little success with pyrrole itself, for the reasons given above, but Rinkes,[3] by treating pyrrole in acetic anhydride at — 10° with a small excess of nitric acid, isolated 21% of 2-nitropyrrole. Similarly, he converted 2-acetylpyrrole



into a mixture of its 4- and 5-nitro-derivatives, and the same isomers were obtained from methyl pyrrole-2-carboxylate and pyrrole-2-carboxylic acid. Rinkes pointed out that pyrrole derivatives containing a powerful meta-directing group (NO_2) behave like similar thiophen compounds in giving the 4-isomer as the principal nitration product, whilst with a less powerful group (CO_2Me) the 5-isomer predominates. Clearly, when one of the

TABLE I

pK_a *Values of some heterocyclic nitrogen compounds* [4]

Compound.	pK_a.	Compound.	pK_a.	Compound.	pK_a.
Pyrrole . .	0·4	Cinnoline . .	2·70	4-Hydroxyquinoline .	2·41
Pyrazole . .	2·53	Quinazoline .	3·51	4-Hydroxyquinazoline	2·07
Glyoxaline .	7·03	Quinoline. .	4·94	4-Hydroxycinnoline .	1·77
Indazole . .	1·3	*iso*Quinoline .	5·14		
Benziminazole	5·53				
Pyridine . .	5·23				
Aniline . .	4·57[4c]				

α-positions is already blocked there is little to choose in ease of substitution between the α′- and β′-positions. This is not surprising : even in pyrrole itself a consideration of the two transition states (II) and (III) suggests that the energy difference between them is small.

The ease with which the nitro-group replaces other groups already present in pyrrole derivatives is striking. Such replacements were observed by early workers,[5] who used more severe conditions than those described

[3] *Rec. Trav. chim.*, 1934, **53**, 1167 ; 1941, **60**, 650 ; see also Anderlini, *Ber.*, 1889, **22**, 2503.

[4] (*a*) Albert, Goldacre, and Phillips, *J.*, 1948, 2240 ; (*b*) Keneford, Morley, Simpson, and Wright, *J.*, 1949, 1356 ; (*c*) Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3469.

[5] Ciamician and Silber, *Ber.*, 1885, **18**, 1456 ; 1886, **19**, 1079.

by Rinkes, and this author has also noticed examples.[3] For instance, some 2-nitropyrrole was formed during the nitration of pyrrole-2-carboxylic acid, and hot nitric acid converted 4-nitropyrrole-2-carboxylic acid into 2 : 4-dinitropyrrole. The acetyl group in 2-acetylpyrrole suffers similar displacement. In this respect pyrrole derivatives resemble benzene compounds activated towards electrophilic reagents by the presence of several alkyl or alkoxy-groups.[6]

Pyrrole shows acidic properties, the anion being stabilised by resonance with respect to pyrrole itself. This anion should be even more susceptible to electrophilic attack than is the parent compound, and it is of interest that in ethereal solution in the presence of sodium, pyrrole reacts with ethyl nitrate to give a small amount of 2-nitropyrrole.[7] Although the mechanism of such a nitration is not certain, it seems likely that the reaction is an example of electrophilic substitution into the pyrrole anion.

Glyoxaline (IV) is especially interesting. Probably because of the symmetry of the cation (V) it is a considerably stronger base than pyridine (Table I). By comparison with pyrrole, glyoxaline is itself more symmetrical, and whilst still activated to some extent because of the NH group, is less susceptible than the former to electrophilic attack. Consideration of the transition states (VI) and (VII) led Dewar [2] to conclude that in glyoxaline electrophilic substitution in neutral and alkaline media should proceed at $C_{(2)}$, in support of which he quoted the instances of bromination and of coupling with diazonium salts. Further, since in the transition states the salts of glyoxaline would acquire positive charges on both nitrogen atoms, electrophilic substitution in these salts should be more difficult than in glyoxaline itself. The facts available on the bromination of glyoxaline do not warrant the inclusion of this reaction as an example of electrophilic substitution at $C_{(2)}$. The evidence relating to electrophilic substitution in glyoxaline is of great interest in connection with our present discussion of nitration, and will be briefly outlined. On bromination, glyoxaline and its derivatives readily give di- or tri-bromo-compounds, but in chloroform solution a monobromo-derivative can be produced from 4-methylglyoxaline, and it has been proved to be 5-bromo-4-methylglyoxaline.[8] 1 : 4- and 1 : 5-Dimethylglyoxaline likewise give 5-bromo-1 : 4- and 4-bromo-1 : 5-dimethylglyoxaline, but Langenbeck [9] obtained 2-bromo-1 : 4-dimethylglyoxaline by treating 1 : 4-dimethylglyoxaline with cyanogen bromide in ether. Pauly and Arauner [10] isolated small proportions of 2-iodo-derivatives from the iodination of glyoxaline and 4-methylglyoxaline, and similarly, glyoxaline couples with diazonium salts in alkaline media at $C_{(2)}$.[11] In contrast to this somewhat confused position in halogenation experiments, the nitration of glyoxaline and its derivatives gives consistently the 4- or

[6] (Miss) Nightingale, *Chem. Reviews*, 1947, **40**, 117.

[7] Angeli and Alessandri, *Atti R. Accad. Lincei*, 1911, **20**, I, 311 ; Hale and Hoyt, *J. Amer. Chem. Soc.*, 1915, **37**, 2538.

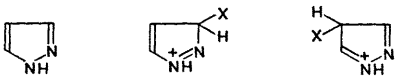
[8] Pyman, *J.*, 1910, **97**, 1814 ; Pyman and Timmis, *J.*, 1923, **123**, 494.

[9] *J. pr. Chem.*, 1928, **119**, 77. [10] *Ibid.*, 1928, **118**, 33.

[11] Pyman and Timmis, *J. Soc. Dyers Col.*, 1922, **38**, 269.

5-nitro-derivatives. Glyoxaline and 4-methylglyoxaline [12a] give the 4-nitro-compounds. Furthermore, nitration of glyoxalines is only possible if either the 4- or the 5-position is free, Fargher and Pyman [12a] having found that they could not nitrate 4 : 5-dimethylglyoxaline.

The situation is thus seen to be complicated, and it has occasionally been suggested that the substitution at $C_{(2)}$, which occurs during iodination, may proceed by other than a normal electrophilic reaction.[13] Whether this is so or not, it seems probable that with a strong base such as glyoxaline the experimental conditions will affect the orientation of substitution. In alkaline or neutral conditions glyoxaline itself would be the entity undergoing substitution, but in nitration (and sulphonation [12b]) the directive effect observed may be that of the glyoxalinium cation. The case is qualitatively similar to the nitration of aniline,[14] but quantitatively distinguished, since aniline, a weaker base (Table I), provides some *p*-nitroaniline along with the *m*-compound even when nitration is conducted in a very large excess of sulphuric acid. The actual position of nitration in the glyoxalinium cation is not easy to explain in qualitative terms. Enumeration of the various forms which might be expected to contribute to the transition state



(VIII) (IX) (X)

leaves little to choose between the 2- and 4(5)-positions. Perhaps the nitronium ion approaches the glyoxalinium cation at the point most remote from the positively charged heterocyclic nitrogen atoms. The nitration of glyoxaline [12a] was effected by hot mixed acids acting for several hours, and although electrophilic substitution in these circumstances is clearly more difficult than in the case of pyrrole, yet it is much less difficult than with pyridine (see below), as indicated by the yield of 4-nitroglyoxaline obtained (63%).

Pyrazole (VIII) is a much weaker base than is glyoxaline (Table I), and even if it were not so, it is doubtful whether electrophilic substitution would proceed differently in the strongly acid conditions used in nitration, as compared with the circumstances in, say, chlorination, for the expected point of attack is in a peculiarly symmetrical situation with respect to the two ring nitrogen atoms, which distinguishes this case from that of glyoxaline. Thus, consideration of the transition states (IX) and (X) leads us to expect electrophilic substitution at $C_{(4)}$. This is the case, not only in nitration [15] but also in chlorination [16] and bromination.[15, 17] The conditions used in

[12] (*a*) Rung and Behrend, *Annalen*, 1892, **271**, 28 ; Behrend and Schmitz, *ibid.*, 1893, **277**, 338 ; Fargher and Pyman, *J.*, 1919, **115**, 217 ; Fargher, *J.*, 1920, **117**, 668 ; (*b*) Barnes and Pyman, *J.*, 1927, 2711.

