The Chemistry of Arylhydrazones

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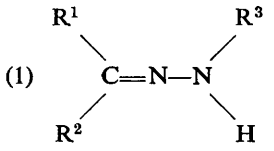
1 Introduction

Arylhydrazone chemistry owes its foundation to Emil Fischer, who discovered phenylhydrazine[1] and showed[1,2] that it combines with carbonyl compounds, to form substances of general formula (1a).



(1)

a; R^3 = Aryl b; R^3 = Alkyl c; R^3 = $CO{\cdot}NH_2$

In seeking to extend this reaction, he discovered both the Fischer indole cyclisation and the osazone reaction, which later became the key to much of carbohydrate chemistry.

There are similarities between the properties of arylhydrazones and those of other types of hydrazone, for example alkylhydrazones (1b) and semicarbazones (1c), but also important differences.[3]

The present-day importance of arylhydrazones lies in three factors. Firstly, they form one of the main classes of insoluble derivative by means of which carbonyl compounds are commonly characterised (unlike the alkylhydrazones, which usually have an unfavourable equilibrium constant of formation and low melting-point). Although phenylhydrazine remains an adequate reagent for the characterisation of many individual aldehydes and ketones, as a routine tool it was replaced, first by *p*-nitrophenylhydrazine,[4] and later by 2,4-dinitrophenylhydrazine (DNPH),[5] because their derivatives are coloured, often more highly crystalline, and less prone to oxidation and cyclisation. Dinitrophenylhydrazones (DNPs) in particular have an extensive analytical chemistry.

Secondly, arylhydrazones are important as intermediates in the preparation

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[1] E. Fischer, *Annalen*, 1877, **190**, 67.
[2] E. Fischer, *Ber.*, 1884, **17**, 572.
[3] For a general summary of the chemistry of hydrazones and related substances, see P. A. S. Smith, 'The Chemistry of Open-chain Organic Nitrogen Compounds', Benjamin, New York, vol. II, 1965.
[4] E. Bamberger, *Ber.*, 1899, **32**, 1806; W. A. van Ekenstein and J. J. Blanksma, *Rec. Trav. chim*, 1903, **22**, 434.
[5] (*a*) C. F. H. Allen, *J. Amer. Chem. Soc.*, 1930, **52**, 2955; (*b*) C. F. H. Allen and J. H. Richmond, *J. Org. Chem.*, 1937, **2**, 222; (*c*) O. L. Brady, *J. Chem. Soc.*, 1931, 756.

of many heterocyclic compounds. (Some cannot be prepared without simultaneous cyclisation.)

Thirdly, they undergo a variety of other reactions, which as well as being of intrinsic interest, give products which may themselves be useful in heterocyclic syntheses. Many of these have been recently reinvestigated, with the clarification of phenomena which have been known for many years but which have been misunderstood.

Most work has naturally been done on the arylhydrazones of simple carbonyl compounds, *i.e.* (1a), where R^1 and R^2 are alkyl, aryl, or hydrogen; when one or both is complex, *e.g.* acyl, appreciable differences in properties are usually encountered. Bisarylhydrazones of 1,2-diketones are frequently known as osazones; their chemistry has been reviewed.[6]

2 Nomenclature

Hydrazones are usually named after the carbonyl compounds from which they are (at least in theory) derived; thus benzaldehyde and phenylhydrazine give benzaldehyde phenylhydrazone (1;R^1 = R^3 = Ph, R^2 = H). The original name was 'benzylidenephenylhydrazine'. Some authors have recently reverted to this system (or to 'benzylidenephenylhydrazone'), which is, however, cumbersome when applied to more complex hydrazones.

3 Preparation of Arylhydrazones[7]

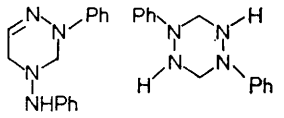
The most important synthesis is of course the reaction of an arylhydrazine with a carbonyl compound. Care may be necessary in the choice of conditions, particularly when the carbonyl compound contains other functional groups, and unnecessarily drastic conditions should in any case be avoided in case of Fischer indole and other cyclisations. Furthermore, arylhydrazines are capable of acting as reducing agents towards carbonyl compounds under forcing conditions.

Phenylhydrazine is completely miscible with most solvents except light petroleum and water, and phenylhydrazones have thus been prepared in a variety of solvents, with or without an acidic catalyst.[2,8,9] Almost quantitative yields are usually obtained in ethanol.[8] The low-melting acetaldehyde phenylhydrazone is conveniently prepared in ether solution, cooled in a freezing mixture.[9] Most nuclear-substituted phenylhydrazines can be employed similarly to the parent compound, but the conditions for the preparation of DNPs require more attention and are considered separately below.

Failure to react has been observed with some sterically hindered ketones, *e.g.* 11-oxo-steroids[10,11] and tetracyclone (tetraphenylcyclopentadienone), which

[6] H. El Khadem, *Adv. Carbohydrate Chem.*, 1965, **20**, 139.
[7] This topic is covered in great detail by E. Enders in Houben-Weyl, 'Methoden der Organischen Chemie', 4th edn., Thieme Verlag, Stuttgart, 1967, vol. X2, p. 171.
[8] P. Grammaticakis, *Compt. rend.*, 1948, **226**, 189.
[9] E. Bamberger and W. Pemsel, *Ber.*, 1903, **36**, 85.
[10] H. Reich, K. F. Crane, and S. J. Sanfilippo, *J. Org. Chem.*, 1953, **18**, 822.
[11] P. Bladon, H. B. Henbest, E. R. H. Jones, B. J. Lovall, G. W. Wood, G. F. Woods, J. Elks, R. M. Evans, D. E. Hathaway, J. F. Oughton, and G. H. Thomas, *J. Chem. Soc.*, 1953, 2921.

reacts with DNPH but not with phenylhydrazine.[12] Difficulties due to steric hindrance may often be overcome by changing the reaction conditions.[13] Formaldehyde likewise forms a normal DNP and *p*-nitrophenylhydrazone, but with phenylhydrazine the reaction is complex, affording glyoxal bisphenylhydrazone and the heterocyclic compounds (2—5).[14] Formaldehyde phenylhydrazone appears to be unknown.*