[13] Brunings, *J. Amer. Chem. Soc.*, 1947, **69**, 205.

[14] Holleman, " Die direkte Einführung von Substituenten in den Benzolkern ", Leipzig, 1910.

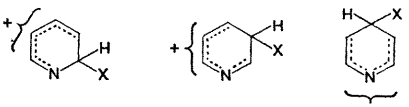
[15] Buchner and Fritsch, *Annalen*, 1893, **273**, 262.

[16] Knorr, *Ber.*, 1895, **28**, 715. [17] Buchner, *ibid.*, 1889, **22**, 2166.

this nitration do not permit us to judge of the relative ease of nitration of pyrazole and glyoxaline, but it seems clear that the reaction proceeds more readily than with pyridine.

III. Pyridine and its Derivatives

The nitrogen atom in pyridine differs from the NH group of the compounds discussed so far, in that the latter is an activating factor, whilst the former lowers the availability of electrons at all points in the ring,[18] rendering pyridine less susceptible to electrophilic attack than is benzene. The situation is therefore similar to that in nitrobenzene. Consideration of the three transition states (XI), (XII), and (XIII), leads to the conclusion [2] that (XII) would be the most stable, since in (XI) and (XIII) " the nitrogen atom occupies a more highly (positively) charged position in the mesomeric cation ". Thus, we should expect electrophilic substitution in pyridine to occur at $C_{(3)}$, with more difficulty than in benzene, and in the pyridinium cation with even more difficulty but at the same position. In the last respect pyridine resembles pyrazole ; *i.e.*, in both cases protonisation is not expected to change the site of nitration.



(XI.) (XII.) (XIII.)

Pyridine has proved extremely difficult to nitrate. Friedl,[19] by distilling pyridine in a current of air with fuming sulphuric acid and potassium nitrate, obtained 15% of 3-nitropyridine, and later prepared the same derivative by treating pyridine with sulphuric acid and potassium nitrate at 330°.[20] Kirpal and Reiter,[21] in repeating this method, found traces of iron to be essential to success, and in the light of this finding raised the yield to 22%. However, den Hertog and Overhoff,[22] in the most careful examination so far described, were unable to realise the yield claimed by Kirpal and Reiter, but noticed an important new point. They nitrated pyridine in 100% sulphuric acid with a mixture of potassium and sodium nitrates, at temperatures varying between 300° and 450°. Fifty % of the pyridine was recovered, and 6% of nitropyridines isolated. This product proved to be a mixture of 2- and 3-nitropyridine, the proportions of which varied with the temperature, being at 300°, 0·5% and 4·5% ; at 370°, 2% and 4% ; at 450°, 2·5% and 0%, respectively. Similar variations, though with higher yields, are observed in the halogenation of pyridine at different temperatures,[23] and in both the nitration and the halogenation experiments it is likely that the mechanism of substitution changes from the electrophilic

[18] Longuet-Higgins and Coulson, *Trans. Faraday Soc.*, 1947, **43**, 87.
[19] *Ber.*, 1912, **45**, 428. [20] *Chem.-Ztg.*, 1913, **36**, 589 ; *Monatsh.*, 1913, **34**, 760.
[21] *Ber.*, 1925, **58**, 699. [22] *Rec. Trav. chim.*, 1930, **49**, 552.
[23] The results of several investigations are summarised by Wibaut, *Experientia*, 1949, **5**, 337.

to the free-radical type as the temperature rises. This being so, it is not possible to attach such significance to the formation of 2-nitropyridine as is attributable to the production of a proportion of *o*-substitution in benzene derivatives containing meta-directing groups. Dinitrogen tetroxide nitrates pyridine in the vapour phase to give low yields of 3-nitropyridine, but the mechanism is uncertain.[24]

The nitration of alkylpyridines described by Plazek [25] shows no new features, but, as would be expected, the introduction into pyridine of a hydroxyl group greatly facilitates nitration, the hydroxyl group controlling the orientation. For instance, mixed acids convert 2-hydroxypyridine into the 3-nitro-, 3 : 5-dinitro-, and 5-nitro-derivatives, in that order of predominance,[26] whilst 3-hydroxypyridine provides 3-hydroxy-2-nitropyridine,[27] and 4-hydroxypyridine gives 4-hydroxy-3-nitropyridine.[28] The first two cases are worthy of comment. The predominant formation of 2-hydroxy-3-nitropyridine from 2-hydroxypyridine may be an illustration of chelation in the transition complex, between the entering nitro-group and the hydroxyl group, affecting the *o* : *p*-ratio, as suggested by Waters,[29] whilst the case of 3-hydroxypyridine might suggest that the ring nitrogen atom (perhaps protonised) can also contribute to such an effect. It is interesting that 3-ethoxypyridine is converted by mixed acids to 3-ethoxy-2-nitropyridine in 75—80% yield.[30] These examples in the pyridine series make interesting comparisons with similar benzene compounds. For example, *m*-nitrophenol on nitration gives mainly 3 : 4-dinitrophenol together with smaller amounts of 2 : 3- and 2 : 5-dinitrophenol,[14] whilst *m*-nitroanisole gives 2 : 3- (51·2%), 2 : 5- (40·6%), and 3 : 4-dinitroanisole (8·2%).[14] The effect of the ring nitrogen atom in pyridine clearly differs considerably in these cases from the effect of the nitro-group with which it is so frequently compared. Protonisation and some form of chelation may be responsible for this, and the steric factors must be very different in the two cases.

As is well known, the properties of amino-groups in heterocyclic compounds vary considerably with their positions in the molecule. 2- and 4-Aminopyridine are considerably removed from the category of primary aromatic amines into which 3-aminopyridine falls. It is therefore not surprising that in their behaviour towards nitric acid these two amines represent the extreme examples of the change in character noticeable in moving from anilines containing electron-releasing groups to those containing, say, several nitro-groups. 2-Aminopyridine is readily converted into 2-pyridylnitramine,[31] which rearranges in the presence of sulphuric acid,

[24] Shorigin and Topchiev, *Ber.*, 1936, **69**, 1874. [25] *Ibid.*, 1939, **72**, 577.
[26] Binz and Maier-Bode, *Angew. Chem.*, 1936, **49**, 486.
[27] Plazek and Rodewald, *Rocz. Chem.*, 1936, **16**, 502.
[28] Bremer, *Annalen*, 1937, **529**, 290. [29] *J.*, 1948, 727.
[30] den Hertog, Jouwersma, van der Waal, and Willebrands-Schogt, *Rec. Trav. chim.*, 1949, **68**, 275.
[31] (*a*) Tschitschibabin and Rasorenow, *J. Russ. Phys. Chem. Soc.*, 1915, **47**, 1286; (*b*) Tschitschibabin and Builinkin, *ibid.*, 1920, **50**, 47; Phillips, *J.*, 1941, 9; Caldwell and Kornfeld, *J. Amer. Chem. Soc.*, 1942, **64**, 1696; (*c*) Plazek and Sucharda, *Ber.*, 1928, **61**, 1813.

producing 2-amino-3- and -5-nitropyridine, the latter being the major product. The mechanism of the rearrangement has not been examined, and the evidence in the case of analogous phenylnitramines is not clear cut.[32] One difference to be noted is that, although a surprisingly large amount of *o*-nitroaniline is formed in the benzene series, the 5-nitro-compound is the main product from 2-pyridylnitramine, although higher temperatures in the rearrangement are said to favour the formation of 2-amino-3-nitropyridine. A halogen or nitro-group at $C_{(5)}$ does not prevent the formation and rearrangement of nitramines from substituted 2-aminopyridines,[31a, 33] and 4-aminopyridine behaves similarly.[34] It is a curious fact that 2-acetamidopyridine resists nitration.[31c]

3-Aminopyridine also forms the related nitramine when it is treated with nitric acid in sulphuric acid solution, but unlike the isomeric compounds already mentioned, 3-nitraminopyridine cannot be isomerised to a 3-amino-nitropyridine.[35a] This stability has not been explained. In contrast, the nitramine from 3-methylaminopyridine rearranges to 3-methylamino-2-nitropyridine.[35b]

In 2-dimethylaminopyridine, where nitramine formation is impossible, nitration occurs mainly *para* (90%) to the dimethylamino-group, together with some *ortho* (10%) substitution ;[36] *i.e.*, the dimethylamino-group behaves as an *op*-directing group, rendering nitration easier by comparison with pyridine itself. This is not surprising when it is remembered that protonisation probably occurs on the nuclear nitrogen atom rather than on the NMe_2 group,[4a] and the result is in contrast to that found with dimethylaniline which, when nitrated in concentrated sulphuric acid, gives mainly *m*-nitrodimethylaniline,[14] The results with 2-dimethylaminopyridine suggest that direct nitration of 2-aminopyridine in the work already discussed is at least a possibility.

IV. Bicyclic Compounds

(*a*) *The Work of Fries.*—A review of the known facts of the nitration of heterocyclic compounds would not be complete without reference to the long sequence of publications by Fries and his co-workers.[37] He set out to study the properties of numerous heterocyclic systems, of which we shall mention only those containing nitrogen, in an attempt to decide whether they should be regarded as resembling benzene or naphthalene the more closely. The tests chosen by Fries to distinguish benzenoid from naphthalenoid compounds include some typical electrophilic reactions such as nitration, and the work has revealed an interesting variety of behaviour

[32] Bradfield and Orton, *J.*, 1929, 915.

[33] Tschitschibabin and Tjashelowa, *J. Russ. Phys. Chem. Soc.*, 1920, **50**, 483 ; Magidson and Menchikov, *Ber.*, 1925, **58**, 113.

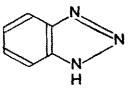
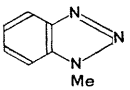
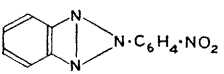
[34] Koenigs, Kinne, and Weiss, *ibid.*, 1924, **57**, 1172 ; Koenigs, Mields, and Gurlt, *ibid.*, p. 1179 ; Rath and Prange, *Annalen*, 1928, **467**, 1.

[35] (*a*) Tschitschibabin and Kirssanow, *Ber.*, 1927, **60**, 2433 ; (*b*) Plazek, Marcinikow, and Stammer, *Rocz. Chem.*, 1935, **15**, 365.

[36] Tschitschibabin and Knunyantz, *Ber.*, 1929, **62**, 3053.

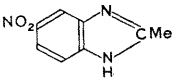
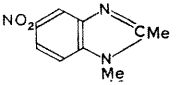
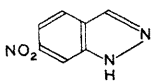
[37] (*a*) *Annalen*, 1912, **389**, 305 ; (*b*) *ibid.*, 1914, **404**, 50 ; (*c*) *ibid.*, 1927, **454**, 121 ; (*d*) *ibid.*, 1934, **511**, 213 ; (*e*) *ibid.*, 1937, **527**, 38 ; (*f*) *ibid.*, 1941, **550**, 31.

TABLE II

Compound.	Position of nitration.	Conditions.	Type.*	Ref.
Quinoline	α (5 and 8)	Mixed acids	N.	38
Azimidobenzene				
	α (4 or 7)	,,	,,	37*d*
	α (7)	,,	,,	37*d*
ψ-Azimidobenzene				
	α (4)	,,	,,	37*d*
Benziminazole	β (5)	,,	B.	40
2 : 3-Dimethylindole . . .	β (5)	,,	,,	41, 42
Indazole	β (5)	Fuming HNO_3	,,	39

* N. = Naphthalenoid ; B. = benzenoid.

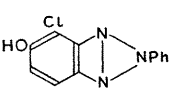
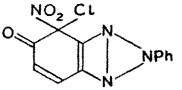
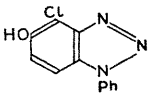
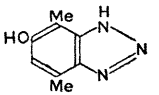
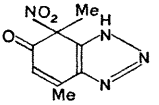
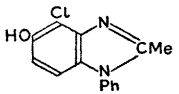
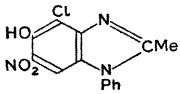
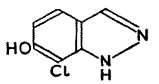
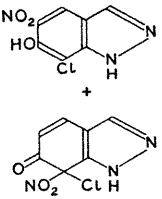
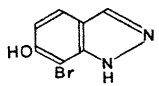
TABLE III

Compound.	Position of nitration.	Ref.
5-Nitroquinoline	7	43, 44
6-Nitroquinoline	5 and 8	44, 45
7-Nitroquinoline	5 and 8	44, 45
8-Nitroquinoline	6	45
	6	46
	6 (+ 4)	37*c*
	5	37*f*

[38] *J. Amer. Chem. Soc.*, 1940, **62**, 1640 ; *J.*, 1947, 1613.
[39] von Auwers and Kleiner, *J. pr. Chem.*, 1928, **118**, 67.
[40] Bamberger and Berlé, *Annalen*, 1893, **273**, 340 ; Fischer and Hess, *Ber.*, 1903, **36**, 3967.
[41] Bauer and Strauss, *ibid.*, 1932, **65**, 308.
[42] Plant and (Miss) Tomlinson, *J.*, 1933, 955.
[43] Claus and Hartmann, *J. pr. Chem.*, 1896, **53**, 199.
[44] Kaufmann and Hüssy, *Ber.*, 1908, **41**, 1735.
[45] Kaufmann and Decker, *ibid.*, 1906, **39**, 3648.
[46] Kym and Ratner, *ibid.*, 1912, **45**, 3248.

in heterocyclic compounds. The facts discovered or quoted concerning nitrations fall into three groups: the position of mononitration of bicyclic compounds, the orientation of the second nitro-group in the dinitration of similar systems, and the behaviour of chloro- or bromo-hydroxy-derivatives of these heterocyclic systems on nitration.

TABLE IV

Compound.	Product.	Conditions.	Type.	Ref.
		HNO_3–$CHCl_3$	N.	37*a*
		,,	,,	,,
		HNO_3	,,	,,
		HNO_3–AcOH	B.	37*c*
		,,	Intermediate	37*b*
		,,	B.	37*b*

The positions of mononitration of some of the nitrogen compounds examined by Fries are indicated in Table II. A distinction is made between those which react at "α" positions and those initially nitrated at "β" carbon atoms. The former are regarded as showing naphthalenoid character, the latter as being benzenoid.

Table III summarises the facts relating to the dinitration of some nitrogen compounds. It is striking that in the quinoline series the second nitro-group enters mainly *meta* to the first, whilst in several of the bicyclic compounds with a five-membered ring fused to a benzene ring, the second nitro-group is substituted adjacently to the first.

The third type of nitration reaction examined by Fries is illustrated in Table IV. Some heterocyclic compounds containing adjacent hydroxyl and halogen groups behave like similar halogeno-naphthols in forming with nitric acid chloronitro-ketones, whilst others react like ordinary members of the benzene series and give normal nitro-compounds. Once again, on the basis of this reaction, systems are classified as naphthalenoid or benzenoid.

Clearly, this work has produced a mass of interesting facts which future theory must accommodate, but for several reasons its present value as a contribution to comparative heterocyclic chemistry is limited. The classification into naphthalenoid or benzenoid types is vague, and often it is not clear whether the nature of the parent heterocyclic compound or one of its derivatives is indicated. All of the evidence is qualitative, and the choice of criteria for classifying compounds arbitrary. The latter point is clearly seen in the different behaviour of, say, 7-chloro- and 7-bromo-6-hydroxyindazole on nitration ; according to the particular case chosen, the nature of the indazole system would require different description. The fact that different conditions in nitration experiments may lead to different results is not taken into account, and the mechanisms of the various reactions are uncertain.