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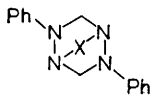
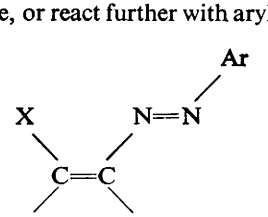
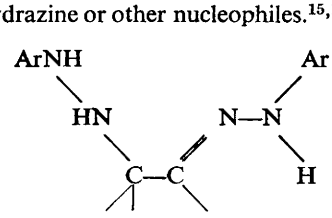


(4) X = CH_2
(5) X = $CH_2 \cdot O \cdot CH_2$

When the aldehyde or ketone has a reactive α- or β-substituent a variety of secondary reactions frequently follow on the initial hydrazone formation; probably the best-known of these is the formation of osazones from α-ketols.[6] An α-halogen or other similar negative α-subsituent normally provokes an elimination reaction, to give an arylazoalkene (6a),[15,16] which may then dimerise, isomerise, or react further with arylhydrazine or other nucleophiles.[15,16] Arylazo-



(6a) X = H
(6b) X = OH



(7)

alkenes (6a) are now thought to be of some significance in the much disputed question of the mechanism of osazone formation;[16] 1,4-addition of a second molecule of arylhydrazine to the azoalkene produces an α-(arylhydrazino)-arylhydrazone (7), which then undergoes oxidation to the osazone, but it is not

* B. V. Ioffe and V.S. Stopskii [*Doklady Akad. Nauk S.S.S.R.*, 1967, **175**, 1064 (*Chem. Abs.*, 1968, **69**, 2624e)] have now described the preparation of formaldehyde phenylhydrazone and its conversion to phenylazomethane by distillation from alkali.

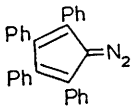
[12] W. Josten, *Ber.*, 1938, **71**, 2230.
[13] D. E. Pearson and F. Greer, *J. Amer. Chem. Soc.*, 1955, **77**, 1294.
[14] E. Schmitz and R. Ohme, *Annalen*, 1950, **635**, 82.
[15] D. Y. Curtin and E. W. Tristram, *J. Amer. Chem. Soc.*, 1950, **72**, 5238; J. van Alphen, *Rec. Trav. Chim*, 1945, **64**, 109; F. D. Chattaway and H. Irving, *J. Amer. Chem. Soc.*, 1932, **54**, 263 and earlier papers; S. Veibel and T. Vrang, *Dansk Tidsskr. Farm.*, 1943, **17**, 112; M. L. Wolfrom, A. Thompson, and D. R. Lineback, *J. Org. Chem.*, 1962, **27**, 2563.
[16] (*a*) L. Caglioti, G. Rosini, and F. Rossi, *J. Amer. Chem. Soc.*, 1966, **88**, 3865; (*b*) J. Buckingham and R. D. Guthrie, *Chem. Comm.*, 1966, 781; (*c*) A. Hassner and P. Catsoulacos, *ibid.* 1967, 121; (*d*) H. Simon, G. Heubach, and H. Wacker, *Chem. Ber.*, 1967, **100**, 3101, 3106.

yet clear to what extent this process is important in osazone formation from α-ketols.

The presence of nitro-groups in the arylhydrazine ring inhibits such secondary reactions; α-halogeno-ketone DNPs are usually isolable,[17] whereas the phenylhydrazones are not.

Arylhydrazones have also been prepared by reaction of arylhydrazines with other derivatives of carbonyl compounds, such as semicarbazones,[18] bisulphite compounds,[8,19] acetals,[8] imines,[8] oximes,[8] and *gem*-dihalogeno-compounds.[8,20] Some heterocyclic compounds, including furans,[21] oxazoles,[22] and isoxazoles[23] have been observed to react with ring-opening to furnish open-chain arylhydrazones or their cyclisation products. Alcohols with two or more unsaturated or aryl groups in conjugation with the hydroxy-group are oxidised by DNPH reagent to the corresponding ketone DNPs, although the yields are not of preparative value; the oxidation mechanism is not known with any certainty.[24]

An important method in certain cases is the isomerisation of mixed azo-compounds $R^1R^2CH{\cdot}N{:}NAr$, by use, where necessary, of heat,[25] acid,[26] or base.[26] Although the reaction is a general one, it is usually of synthetic use only when the azo-compound can be made by a coupling reaction between an aryldiazonium compound and a compound with an active methylene group. This reaction has been reviewed.[27] A special case is the Japp–Klingemann reaction,[28] in which R^1 and R^2 are typically both acyl, and azo-coupling is followed by (usually spontaneous) azo → hydrazone tautomerism accompanied by the elimination of one of them, the product thus being a 1,2-diketone mono(arylhydrazone). Mixed azo-compounds of the type mentioned are also obtained by the reaction of diazo-compounds with organometallic reagents; about the only practical application to date in the synthesis of an arylhydrazone has been the preparation



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[17] (*a*) F. Ramirez and A. F. Kirby, *J. Amer. Chem. Soc.*, 1952, **74**, 4331; 1953, **75**, 6026; (*b*) W. F. McGuckin and E. C. Kendall, *ibid.*, 1952, **74**, 3951.
[18] D. P. Schwartz, *Microchem. J.*, 1962, **6**, 261.
[19] P. Grammaticakis, *Compt. rend.*, 1947, **224**, 1568.
[20] B. Overton, *Ber.*, 1893, **26**, 18; L. Omarini, *Gazzetta*, 1915, **45b**, 304.
[21] J. Levisalles, *Bull. Soc. chim. France*, 1957, 997; I. M. Heilbron, E. R. H. Jones, and H. P. Koch, *J. Chem. Soc.*, 1942, 735.
[22] J. W. Cornforth and R. H. Cornforth, *J. Chem. Soc.*, 1947, 96; H. Bredereck, R. Gompper, F. Reich, and U. Gotsmann, *Chem. Ber.*, 1960, **93**, 2010.
[23] S. Cusmano, *Gazzetta*, 1940, **70**, 227.
[24] E. A. Braude and W. F. Forbes, *J. Chem. Soc.*, 1951, 1762; R. Heilmann and R. Glénat, *Compt. rend.*, 1952, **234**, 1557.
[25] O. Dimroth and M. Hartmann, *Ber.*, 1907, **40**, 4460.
[26] J. Thiele, *Annalen*, 1910, **376**, 239; A. J. Bellamy and R. D. Guthrie, *J. Chem. Soc.*, 1965, 3528.
[27] S. M. Parmerter, *Org. Reactions*, 1959, **10**, 1.
[28] R. R. Phillips, *Org. Reactions*, 1959, **10**, 143.