(*b*) *Indole and its Derivatives.*—The indole series demands further mention because of the variety of its reactions with nitric acid under different conditions. Indole itself, like pyrrole, is very susceptible to electrophilic attack, but consideration of the transition states [2] leads us to expect substitution in this case to proceed initially at $C_{(3)}$, $C_{(2)}$ coming next in reactivity. Indole itself, and its derivatives, unsubstituted at $C_{(2)}$ and $C_{(3)}$, are so reactive as to render difficult the observation of mononitration. Although 3-nitroindole cannot be obtained by the action of nitric acid upon indole, it is formed when the latter is treated with ethyl nitrate and sodium ethoxide in ether.[47] 2-Methylindole with the same reagents provides 2-methyl-3-nitroindole,[47] although an apparently different mononitroindole is obtained with mixed acids.[48] Warm nitric acid converts 2-methylindole into a dinitro-derivative in which one of the nitro-groups is probably at $C_{(3)}$.[48, 49]

The work of Perkin, and of Plant, has shown that with indoles of the type (XIV), nitric acid reacts differently according to the nature of the substituents. Nitration with mixed acids of tetrahydrocarbazole (XIV ; R = H, R′R″ = <[CH_2]$_4$),[50a] 1 : 2 : 3 : 4-tetrahydro-3-methylcarbazole

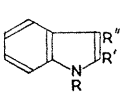
[47] Angelico and Velardi, *Atti R. Accad. Lincei*, 1904, **13**, I, 242 ; *Gazzetta*, 1904, **34**, 60.

[48] von Walther and Clemen, *J. pr. Chem.*, 1900, **61**, 268.

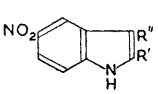
[49] Mathur and Robinson, *J.*, 1934, 1415 ; see also Zatti, *Gazzetta*, 1899, **19**, 260.

[50] (*a*) Perkin and Plant, *J.*, 1921, **119**, 1825 ; (*b*) *idem*, *J.*, 1923, **123**, 676 ; (*c*) *idem*, *ibid.*, p. 3242 ; (*d*) Manjunath and Plant, *J.*, 1926, 2260 ; (*e*) Plant and Rosser, *J.*, 1928, 2454 ; (*f*) Plant and Rutherford, *J.*, 1929, 1970 ; (*g*) Plant, *ibid.*, p. 2493 ; (*h*) Fennell and Plant, *J.*, 1932, 2872 ; (*i*) Massey and Plant, *J.*, 1931, 1990 ; (*j*) Plant, *J.*, 1936, 899 ; (*k*) Moggridge and Plant, *J.*, 1937, 1125 ; (*l*) Plant and (Miss) Wilson, *J.*, 1939, 237 ; (*m*) Plant and Whitaker, *J.*, 1940, 283 ; (*n*) Gaudion, Hook, and Plant, *J.*, 1947, 1631 ; (*o*) Bannister and Plant, *J.*, 1948, 1247.

(XIV; R = H, R′R″ = —[CH$_2$]$_2$·CHMe·CH$_2$—),[50e] and of 2 : 3-dimethylindole (XIV; R = H, R′ = R″ = Me) [41, 42] gives the corresponding derivatives of type (XV). Only when the indicated position is already occupied does nitration proceed elsewhere.[50e,k] 1 : 2 : 3 : 4-Tetrahydro-*N*-methylcarbazole likewise undergoes nitration at C$_{(6)}$.[50a]



(XIV.)



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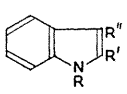

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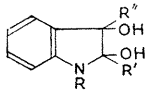

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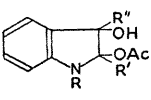

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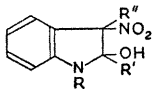
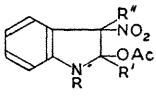
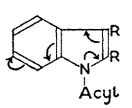


(XIX.)



(XX.)



(XXI.)

In contrast, compounds in which the indole nitrogen atom is acylated show a surprising degree of variety. Almost all the nitrations of these acyl derivatives have been affected in acetic acid–nitric acid, and the results are outlined in Table V.

TABLE V

Products formed from nitric acid and substituted indole derivatives

N-Acyl derivative.	Heterocyclic series.			
	1 : 2 : 3 : 4-Tetrahydrocarbazole.*	2 : 3-Dimethylindole.	2 : 3-Diphenylindole.	Dihydropentindole.
Acetyl . . .	XVI + XVII (50*a,b,d,e,l,j*)	XVI + XVII (42, 50*m*)	XVI (50*h*)	XVI + XIX (50*c,g,i,m*)
Cinnamoyl . .	XVI + XVII (50*f,j*)	—	XVI + complex products (50*h*)	XVI + XIX (50*i*)
Carbethoxy . .	XVI + XVII (50*b,j*)	—	XVI (50*h*)	XVI + XIX (50*g,i*)
Benzyl . . .	XVI + XVII (50*b,j*)	—	—	—
Benzoyl . . .	XVI + XIX (50*b,j,e,k*)	XIX (42)	XVI (50*h*)	XVI + XIX (50*g*)
p-Toluoyl, *p*-Chlorobenzoyl	XVI + XIX (50*f,j*)	—	—	—
o- and *m*-Toluoyl, *o*- and *m*-Chlorobenzoyl	XVI (50*f,h*)			

Broadly speaking, *N*-acetyl, *N*-cinnamoyl, and *N*-carbethoxy-derivatives of all the series examined, except the dihydropentindole one, give derivatives of the type (XVI)* and (XVII), whilst the corresponding dihydropentindoles give products of the types (XVI)* and (XIX). The proportions of the two products formed in any case may vary with the relative amounts of acetic and nitric acids, and with the temperature. Minor aberrations from the above general scheme have been observed; *e.g.*, 3-methyl- and *N*-carbethoxy-

* A 6-nitro-group should have been shown in (XVI).

6-chloro-1 : 2 : 3 : 4-tetrahydrocarbazole give, unexpectedly, compounds of the types (XVI)* and (XIX).[50e,k] Further, 5-chloro-8-cinnamoyldihydropentindole provides, as well as the expected (XVI)* and (XIX), a small proportion of (XX).[50i] Also noteworthy is the fact that *N*-acetyl derivatives of 2 : 3-dimethylindoles containing electronegative substituents give products of type (XIX).[50m,n]

Little discussion or explanation of the large number of observations of this kind has yet been attempted. The fact that the unacylated indoles are nitrated to give compounds of the type (XV), whilst acylated systems give rise to compounds (XVI),* was at first considered to be anomalous, but it was suggested that the nitrogen atom exerts its influence through the very reactive indole double bond, in the sense of the expression (XXI),[49, 50b,k] from which point of view the NH group becomes *meta*-, and the *N*-acyl groups *para*-directing, as was expected. Such an explanation, whilst it stresses the interesting character of the indole double bond, is not entirely adequate for present-day theories, which consider the molecule as a whole rather than isolating particular elements in it. Whatever the true significance of these results, certain points may be stressed. First, in no case has a reaction of the present type been studied quantitatively. Such a study would present great difficulties, and it is perhaps significant that in many of the examples mentioned the yields obtained are not quoted. Secondly, little is known of the mechanism whereby solutions of nitric acid in acetic acid are able to effect additions to double bonds, and whether the variety of addition products noted arises from different modes of direct addition of the medium or from subsequent changes in one primary addition product is not clear. The indole double bond is, of course, not unique in its ability to add on the elements of nitric acid. Several examples are known of such additions to ethylenic linkages, and were responsible for the mistaken notion that aromatic nitration proceeds by addition of nitric acid followed by the elimination of water.[51]

(*c*) *Quinoline and Related Compounds.*—The series—quinoline, *iso*quinoline, quinazoline, and cinnoline (no data are available for quinoxaline and phthalazine)—presents a more homogeneous group for discussion than the bicyclic compounds already mentioned. A very large number of quinoline derivatives has been nitrated from time to time, and we shall not attempt to deal with these exhaustively since many are of no special significance.

The nitration of quinoline in sulphuric acid has been described by several workers, most recently by Fieser and Hershberg, and by Curd, Graham, (Miss) Richardson, and Rose.[38] Although the conditions have varied from case to case, it has always been found that 5- and 8-nitroquinoline are formed in roughly equal proportions. Dufton [52] obtained a by-product which was later shown to be 5-hydroxy-6 : 8-dinitroquinoline.[53] Bacharach, Haut, and Caroline,[54] by nitrating quinoline with lithium nitrate and a

[51] Gilman, " Organic Chemistry, An Advanced Treatise ", 2nd edn., Vol. II, p. 175, New York, 1943.