of the otherwise inaccessible tetracyclone phenylhydrazone from phenyl-lithium and diazocyclopentadiene (8).[29]

Another method is the base-catalysed condensation of amidines $R^1R^2C{:}N{\cdot}NH_2$ with aryl halides; this is useful for diaryl ketone DNPs, where the usual method gives an intractable mixture of stereoisomers.[30]

Preparation of DNPs.—Special techniques are often required to bring about cleanly the reaction of DNPH with specific aldehydes and ketones. This is because of the relative insolubility of DNPH and because many DNPs show geometrical isomerism, polymorphism, and solid-solution formation with each other, with unchanged DNPH, and with unrelated compounds. It has been recommended that the reaction be carried out in the presence of an excess of carbonyl compound;[5b] alternatively, the excess of reagent may be removed with an ion-exchange resin,[31] by oxidation with Benedict's reagent,[10] or by reaction with a second carbonyl compound having an easily separable DNP.[10]

The original DNPH reagent[5] was a solution of DNPH in ethanol containing a strong acid. (Acetic acid has been used, but may cause acetylation of the DNPH.[10,32]) Strong acids, however, may bring about a variety of secondary reactions; esterification,[5b,32a,33] de-esterification,[32b] decarboxylation,[34] epimerisation at nearby asymmetric centres,[35] and elimination,[36–38] alcoholysis,[36] and rearrangement[38] of active halogen atoms, to name but a few. More recent workers have used solvents (diglyme,[39] dioxan,[12,40] dimethylformamide,[41] dimethyl sulphoxide,[41] and diethyl phosphite[42]) in which DNPH is more soluble, in order to prepare the DNPs of sensitive compounds.

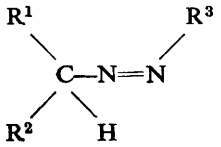
It is widely recognised that, owing to factors already mentioned, melting-point data are insufficient criteria for the identification of DNPs, and that some form of spectroscopy or crystallography (*X*-ray[43] or visible[44]) should always be used in conjunction. Extensive compilations of the spectroscopic characteristics, particularly for u.v. and visible spectra[45] of DNPs have appeared.

4 Arylhydrazone Isomerism

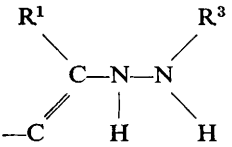
Few topics in the whole of chemistry can have produced as much argument and

[29] P. L. Pauson and B. J. Williams, *J. Chem. Soc.*, 1961, 4162.
[30] M. E. Umstead, *Diss. Abs.*, 1957, **17**, 960.
[31] D. P. Schwartz, A. R. Johnson, and O. W. Parks, *Microchem. J.*, 1962, **6**, 37.
[32] (*a*) H. H. Strain, *J. Amer. Chem. Soc.*, 1935, **57**, 758; (*b*) G. A. Fleisher and E. C. Kendall, *J. Org. Chem.*, 1951, **16**, 556.
[33] E. A. Braude and C. J. Timmons, *J. Chem. Soc.*, 1953, 3131.
[34] R. Braine, *Bull. Soc. chim. belges*, 1954, **63**, 419.
[35] M. Gates and G. Tschudi, *J. Amer. Chem. Soc.*, 1952, **74**, 1109.
[36] D. H. R. Barton and E. Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 370, 5309.
[37] V. R. Mattox and E. C. Kendall, *J. Amer. Chem. Soc.*, 1948, **70**, 882.
[38] C. Djerassi, *J. Amer. Chem. Soc.*, 1949, **71**, 1003.
[39] H. J. Shine, *J. Org. Chem.*, 1959, **24**, 252.
[40] L. M. White and G. E. Secor, *J. Amer. Chem. Soc.*, 1953, **75**, 6343.
[41] J. Parrick and J. W. Rasburn, *Canad. J. Chem.*, 1965, **43**, 3453.
[42] J. A. Maynard, *Austral. J. Chem.*, 1962, **15**, 867.
[43] G. L. Clark, W. I. Kaye, and T. D. Parks, *Ind. and Eng. Chem.* (*Analyt. Edn.*), 1946, **18**, 310.
[44] W. M. D. Bryant, *J. Amer. Chem. Soc.*, 1938, **60**, 2814, and references therein.
[45] Z. Rappoport and T. Sheradsky, *J. Chem. Soc.* (*B*), 1968, 277, and references therein.

speculation, often based on insufficient experimental evidence, as the question of whether arylhydrazones exist only in the normal form (1a), or whether they are capable of tautomerising to the isomeric azo- (9a) and ene-hydrazine (10) forms. The early literature has been summarised;[46a,47] in the words of O'Connor,[46c] 'By 1957 . . . . the question of the tautomerism of phenylhydrazones seemed thoroughly confused'. The situation is further complicated by the ability (in



(9a) R^3 = aryl
(9b) R^3 = alkyl



(10)

theory) of all three forms to exist as geometrical isomers.

Mixed azo-compounds (9a) are well known (although for a time even their separate identity was a subject of contention[48]); on treatment with acid or base they isomerise to the hydrazones (1a).[26] No simple compounds containing the ene-hydrazine grouping (10) are known.