[52] *J.*, 1892, **61**, 782.

[53] Bennett and Grove, *J.*, 1945, 378.

[54] *Rec. Trav. chim.*, 1933, **52**, 413.

* A 6-nitro-group should have been shown in (XVI).

TABLE VI

Nitration of quinoline derivatives and related compounds [a,f]

Compound.	Product.[b]	Conditions.[c]	Ref.
Quinoline	5 : 8	M	38
	7	$LiNO_3$/ $Cu(NO_3)_2$/ Ac_2O	54, 24
*iso*Quinoline	5 : 8	M	55
Quinazoline	6	M	56
Quinaldine	5 : 8	M	57
Lepidine	8 : 5 (?)	M	58
4-Methylcinnoline	8	M	56*b*
2-Chloroquinoline	8 : 5	M	59, 60
2-Bromoquinoline	5 : 8	M	61*a*,*b*
3-Chloroquinoline	5 : 8 (?)	M	62*a*,*b*
3-Bromoquinoline	5 : 8	M	63
4-Chloroquinoline	8 : 5	M	62*b*, 64
4-Chlorocinnoline	8	M	65
2 : 4-Dimethylquinoline	8 : 6 : 5 (?)	M	66, 67
2-Chlorolepidine	8 : 6 : 5 (?)	M	68, 69
4-Chloroquinaldine	8 : 5 : 6	M	70
4-Chloro-3-methylquinoline	5 : 8	M	71
2 : 4-Dimethylquinazoline	4-Hydroxy-2-methyl-6-nitroquinazoline	M	72
Carbostyril	6	M	73, 60
2-Alkoxyquinolines	6	M	74
N-Alkylcarbostyrils	6	N	61*b*
4-Hydroxyquinoline	6 : 8	M	56*b*, 75
	3	N	56*b*
4-Hydroxyquinazoline	6	M	76
4-Hydroxycinnoline	6 : 8	M	77
	6 : 3 (?)	N	77, 56*b*
1-Methyl-4-cinnolone	8	M	56*b*
4-Hydroxyquinaldine	6	M	78, 69
	3	N	70, 79
2-Hydroxylepidine	6	M	80
4-Hydroxy-3-methylquinoline	6 : 8	M	71
2 : 4-Dihydroxyquinoline	3	N	81
7-Chloro-4-hydroxyquinoline	3 (?)	N/AcOH	82
4-Hydroxyquinaldine *N*-oxide	3	(*d*)	83
4-Hydroxy-2-methylquinazoline	6	M	76
2-Aminoquinoline	6[e]	M	84
4-Aminoquinoline	6[e]	M	84, 85
4 : 6-Diaminoquinoline	3	M	86*a*

[a] Only the initial mononitration product is indicated.
[b] As far as possible the major product is named first.
[c] M = "mixed acids"; N = nitric acid.
[d] The *N*-oxide, when treated in hot acetic acid solution with nitric acid, gave 4-hydroxy-3-nitroquinaldine. The *N*-oxide of the latter resulted when nitric acid was added to a dilute sulphuric acid solution of the parent compound.
[e] Through the nitramine.
[f] Cinnoline has given two nitro-compounds, differing from 6-nitrocinnoline. One is identical with 8-nitrocinnoline (Morley, and Alford and Schofield, unpublished).

[55] Claus and Hoffmann, *J. pr. Chem.*, 1893, **47**, 253; Fortner, *Monatsh.*, 1893, **14**, 146; Le Fèvre and Le Fèvre, *J.*, 1935, 1470; Andersag, *Chem. Zentr.*, 1934, I, 3595.
[56] (*a*) Elderfield, Williamson, Gensler, and Kremer, *J. Org. Chem.*, 1947, **12**, 405; (*b*) Schofield and Swain, *J.*, 1949, 1367.

trace of cupric nitrate in acetic anhydride, obtained 7-nitroquinoline, and the same product, together with some 3 : 7-dinitroquinoline, resulted from the reaction between liquid quinoline and dinitrogen tetroxide.[24] These results, and those for some quinoline derivatives and for the other heterocyclic compounds mentioned above, are summarised in Table VI.

It is clear that in the quinoline series (and probably in the *iso*quinoline group also, though the evidence here is not extensive), except for the cases of hydroxy- and amino-derivatives, there is a powerful tendency for nitration to occur at $C_{(5)}$ and at $C_{(8)}$, where that is possible. This is true of *Bz*-substituted quinolines as well, as we have already seen in the case of the further nitration of 6- and 7-nitroquinoline (Table III), some substitution occurring *ortho* to the nitro-group in each case. 6- and 7-Halogenoquinolines

[57] Doebner and von Miller, *Ber.*, 1884, **17**, 1698 ; Gerdeissen, *ibid.*, 1889, **22**, 245 ; Decker and Remfrey, *ibid.*, 1905, **38**, 2773 ; Hammick, *J.*, 1926, 1302.

[58] Busch and Koenigs, *Ber.*, 1890, **23**, 2687 ; Johnson and Hamilton, *J. Amer. Chem. Soc.*, 1941, **63**, 2864 ; Buchman *et al.*, *ibid.*, 1947, **69**, 380.

[59] Fischer and Guthmann, *J. pr. Chem.*, 1916, **93**, 378 ; Deinet and Lutz, *J. Amer. Chem. Soc.*, 1946, **68**, 1325.

[60] Bennett, Crofts, and Hey, *J.*, 1949, 277.

[61] (*a*) Claus and Pollitz, *J. pr. Chem.*, 1890, **41**, 41 ; (*b*) Decker and Pollitz, *ibid.*, 1901, **64**, 85.

[62] (*a*) Edinger and Lubberger, *ibid.*, 1896, **54**, 340 ; (*b*) Baker *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 1532.

[63] Claus *et al.*, *J. pr. Chem.*, 1889, **39**, 301 ; 1893, **48**, 157 ; 1896, **53**, 413 ; Decker, *Ber.*, 1905, **38**, 1274.

[64] Gowley *et al.*, *J. Amer. Chem. Soc.*, 1947, **69**, 303 ; Simpson and Wright, *J.*, 1948, 1707.

[65] Keneford, Morley, and Simpson, *ibid.*, p. 1702.

[66] Price, Velzen, and Guthrie, *J. Org. Chem.*, 1947, **12**, 203 ; Vaughan, *J. Amer. Chem. Soc.*, 1948, **70**, 2294.

[67] Ochiai and Shimizu, *J. Pharm. Soc. Japan*, 1943, **63**, 398.

[68] Johnson and Hamilton, *J. Amer. Chem. Soc.*, 1941, **63**, 2867 ; Krahler and Burger, *ibid.*, 1942, **64**, 2417.

[69] Adams and Hey, *J.*, 1949, 3185.

[70] Halcrow and Kermack, *J.*, 1945, 415.

[71] Adams and Hey, *J.*, 1950, 2092.

[72] Tomisek and Christensen, *J. Amer. Chem. Soc.*, 1948, **70**, 2423.

[73] Friedlander and Lazarus, *Annalen*, 1885, **229**, 233 ; Decker and Kasatkin, *J. pr. Chem.*, 1901, **64**, 85.

[74] Kaufmann and de Petherd, *Ber.*, 1917, **50**, 336.

[75] Morley and Simpson, *J.*, 1948, 2024 ; Adams and Hey, *J.*, 1949, 255.

[76] Bogert and Geiger, *J. Amer. Chem. Soc.*, 1912, **34**, 524 ; Morley and Simpson, *J.*, 1948, 360.

[77] Schofield and Simpson, *J.*, 1945, 512 ; Simpson, *J.*, 1947, 237.

[78] Kermack and (Miss) Weatherhead, *J.*, 1939, 563.

[79] Conrad and Limpach, *Ber.*, 1887, **20**, 948.

[80] Balaban, *J.*, 1930, 2346.

[81] Gabriel, *Ber.*, 1918, **51**, 1500 ; cf. Ashley, Perkin, and Robinson, *J.*, 1930, 382.