A. Azo-tautomerism.—Here the principal cause of confusion has been the ready oxidation of phenylhydrazones in air to give the yellow phenylazo-hydroperoxides (see below), which have visible and u.v. spectra similar to those of azo-compounds (9). The spectra may, however, be distinguished by careful measurement.[47] The most recent claim that the yellow coloration observed when phenylhydrazone solutions stand in air was that of the mixed azo-compounds (9a) was made by O'Connor and his co-workers;[46] this work was hotly disputed by others,[47,49–51] who used isotopic labelling,[49] n.m.r.[47,50] and other techniques[47,51] to show that neutral solutions of phenylhydrazones are not capable of azo-tautomerism. A claim that tetra-*O*-benzoyl-D-glucose phenylhydrazone exhibits azo-tautomerism has also been refuted.[52]

This finding, however, is still subject to some qualifications. Firstly, the results obtained[48–51] apply to neutral solutions at room temperature; under forcing conditions (*e.g.* in the presence of strong acid or base) the equilibrium may shift to favour the azo-form. Secondly, it is not valid to generalise from one

[46] (*a*) R. O'Connor, *J. Org. Chem.*, 1961, **26**, 4375; (*b*) R. O'Connor and W. Rosenbrook, *ibid.*, 1961, **26**, 5208; (*c*) R. O'Connor, Ph.D. Thesis, University of California; (*d*) R. O'Connor and G. Henderson, *Chem. and Ind.*, 1965, 850.
[47] A. J. Bellamy and R. D. Guthrie, *J. Chem. Soc.*, 1965, 2788.
[48] E. Fischer, *Ber.*, 1896, **29**, 793.
[49] H. Simon and W. Moldenhauer, *Chem. Ber.*, 1967, **100**, 1949.
[50] (*a*) G. J. Karabatsos and R. A. Taller, *J. Amer. Chem. Soc.*, 1963, **85**, 362; (*b*) G. J. Karabatsos, F. M. Vane, R. A. Taller, and N. Hsi, *ibid.*, 1964, **86**, 3351.
[51] A. V. Chernova, R. R. Shagidullin and Yu. P. Kitaev, *Izvest. Akad. Nauk* S.S.S.R., *Ser. khim.*, 1964, 1555.
[52] J. Buckingham and R. D. Guthrie, *J. Chem. Soc.* (*C*), 1967, 2268.

class of hydrazones to another. Two recent publications each support both these viewpoints. Robinson[53] has indicated that the cyclisation of certain *p*-nitrophenylhydrazones to indazoles, which is catalysed by polyphosphoric acid, probably proceeds through the azo-tautomer, and suggests that the presence of the azo-form is due to the presence of the ring nitro-group or to a specific catalytic effect of the polyphosphoric acid. Ioffe and Stopskii[54] were able to prepare a number of mixed azo-compounds (9b) in low yields by distilling alkylhydrazones (1b) from alkali, but were unable to extend the preparation to arylhydrazones, the explanation being[54] that π–p–π conjugation in arylhydrazones increases the relative stability of the hydrazone form.*

The situation is further complicated by the claims of other Russian workers[55] that the azo-compounds (9a) arise not by direct tautomerism but as decomposition products of the phenylazo-hydroperoxides produced by autoxidation, a claim which was also, perhaps, implied in the paper by O'Connor and Henderson.[46d] More work is obviously required in this direction.

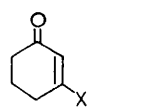
B. Ene-hydrazine Tautomerism.—N.m.r.[50b] and Raman[56] spectroscopy and labelling experiments[49] have likewise failed to detect the ene-hydrazine form (10) in neutral specimens of arylhydrazones; a band in the i.r. spectrum of phenylhydrazones, said[57] to indicate the presence of this form, was recently reattributed.[58] This tautomer, however, is thought to be a transient intermediate in the Fischer indole synthesis[59] and in β-elimination reactions of arylhydrazones,[16b] and has been trapped as the di-*N*-acetate.[60]

C. Complex Arylhydrazones.—The above remarks concern only the arylhydrazones of simple aldehydes and ketones. When one or both of R^1 or R^2 in (1a) is replaced by an acyl or other complex radical, the situation is of necessity different. Thus 1,2-diketone monoarylhydrazones (1a; R^1 = acyl) frequently exist in the azo-enol form (6b);[61] the tautomerism between quinone mono(arylhydrazone)s and arylazo-phenols is well known. Cyclohexane-1,3-dione mono(phenylhydrazone) exists partially in the ene-hydrazine form (11a) and may be readily oxidised to the azo-ketone (11b).[62] A further interesting case is exemplified by the 1,2,3-triketone 1,3-bisarylhydrazones, which exist in the yellow

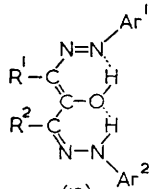
* See footnote on p. 39.

[53] B. Robinson, *Tetrahedron Letters*, 1967, 5085.
[54] B. V. Ioffe and V. S. Stopskii, *Tetrahedron Letters*, 1968, 1333.
[55] A. V. Chernova, R. R. Shagidullin and Yu. P. Kitaev, *Zhur. org. Khim.*, 1967, **3**, 916 (*Chem. Abs.*, 1967, **67**, 53349k).
[56] A. E. Arbuzov, Yu. P. Kitaev, R. R. Shagidullin, and L. E. Petrova, *Izvest. Akad. Nauk* S.S.S.R., *Ser. khim.*, 1967, 1897 (*Chem. Abs.*, 1968, **68**, 29154t).
[57] R. R. Shagidullin, F. K. Sattarova, T. V. Troepol'skaya, and Yu. P. Kitaev, *Izvest. Akad. Nauk* S.S.S.R., *Otdel. khim. Nauk*, 1963, 385.
[58] H. S. Blair and G. A. F. Roberts. *J. Chem. Soc.* (*C*), 1967, 2425.
[59] B. Robinson, *Chem. Rev.*, 1963, **63**, 373.
[60] N. N. Suvorov and N. P. Sorokina, *Doklady Akad. Nauk* S.S.S.R., 1961, **136**, 840.
[61] R. H. Altiparmakian and R. S. W. Braithwaite, *J. Chem. Soc.* (*C*), 1967, 1973.
[62] H-J. Teuber and R. Braun, *Chem. Ber.*, 1967, **100**, 1353.

'normal' form when freshly prepared, but which readily isomerise to the red bischelate form (12).[63–64]



(IIa) X = NH·NHAr
(IIb) X = N:NAr



(12)

D. Geometrical Isomerism.—Geometrical (*syn–anti*) isomerism in arylhydrazones is well known[50b,65] and is mostly responsible for the large number of literature discrepancies concerning the melting points of DNPs. The existence of two forms of acetaldehyde phenylhydrazone is due to geometrical isomerism and not to the previously suggested ene-hydrazine tautomerism.[46a,50b]

The geometrical isomers of simple DNPs are readily interconverted but may be separated by thin-layer chromatography;[66] their stability is increased by the absence of hydrogen atoms α to the arylhydrazone group[30] and by the presence of unsaturated, aromatic, or especially hydrogen-bonding groups in the carbonyl part of the molecule. A particularly well marked case is that of the α keto-acid DNPs in which the *syn*-form is stabilised by intramolecular hydrogen bonding.[67] In the bromination of alkanal DNPs the rate-determining step is the conversion of the *syn*-form into the more reactive *anti*-form; the reaction does not proceed *via* the ene-hydrazine tautomer.[68]

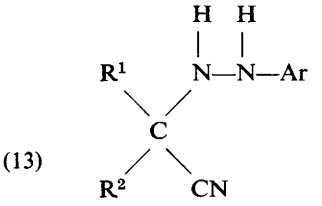
E. Isomerism of Carbohydrate Arylhydrazones.—In the case of the arylhydrazones of monosaccharides, there is the additional possibility of tautomerism between cyclic and acyclic forms, resembling that of the parent sugars. The mutarotation of glucose phenylhydrazone shows that at least three species are present[69] and three solid forms are known,[70] but because of their ready interconversion in solution, chemical methods are probably inadequate for the determination of their structures.[58] In the most recent investigation, based on i.r. spectroscopy, Blair and Roberts[58] have shown that D-mannose and D-galactose phenylhydrazones and the 'β'-form of D-glucose phenylhydrazone are probably

[63] H. S. Isbell and A. J. Fatiadi, *Carbohydrate Res.*, 1967, **5**, 302.
[64] F. W. Lichtenthaler, H. Leinert, and T. Suami, *Chem. Ber.*, 1967, **100**, 2383.
[65] G. J. Karabatsos, J. D. Graham and F. M. Vane, *J. Amer. Chem. Soc.*, 1962, **84**, 753; G. J. Karabatsos, B. L. Shapiro, F. M. Vane, J. S. Fleming, and J. S. Ratka, *ibid.*, 1963, **85**, 2784; G. J. Karabatsos and R. A. Taller, *Tetrahedron*, 1968, **24**, 3923.
[66] H. M. Edwards, *J. Chromatog.*, 1966, **22**, 29.
[67] F. A. Isherwood and D. H. Cruickshank, *Nature*, 1954, **173**, 121.
[68] A. F. Hegarty and F. L. Scott, *J. Org. Chem.*, 1968, **33**, 753.
[69] G. H. Stempel, *J. Amer. Chem. Soc.*, 1934, **56**, 1351; E. G. V. Percival, *Adv. Carbohydrate Chem.*, 1948, **32**, 23.
[70] L. Mester and A. Major, *J. Amer. Chem. Soc.*, 1955, **77**, 4297.

all cyclic, thus questioning earlier work based on acetylation[71] and the formazan reaction.[70] Thus apart from a few sugar *p*-bromophenylhydrazones, the structures of which have been determined by *X*-ray crystallography (some are cyclic and some acyclic),[72] the situation remains confused.

5 Reactions of Arylhydrazones

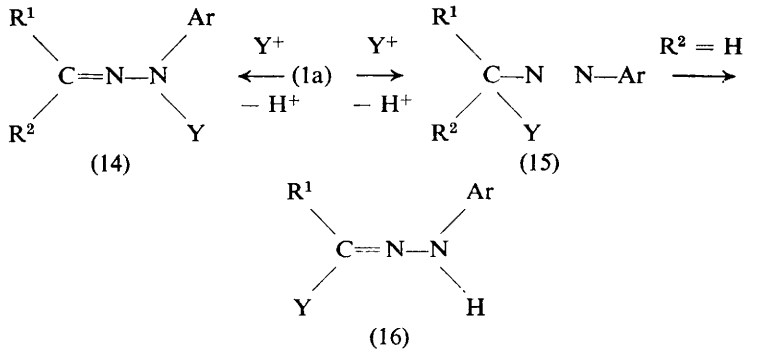
A. General.—Arylhydrazones are amphoteric, forming salts with both strong acids[73] and bases;[74] the presence of nitro-groups in the ring increases the acidity. The tendency of the C=N bond to undergo nucleophilic attack is small; the compounds are not readily hydrolysed (attacked by OH^-), hence their use as analytical derivatives, and there is apparently only one other known reaction, the attack by cyanide ion to produce α-cyano-hydrazines (13)[75] which proceeds in this manner. Most base-catalysed reactions take place only under anhydrous



(13)

conditions and are reactions of the anion, $R^1R^2C{:}N{\cdot}\bar{N}Ar \longleftrightarrow R^1R^2\bar{C}{\cdot}N{:}NAr$.

The most characteristic reactions of arylhydrazones are their attack by electrophilic reagents. The group C:N·NHAr is a good example of a potentially ambidentate nucleophile, *i.e.* the electrophilic attack may theoretically take place at the basic NH nitrogen atom or at the hydrazone carbon atom [see (14—16)] (as well as at the *ortho*- and *para*-positions of the aryl ring). In the latter case, the products have the azo-structure (15).



(14) (15)

(16)

[71] M. L. Wolfrom and C. C. Christman, *J. Amer. Chem. Soc.*, 1931, **53**, 3413.
[72] T. Dukefos and A. Mostad, *Acta Chem. Scand.*, 1965, **19**, 685; K. Bjåmer, S. Furberg, and C. S. Petersen, *ibid.*, 1964, **18**, 587 and references therein.
[73] F. Schmidt, *Annalen*, 1889, **252**, 300.
[74] R. Ciusa, *Gazzetta*, 1920, **50a**, 194; R. Ciusa and G. Rastelli, *ibid.*, 1922, **52b**, 121.
[75] F. Eckstein, *Ber.*, 1892, **25**, 3319.