[82] Breslow *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 1232.

[83] Gabriel and Gerhard, *Ber.*, 1921, **54**, 1067, 1613.

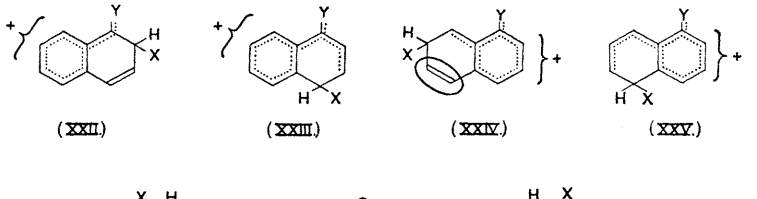
[84] Tschitschibabin, Witkowski, and Lapschin, *ibid.*, 1925, **58**, 803.

[85] Simpson and Wright, *J.*, 1948, 2023 ; Jensch, *Annalen*, 1950, **568**, 73.

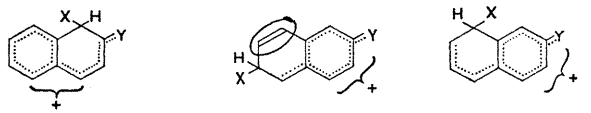
[86] (*a*) G.P. 613,065 (1935) ; F.P. 779,092 (1935) ; (*b*) Kaufmann and Zeller, *Ber.*, 1917, **50**, 1630.

probably behave similarly.[87] The tendency to nitrate at $C_{(5)}$ and $C_{(8)}$ clearly persists in quinoline substituted by one methyl or halogen group in the heterocyclic ring (Table VI), and it is usually supposed that the predominance of the 8-nitro-compound in the nitration product of lepidine is due to a steric effect (although the methyl group in 1-methyl-4-cinnolone appears to exert no hindrance). 4-Methylcinnoline seems to be directly comparable. In view of all these results, the case of quinazoline is of outstanding interest, being the only one so far encountered in this series where the parent heterocyclic compound is nitrated at $C_{(6)}$. The production of 4-hydroxy-2-methyl-6-nitroquinazoline from the action of mixed acids upon 2 : 4-dimethylquinazoline stresses the peculiarity of the quinazoline nucleus.

The orientation of substituents entering heterocyclic molecules has rarely been discussed. Roberts and Turner [88] considered the problem in terms of Thiele's theory, and related the behaviour of quinoline and *iso*quinoline to that of naphthalene. More recently, Dewar [2] has compared these compounds with 1- and 2-nitronaphthalene, respectively. It is interesting to



(XXII.) (XXIII.) (XXIV.) (XXV.)



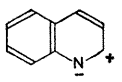
(XXVI.) (XXVII.) (XXVIII.)

examine Dewar's views in some detail, since they illustrate a difficulty always encountered by qualitative discussion of this problem. In examining further substitution into a monosubstituted naphthalene, Dewar enumerates the transition states (XXII → XXV) and (XXVI → XXVIII), the substituent Y already present being electron releasing. These transition states are supposed to contain elements of structure resembling benzyl and phenylallyl cations, and Dewar concludes that an electron-releasing 1-substituent should direct further electrophilic substitution mainly to $C_{(2)}$ and $C_{(4)}$, and less powerfully to $C_{(5)}$ and $C_{(7)}$. [Dewar's analogy to the benzyl cation entirely neglects the portion of the system represented as a circled double-bond in (XXIV) and (XXVII).] A similar 2-substituent likewise activates the adjacent 1-position strongly, and the 6- and 8-positions weakly. With an electron-attracting first substituent the position is reversed, and Dewar is led to state that in 1-nitronaphthalene, for example, the 5- and 7-positions

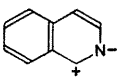
[87] Claus and Schedler, *J. pr. Chem.*, 1894, **49**, 359; Gilman *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 1577; Claus and Junghanns, *J. pr. Chem.*, 1893, **48**, 253; La Coste, *Ber.*, 1885, **18**, 2940; Andersag, *Chem. Ber.*, 1948, **81**, 499.

[88] *J.*, 1927, 1832.

will be deactivated more strongly than the 6- and 8-positions, whilst in 2-nitronaphthalene the 6- and 8-positions will be more strongly deactivated than $C_{(5)}$ and $C_{(7)}$. Thus, nitration of 1-nitronaphthalene should give 1 : 8- and 1 : 6-dinitronaphthalene, whilst 2-nitronaphthalene should provide 1 : 6-, (2 : 5)-, and 2 : 7-dinitronaphthalene. This expectation is only partly in accordance with experiment. In fact, 1-nitronaphthalene when nitrated in sulphuric acid yields 1 : 8- (64%) and 1 : 5-dinitronaphthalene (36%),[89] whilst 2-nitronaphthalene under the same conditions gives 1 : 3 : 8-trinitronaphthalene, but in glacial acetic acid it provides 1 : 6- and 1 : 7-dinitronaphthalene.[90] Proceeding then to discuss quinoline and *iso*quinoline, Dewar states that " both undergo substitution in the benzene ring exclusively, and in the 5- and 8-positions for the same reasons that mononitronaphthalenes give 5- and 8-substitution products ". The previous argument implies, rather, that quinoline should give 6- and 8-nitroquinoline, and that *iso*quinoline should be converted into 5- and 7-nitro*iso*quinoline. The same difficulty arises if, instead of considering transition states, one simply writes down the various resonance forms of the types (XXIX) and (XXX).[91] Waters [29] has referred to the transition-state theory of aromatic



(XXIX)



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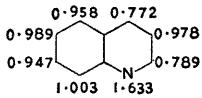
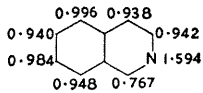


(XXXI)



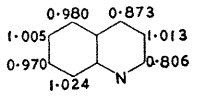
(XXXII)

substitution in this connection. Discussing naphthalene, he points out that, since the transition state for 1-substitution is related to that for 2-substitution as are 1 : 4- and 1 : 2-naphthaquinone, the former should be the more stable and 1-substitution should be favoured. Similar arguments apply to quinoline and *iso*quinoline, although the limitations of this viewpoint are severe since, like those already discussed, it tells us nothing of the relative ease of substitution of $C_{(5)}$ compared with $C_{(8)}$. Measurements of oxidation–reduction potentials of heterocyclic quinones related to this question are satisfactory as far as they go.[92] Quinazoline is interesting in the light of this suggestion, and it may be that in this case,[56b] as well as with 2 : 4-dimethylquinoline, 2-chlorolepidine, and 4-chloroquinaldine (see Table VI), the *amphi*-quinonoid form of the activated complex is of importance.

This account of attempts to explain the orientation of substituents entering quinoline and related molecules would be incomplete without reference to recent quantum-theory calculations, which promise eventually to provide a quantitative estimate of the reactivities of the several positions in heterocyclic nuclei. Earlier workers concentrated on evaluating the net charges (π-electron distributions) on the nuclear carbon atoms. Depending on whether molecular-orbital or valence-bond theory is used, and also on the

[89] Hodgson and Whitehurst, *J.*, 1945, 202.
[90] Vesely and Jakeš, *Bull. Soc. chim.*, 1923, **33**, 952.
[91] Schofield and Swain, *Nature*, 1948, **161**, 690.
[92] Fieser and Martin, *J. Amer. Chem. Soc.*, 1935, **57**, 1840.

somewhat arbitrary choice of parameters, slightly different results are obtained, but on the whole the theories agree satisfactorily about the relative values of the charges at the nuclear positions. The earlier calculations of Longuet-Higgins and Coulson [93a] from molecular-orbital theory might be used as an illustration. They give for quinoline and *iso*quinoline the π-electron densities shown in (XXXI) and (XXXII). Taken alone, these results indicate that in quinoline and *iso*quinoline susceptibility to electrophilic attack would decrease in the order $C_{(8)} > C_{(6)} > C_{(3)} > C_{(5)}$, etc., and $C_{(5)} > C_{(7)} > C_{(8)} > C_{(3)}$, etc., respectively (availability of electrons being assumed to be the controlling factor [93b]). These sequences do not wholly fit the facts of nitration (or sulphonation) and it soon became clear that, since differences between charges at different positions are small, other factors must be taken into account. Other quantities now used are the bond order, the free-valency index, the polarisability, and the potential



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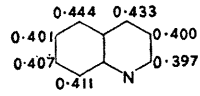

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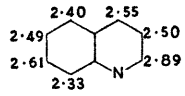
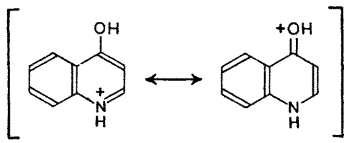


(XXXV.)