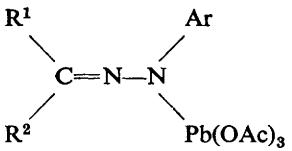
It was at one time thought[76–79] that *N*-substituted compounds (14) were the initial products of many reactions, but more recent investigations have in many cases shown the *C*-substituted nature of the products. Specific cases are further discussed below. When aldehyde arylhydrazones (1a; $R^2 = H$) are concerned, the initial azo-products (15) are capable of isomerising, often rapidly (and irreversibly—see above) to the isomeric hydrazones (16), giving the overall effect of a replacement of the CH proton. Some reactions, notably the formazan reaction, do not take place without the driving force provided by this irreversible isomerisation, and are thus specific for aldehyde arylhydrazones.

The autoxidation of arylhydrazones is thought to be free-radical in character.[80]

B. Oxidation.—The autoxidation of phenylhydrazones proceeds rapidly at room temperature to produce the yellow phenylazo-hydroperoxides (15; Y = O·OH).[47,80,81] The appearance of the arylazo-chromophore meant that autoxidation has several times been confused with azo-tautomerism (see above). The peroxides of low molecular weight are unstable oils[47] but those of steroidal ketones may be recrystallised without decomposition;[81] part of this stability is probably attributable to intramolecular hydrogen bonding.[80b] Phenylazo-hydroperoxides decompose homolytically on treatment with cuprous salts and have been used as radical sources in Sandmeyer and Meerwein arylations.[82] Their decomposition has also been employed in a degradation of hexoses to pentoses.[83]

A reaction formally analogous to autoxidation takes place when arylhydrazones are treated with lead(IV) carboxylates[84] or benzoyl peroxide,[85] when the typical products are arylazo-acyloxy-compounds (15; Y = O·CO·R). (Some aromatic aldehyde arylhydrazones react with lead tetra-acetate to give predominantly *N*-substituted products; these appear, however, to be secondary products derived by rearrangement of the initially formed azo-acetates.[86]) The mechanism of lead tetra-acetate oxidation, unlike that of autoxidation, is ionic;[87] the intermediate (17) undergoes intramolecular breakdown to produce the azo-acetate, or in the presence of alcohols, competing nucleophilic attack to produce azo-ethers (15; Y = OR). Treatment of azo-acetates with base affords indazoles.[88]

[76] (*a*) M. Busch and J. Schmidt, *J. prakt. Chem.*, 1931, **131**, 182; (*b*) H. Hauptmann and A. C. de M. Périssé, *Chem. Ber.*, 1956, **89**, 1081.
[77] M. Busch and H. Kunder, *Ber.*, 1916, **49**, 317.
[78] M. Busch and H. Pfeiffer, *Ber.*, 1926, **59**, 1162.
[79] M. Busch, H. Müller, and E. Schwarz, *Ber.*, 1923, **56**, 1600.
[80] (*a*) K. H. Pausacker, *J. Chem. Soc.*, 1950, 3478; (*b*) R. Criegee and G. Lohaus, *Chem. Ber.*, 1951, **84**, 219.
[81] A. F. Chaplin, D. H. Hey, and J. Honeyman, *J. Chem. Soc.*, 1959, 3194.
[82] F. Minisci and U. Pallini, *Gazzetta*, 1960, **90**, 1318 and references therein.
[83] M. Schulz and L. Somogyi, *Angew. Chem.*, 1967, **79**, 145.
[84] D. C. Iffland, L. Salisbury, and W. R. Schafer, *J. Amer. Chem. Soc.*, 1961, **83**, 747.
[85] J. T. Edward and S. Samad, *Canad. J. Chem.*, 1963, **41**, 1638.
[86] R. N. Butler, *Chem. and Ind.*, 1968, 437.
[87] M. J. Harrison, R. O. C. Norman, and W. A. F. Gladstone, *J. Chem. Soc.* (*C*), 1967, 735.
[88] W. A. F. Gladstone and R. O. C. Norman, *J. Chem. Soc.*, 1965, 3048, 5177.



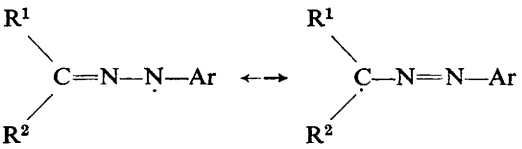
(17)

Peroxyacids oxidise aromatic aldehyde arylhydrazones to the high-melting so-called 'hydrazone oxides', which were eventually shown to be mixed aliphatic–aromatic azoxy-compounds[89–90] with structure (18), *i.e.* the oxidised nitrogen atom is that adjacent to the hydrazone aryl group,[90] contrary to the assignment

(18)

of the earlier workers.[89] A mechanism for the oxidation has been suggested.[91] Interest in this type of compound was stimulated by the occurrence of the aliphatic azoxy-chromophore in the antibiotic Macrozamin.

Yet another type of product is produced when phenylhydrazones are oxidised with reagents such as manganese dioxide,[92] iodine,[93] and ammoniacal silver nitrate.[94] Variable mixtures of dimeric products are obtained; these are derived from the radical species (19) by C—C, C—N, and N—N coupling, followed

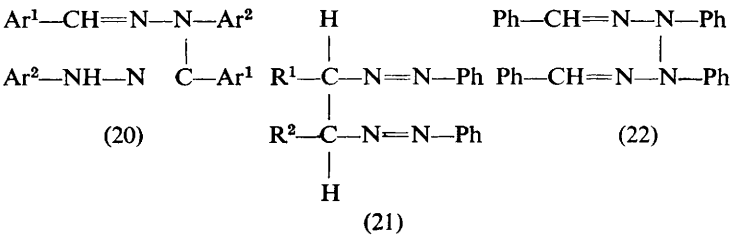


(19)

by secondary reactions.[95] Thus the oxidation of benzaldehyde phenylhydrazone with manganese dioxide[92] afforded, under various conditions, the benzohydrazide hydrazone (20; $Ar^1 = Ar^2 = Ph$), 1,2-diphenyl-1,2-bisphenylazoethane (21; $R^1 = R^2 = Ph$), and the tetrazane (22), together with benzil osazone [by isomerisation of (21)] and biphenyl and 2,4,5-triphenyl-1,2,3-triazole (by oxidation of benzil osazone). Such products may also arise by autoxidation;[95,96] from