(XXXVI.)

barrier.[93b,c] It is beyond the scope of this article, and the competence of the Reviewer, to discuss these quantities closely, but it can be said that the last three are of significance in substitution reactions. The potential barrier [93b] is a quantitative means of accommodating the relative stabilities of transition states associated with substitution at various points, and the polarisability measures the ease with which the electron density at a particular point may be augmented during a substitution reaction. As an example we might consider a recent paper by Sandorfy and Yvan.[93d] These authors give figures for the charge (XXXIII), the polarisability (XXXIV), and the potential barrier (XXXV) for quinoline in electrophilic substitutions as shown. Charges being considered, the decreasing order of reactivity to

[93] (*a*) *Trans. Faraday Soc.*, 1947, **43**, 87; (*b*) Wheland, *J. Amer. Chem. Soc.*, 1942, **64**, 900; (*c*) Pauling, Brockway, and Beach, *ibid.*, 1935, **57**, 2705; Penney, *Proc. Roy. Soc.*, 1937, *A*, **158**, 306; Daudel and Pullman, *J. Physique*, 1946, **7**, 59, 74, 105; Coulson and Longuet-Higgins, *Proc. Roy. Soc.*, 1947, *A*, **191**, 39; (*d*) *Compt. rend.*, 1949, **229**, 715; *Bull. Soc. chim.*, 1950, 131; (*e*) Pullman, *Rev. Sci.*, 1948, **86**, 219; Daudel, *Compt. rend.*, 1948, **227**, 1241; Coulson, Daudel, and Daudel, *Bull. Soc. chim.*, 1948, 1181; Daudel, Buu-Hoï, and Martin, *ibid.*, p. 1202; Sandorfy, *ibid.*, 1949, 615; Longuet-Higgins and Coulson, *J.*, 1949, 971; Yvan, *Compt. rend.*, 1949, **229**, 622; Buu-Hoï and Daudel, *Bull. Soc. chim.*, 1949, 801; Sandorfy, Vroelant, Yvan, Chalvet, and Daudel, *ibid.*, 1950, 304.

electrophilic reagents would be $C_{(8)} > C_{(3)} > C_{(6)} > C_{(5)}$, etc., but the differences are small and the potential-barrier diagram gives the sequence $C_{(8)} > C_{(5)} > C_{(6)} > C_{(3)}$, etc. Only by considering the lower potential barrier (or the higher polarisability) of $C_{(5)}$ is that position given its correct place.

In the manner indicated a fairly complete picture of the reactivities of heterocyclic nuclei is being built up.[93e] None of the theoretical work so far published has allowed for protonisation of these heterocyclic molecules, so important in nitration and sulphonation. In view of the success of the theory, and of the behaviour of the nitronaphthalenes, it seems likely that protonisation does not change the site of substitution in these cases, but merely increases the degree of 5-substitution in quinoline and of 8-substitution in *iso*quinoline. Furthermore, free quinoline would nitrate more quickly than the quinolinium ion, and the two would be in equilibrium in solution. It is therefore interesting that nitration of the methylquinolinium ion, which cannot dissociate, gives the 5- and the 8-nitro-compound, the former apparently predominating. Nitration of some substituted methylquinolinium ions also appears to proceed mainly at $C_{(5)}$.[94] It should be mentioned, however, that in many halogenations, some of which may be electrophilic substitutions, but in which protonisation would not be important, initial substitution occurs at $C_{(3)}$.[95]

There can be no doubt that the nitrations discussed above proceed by electrophilic substitution, involving in most cases the nitronium ion. It therefore seems likely that in the reactions which convert quinoline into 7-nitroquinoline (Table VI) some other mechanism is involved. There is no evidence on this point.

The hydroxy-heterocyclic compounds (Table VI) present an interesting problem. Various facts discussed in this Review make it doubtful whether the nitration of these weakly basic compounds (Table I) in sulphuric acid can be referred solely to protonised forms [*e.g.*, (XXXVI)], in which substitution would be expected to occur at $C_{(6)}$ or $C_{(8)}$, as has been previously argued,[56b, 70] and the same facts make unlikely the suggestion [56b] that 4-hydroxyquinoline derivatives, for example, are extensively protonised in nitric acid alone. However, if some of the nitration of these compounds in sulphuric acid is referred to unprotonised forms, it is difficult to explain the absence in the products of appreciable quantities of 3-nitro-compounds, the major products when nitric acid alone is used. Halcrow and Kermack [70] suggested that the 3-nitro-compounds arose as the result of the directing properties of the hydroxyl group in the unprotonised heterocyclic compounds, but the above discussion makes this uncertain, and the effect of nitrous acid may be important.[56b] It is noteworthy that other electrophilic substitutions, namely halogenations, in which protonisation is unlikely, proceed readily at $C_{(3)}$ in 4-hydroxyquinoline derivatives, and somewhat less readily at the same position in 4-hydroxycinnolines.[96]

[94] Decker, *Ber.*, 1905, **38**, 1274.

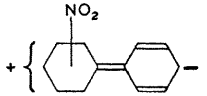
[95] Manske, *Chem. Reviews*, 1942, **30**, 137 ; Beilstein's " Handbuch der Organischen Chemie ", 4th edtn., Vol. 20, p. 342.

[96] Schofield and Swain, *J.*, 1950, 384.

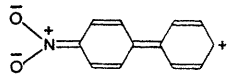
The entries in Table VI concerning 2- and 4-aminoquinoline recall the behaviour of the aminopyridines. It is interesting that 4 : 6-diaminoquinoline and its 6-acetyl derivative should give 3-nitro-compounds [86a] (it is not clear whether this proceeds through nitramine formation or not), whilst 6-toluene-*p*-sulphonamidoquinoline when nitrated with nitric acid alone gives the 5-nitro-derivative.[86b]

V. Phenyl-substituted Heterocyclic Compounds

Several workers have described the nitration of phenyl-substituted heterocyclic compounds. This makes possible an interesting comparison of different heterocyclic groups with phenyl itself, as substituents in the benzene ring, throwing light on the problem of conjugation between linked aromatic systems, and on the question of the effect of protonisation already raised in this Review. The cases so far reported are summarised in Table VII. Unfortunately, not all of the nitrations were effected under the same conditions.



(XXXVII)



(XXXVIII)

It is profitable to consider first the related nitrodiphenyls, and these compounds are therefore included in Table VII. They are a striking example of the " constancy of type of substitution ",[97] *o*-, *m*-, and *p*-nitrophenyl showing the same *op*-directing properties as phenyl itself. Dewar [98] has included phenyl among the $+E$ substituents [99] and has deduced that for this category the *o* : *p*-ratio should fall as the electron affinity of the group rises. 2 : 4-Dinitrophenyl appears to be misplaced in the series. Dewar also suggests that steric influences tend to decrease the ratio, forcing us to conclude that in the present case such influences are of minor importance. This is strange since, if we assume the substituents to be of the $+E$ type, we imply that planar terms of the type (XXXVII) contribute to the structures of the diphenyl derivatives, which would lead us to expect a degree of steric interference in such cases as that of 2-dinitrodiphenyl. Early workers [100] concluded from the absence of *meta*-substitution in this series that the nuclei behaved independently, *i.e.*, that conjugation between them was unimportant and, further, since the *o* : *p*-ratio for 2- and 4-dinitrodiphenyl was very similar, that steric factors were not important here. The problem is complicated, and the inadequacy of naïve resonance pictures [*e.g.*, (XXXVIII)] which would lead us to expect *meta*-substitution is stressed.