[89] B. M. Lynch and K. H. Pausacker, *J. Chem. Soc.*, 1953, 2517; B. Witkop and H. M. Kissman, *J. Amer. Chem. Soc.*, 1953, **75**, 1975.
[90] J. N. Brough, B. Lythgoe, and P. Waterhouse, *J. Chem. Soc.*, 1954, 4069; B. T. Gillis and K. F. Schimmel, *J. Org. Chem.*, 1962, **27**, 413.
[91] J. B. Lee and B. C. Uff, *Quart. Rev.*, 1967, 429.
[92] I. Bhatnagar and M. V. George, *J. Org. Chem.*, 1967, **32**, 2253.
[93] G. Ortoleva, *Gazzetta*, 1903, **33b**, 51; H. Ingle and H. H. Mann, *J. Chem. Soc.*, 1895, 606.
[94] T. W. Milligan and B. C. Minor, *J. Org. Chem.*, 1962, **27**, 4663.
[95] M. F. Grundon and M. D. Scott, *J. Chem. Soc.*, 1964, 5674.
[96] A. J. Bellamy, R. D. Guthrie, and G. J. F. Chittenden, *J. Chem. Soc.* (*C*), 1966, 1989.

adipaldehyde bisphenylhydrazone is obtained 1,2-bisphenylazocyclohexane (21; $R^1R^2 = [CH_2]_4$) by intramolecular dimerisation.[96]

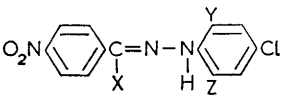


(20) (21) (22)

Strong oxidising agents (chlorine,[97] nitric acid,[97] and selenious acid[98]) oxidise arylhydrazones to the diazonium ion; this constitutes a spot test for arylhydrazones.[98]

C. Halogenation.—The isolation of halogenation products usually requires the presence of nitro-groups in the molecule, which stabilise it towards oxidation by halogen.[97] The type of product isolated depends on the structure of the arylhydrazone.

The first extensive investigations were those of Chattaway and his co-workers,[99] who found that halogenation of the three nitrobenzaldedyde phenylhydrazones takes place at the *ortho*- and *para*-positions of the arylhydrazone ring and at the benzylic (ω) position. Thus from the chlorination of *p*-nitrobenzaldehyde phenylhydrazone the five products (23a—e) were isolated.[99]

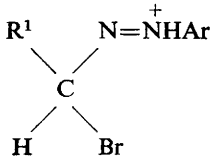


(23)

a; X = Y = Z = H c; X = H, Y = Cl, Z = H
b; X = Cl, Y = Z = H d; X = Y = Cl, Z = H
e; X = Y = Z = Cl

ω-Halogeno-compounds (hydrazidic halides) may be obtained from other types of aldehyde arylhydrazone, and the kinetics of their formation have been studied.[68,100] The typical halogenation mechanism is an S_E2' attack to give the azo-ion (24), followed by rapid proton loss and azo → hydrazone isomerisation, but in some cases the halogenation proceeds by direct S_E2 displacement of the benzylidene proton.[68]

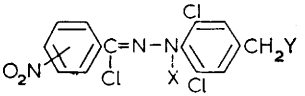
[97] C. Bülow, *Ber.*, 1919, **52**, 632.
[98] F. Feigl, *Mikrochim. Acta.*, 1937, **1**, 127.
[99] F. D. Chattaway and A. J. Walker, *J. Chem. Soc.*, 1925, 1687.
[100] A. F. Hegarty and F. L. Scott, *J. Chem. Soc.*, (*B*), 1966, 1031.



(24)

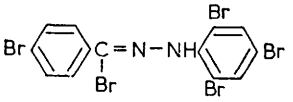
The halogen atom in the hydrazidic halides is highly reactive and they are versatile intermediates in the preparation of heterocyclic and other compounds.[101]

The chlorination of the nitrobenzaldehyde *p*-tolylhydrazones, also studied by Chattaway *et al.*, led to products which, despite the methyl substituent, still contained four chlorine atoms.[102] The initial, labile, products are *N*-chloro-compounds (25a),[102] which readily rearrange to isomers now known[103] to contain the fourth chlorine atom substituted in the *C*-methyl group (25b). This rearrangement resembles the better-known Chattaway–Orton rearrangement of *N*-chloro-amines and the mechanism is presumably similar.[103]



(25a) X = Cl, Y = H (25b) X = H, Y = Cl

Another interesting, though insufficiently understood, halogenation is that of acetophenone phenylhydrazone, which with an excess of bromine in acetic acid gives a pentabromo-hydrazone (26) from which the *C*-methyl group has been lost.[104] Its fate has not been determined.



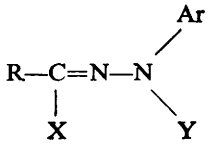
(26)

Aliphatic ketone DNPs may be brominated α to the arylhydrazone function, analogously to the bromination of ketones.[17b,105,106] The resulting α-bromo-ketone DNPs are readily dehydrobrominated to the corresponding $\alpha\beta$-unsaturated ketone DNPs and the arylhydrazone grouping can be removed by a suitable procedure (see below); this is a useful synthesis of $\alpha\beta$-unsaturated ketones. An

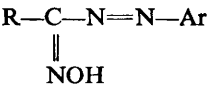
[101] M. S. Gibson, *Tetrahedron*, 1962, **18**, 1377; I. T. Barnish and M. S. Gibson, *J. Chem. Soc.* (*C*), 1968, 8; R. Huisgen, R. Grashey, M. Seidel, H. Knupfer, and R. Schmidt, *Annalen*, 1962, **658**, 169; A. F. Hegarty and F. L. Scott, *J. Chem. Soc.* (*C*), 1967, 2507.
[102] F. D. Chattaway and A. B. Adamson, *J. Chem. Soc.*, 1930, 843.
[103] M. S. Gibson, *J. Chem. Soc.*, 1962, 2270.
[104] J. M. Burgess and M. S. Gibson, *J. Chem. Soc.*, 1964, 1500.
[105] M. Kerfanto and F. Venien, *Compt. rend.*, 1965, **261**, 5535.
[106] V. R. Mattox and E. C. Kendall, *J. Amer. Chem. Soc.*, 1950, **72**, 2290.

alternative method is to brominate the ketone first, then to treat it with DNPH under conditions which lead to dehydrobromination, and finally to remove the DNP group as before. This procedure, the Mattox-Kendall reaction,[37] is milder than conventional methods of dehydrobromination,[38] and has been used for the synthesis of a variety of steroidal ketones, with varying degrees of success.[37,38] It seems to have fallen into disuse recently.