Gull and Turner [100] suggested that in the case of diphenyl derivatives, if a sufficiently strongly polarising group could be introduced into one of

[97] Waters, *Chem. Reviews*, 1930, **7**, 407.
[98] *J.*, 1949, 463.
[99] Ingold's nomenclature is used in this Review.
[100] Gull and Turner, *J.*, 1927, 491.

TABLE VII

Nitration of phenyl-substituted heterocyclic compounds

R in R·C_6H_5.	Isomers, % :			Conditions.	Ref.
	o-.	*m*-.	*p*-.		
2-Pyridyl	5	34·9	42·3	Nitrate added to H_2SO_4	101
3-Pyridyl	?	?	64·3	,, ,, ,, ,,	101
4-Pyridyl	12·7	28·5	38·0	,, ,, ,, ,,	101
2-Quinolyl + 2-C_9H_6NMe	small	30	60	Base added to HNO_3	102
	—	97	—	,, ,, ,, ,,	102
4-Quinolyl	5	40	50	,, ,, ,, ,,	103
2-$C_5H_4N·CH_2$	—	10·4	66·7	Nitrate added to H_2SO_4	104
3-$C_5H_4N·CH_2$	—	—	63·1	,, ,, ,, ,,	104
4-$C_5H_4N·CH_2$	—	4·8	70·2	,, ,, ,, ,,	104
2-$C_5H_4N·[CH_2]_2$	16·0	3·4	64·5	HNO_3 alone, or with H_2SO_4. Ratios changed but little	105
2-$C_5H_4N·CH{:}CH$	40·1	nil	49·0	Variety of conditions	105
2-Benzopyrylium	—	86	—	Perchlorate added to HNO_3	106
4-Glyoxalinyl	25	—	69	Nitrate added to H_2SO_4	107
2-Glyoxalinyl	1·5	0·2	50	,, ,, ,, ,,	108
2-Glyoxaline-4 : 5-dicarboxylic acid	—	52	19	Mixed acids	108
2-Glyoxaline-4-carboxylic acid	—	52	19	Nitrate added to H_2SO_4	108
2-(4 : 5-Dihydroglyoxalinyl)	—	80	—	,, ,, ,, ,,	109
2-Nitrophenyl	39	—	61	HNO_3	100
4-Nitrophenyl	37	—	63	,,	100
2 : 4-Dinitrophenyl	45	—	55	,,	100

the rings, some *meta*-substitution might occur in the other. In passing from the diphenyl to the phenylpyridine series this state of affairs appears to have been reached with respect to nitration, for whilst in this reaction substitution still occurs predominantly *ortho-para*, considerable quantities of *m*-nitro-compounds now appear. Phenylpyridines and phenylquinolines appear therefore to fall into the category of anomalous compounds which undergo *meta-para* rather than *ortho-para* substitution, but the explanation is presumably that we are observing the nitration of both protonised and unprotonised forms of the compounds, the former being responsible for the appearance of *m*-nitro-compounds. As Flürscheim indicated,[101] it is difficult to predict the orientation accurately in such cases because nothing is known of the relative rates of substitution of protonised and unprotonised forms (except that the former will be the greater). Thus, whilst predictions of

[101] Forsyth and Pyman, *J.*, 1926, 2912. This paper contains interesting notes by Flürscheim, Ingold and Robinson.

[102] Le Fèvre and Mathur, *J.*, 1930, 2236.

[103] Koenigs and Nef, *Ber.*, 1887, **20**, 622 ; Koenigs, *ibid.*, 1893, **26**, 713 ; Besthorn and Jaeglé, *ibid.*, 1894, **27**, 907 ; Besthorn, Banzhof, and Jaeglé, *ibid.*, p. 3035.

[104] Bryans and Pyman, *J.*, 1929, 549.

[105] Shaw and Wagstaff, *J.*, 1933, 79.

[106] Le Fèvre, *J.*, 1929, 2771.

[107] Grant and Pyman, *J.*, 1921, 1893.

[108] Pyman and Stanley, *J.*, 1924, 2484.

[109] Forsyth, Nimka, and Pyman, *J.*, 1926, 800.

the direction of nitration of phenylpyridines in a general sense were possible,[101] the significance of the observed *o* : *p*-ratios is at present obscure.

Similar remarks apply to the phenylquinolines, and it is interesting to see that when the dissociation $[(NR_3H)^+ \rightleftharpoons NR_3 + H^+]$ is not possible, as is the case with methyl-2-phenylquinolinium, *meta*-substitution occurs exclusively (see 2-phenylbenzopyrylium also).

As would be expected, with the benzylpyridines the amount of *meta*-substitution is less than with the phenylpyridines. The *meta*-substitution must be attributed to protonisation, but comparison with the case of $Ph{\cdot}CH_2{\cdot}\overset{+}{N}Me_3$ (88% *meta*) [110] shows that this cannot be regarded as effectively complete. Again, as would be expected, the amount of *meta*-nitration varies in the order 2 > 4 > 3.

2-2′-Phenylethylpyridine is nitrated to an even smaller extent in the *meta*-position than are the benzylpyridines, because of the further removal from the phenyl group of the *meta*-directing positive charge in the protonised form, and it is noteworthy that the variation in *o* : *p*-ratio with change in nitrating medium was found to be very small.[105] This is not surprising, since the inductive effect will fall off rapidly along the ethyl chain, and the phenyl group will consequently be insensitive to small changes in the degree of protonisation of the pyridyl residue. [Even with $Ph{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{N}Me_3$, (*o* + *p*)-compounds account for 81% of the product.[110]]

2-Stilbazole (*trans*-?) is the only compound of the type now under discussion for which thorough studies of the variation in *o* : *p*-ratio with change in nitrating medium have been made.[105] The ratio varies considerably (0·37—0·56 for $\frac{1}{2}o : p$). In the absence of sulphuric acid, increase in concentration combined with decrease in quantity of nitric acid decreases the ratio. Addition of soluble nitrates or acetic acid to the nitric acid increases the ratio, but to a smaller extent than an equal weight of water. Nitration in sulphuric acid gives ratios (0·42—0·46) equal to those obtained with 87—92% nitric acid. These variations were attributed to changes in the base–salt–ion equilibria, but a satisfactory theory of the *o* : *p*-ratio was not available at the time. In terms of Dewar's calculations, if we attribute to the pyridylethylene group a + *E* effect, 2-stilbazole is seen to bear a striking resemblance to acetanilide.[98] As the concentration of nitric acid increases, or when sulphuric acid is used, the degree of protonisation of the pyridyl group will be increased; *i.e.*, the electron-affinity of the substituent will be increased, and the *o* : *p*-ratio would be expected to fall, as is actually the case. The observed ratios (which must be regarded as the over-all figures for nitration of both protonised and unprotonised forms) are in the same range as those for other + *E* substituents. These results provide a clear demonstration of the intervention of free base—protonised base equilibria in determining the proportions of isomers formed from compounds of this type, a factor which has likewise been shown to be of importance in oxygen compounds capable of protonisation.[111]

[110] Ingold, *Rec. Trav. chim.*, 1929, **48**, 805; *Ann. Reports*, 1926, **23**, 131.
[111] Baker, *J.*, 1931, 307; Baker and Hey, *J.*, 1932, 1236, 2917.

The phenylglyoxalines (Table VII) seem to represent border-line cases between the nitrodiphenyls and the phenylpyridines. Although in the diphenyl series a nitro-group is not powerful enough to change the directive character of the phenyl group, it appears that in the glyoxaline series carboxyl groups are able to some extent to convert the heterocyclic nucleus containing them into a *meta*-directing entity.

VI. Conclusion

The field reviewed is clearly in need of quantitative investigation, not only kinetically, but also with regard to the proportions of isomers formed in the nitration of a given compound, with due consideration of the effect on these proportions of variations in reaction media.

The evident importance of polarisability factors in some of the nitrations discussed is an interesting vindication of the general ideas of the English school of theoreticians.[112] Accurate experimental testing of quantum-mechanical calculations regarding heterocyclic compounds is a field as yet untouched.

[112] Remick, " Electronic Interpretations of Organic Chemistry ", 2nd edtn., New York, 1949, Chapter V.