D. Nitrosation.—An interesting series of reactions was discovered by Bamberger and Pemsel,[9,107] who treated some aldehyde phenylhydrazones with nitrous acid. The initial products are labile *C*-nitroso-compounds (27a), which are readily isomerised to azo-oximes (28) and oxidised by an excess of nitrous acid to nitro-hydrazones (27b) and to dimeric oxidation products of the type considered earlier.



(27)



(28)

a; X = NO, Y = H
b; X = NO_2, Y = H
c; X = H, Y = NO

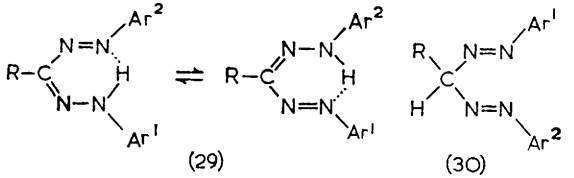
Busch and Kunder[77] re-investigated the reaction, and considered instead that the initial products are *N*-nitroso-compounds (27c), *i.e.* the rearrangement was considered in terms of a nitroso-migration rather than a prototropic shift. They also showed[77] that the nitro-hydrazones are themselves capable of rearrangement, to give aldehyde *p*-nitrophenylhydrazones. In the light of recent work on the mechanisms of arylhydrazone reactions, it seems most likely that Busch's structure (27c) is incorrect and Bamberger's original structure (27a) correct. The reaction scheme may be (15; R^2 = H, Y = NO) ⟶ (27a) ⟶ (28), an interesting example of a three-proton prototropic system.

E. The Formazan Reaction and Related Condensations.—Aldehyde arylhydrazones may condense with diazonium salts under certain conditions at the *para*-position of the aryl ring,[76b] but the typical products are the highly coloured formazans (29).[108–110] N.m.r. studies[108] show that these have the rapidly equilibrating tautomeric structure (29) and not the equivalent mesomeric structure as has also been postulated. The formazan reaction has been much used in structural studies of carbohydrates[109] (but see also Blair and Roberts[58]). Oxida-

[107] E. Bamberger and W. Pemsel, *Ber.*, 1903, **36**, 53, 57.
[108] P. B. Fischer, B. L. Kaul, and H. Zollinger, *Helv. Chim. Acta*, 1968, **51**, 1449.
[109] L. Mester, *Adv. Carbohydrate Chem.*, 1958, **13**, 105.
[110] A. W. Nineham, *Chem. Rev.*, 1955, **55**, 355.

tion of formazans gives the biologically important tetrazolium salts; these are colourless substances used as biological stains; they are reduced back to the coloured formazans at the sites of tissue reduction.[110]

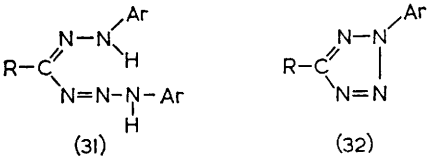
Under carefully controlled conditions, labile yellow intermediates may be isolated from formazan reactions. These were originally thought[76,78] to have the *N*-substituted (tetrazene) structure (14; Y = N:NAr), but have now been shown[111] to be *gem*-bisarylazo-compounds (30). Substituent effects in the formazan reaction resemble those in bromination, indicating a similarity of mechanism.[111a]



(29) (30)

Several related condensations occur between arylhydrazones and other reagents with electron-deficient centres, and produce, at least initially, products with structures analogous to those of the formazan intermediates (30). Some of these may proceed by a straightforward electrophilic attack, but for the reaction with α-carbonyl azo-compounds a mechanism involving a cyclic six-membered transition state has been postulated.[112] In addition, other reactions are known which have not been re-investigated recently, but which will probably turn out to be similar.

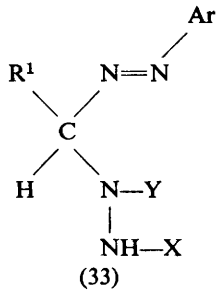
Thus the condensation of aldehyde arylhydrazones with aryl azides produces the *N*-amino-formazans (31), which readily cyclise to tetrazoles (32).[113] Diazo-



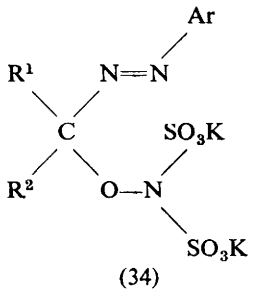
(31) (32)

acetic ester and α-carbonyl azo-compounds afford the products (33a) and (33b) respectively,[112] again correcting earlier structural assignments.[79] Dipotassium nitrosobisulphate similarly gives the azo-adducts (34).[114]

[111] (*a*) A. F. Hegarty and F. L. Scott, *Chem. Comm.*, 1966, 622; (*b*) F. A. Neugebauer and H. Trischmann, *Annalen*, 1967, **706**, 107.
[112] E. Fahr and H-D. Rupp, *Annalen*, 1968, **712**, 93.
[113] O. Dimroth and S. Merzbacher, *Chem. Ber.*, 1910, **43**, 2899; F. D. Chattaway and G. D. Parkes, *J. Chem. Soc.*, 1926, 113.
[114] H-J. Teuber and K-H. Dietz, *Angew. Chem. Internat. Edn.*, 1966, **5**, 1049.



(33)

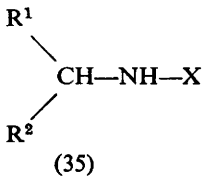


(34)

a; X = Y = CO_2Et
b; X = alkyl, Y = acyl

Aromatic aldehyde arylhydrazones can be tricyanovinylated at the *para*-position of the hydrazone ring to give highly coloured products which were stated to have dyestuff potential.[115] When the *para*-position is blocked, yellow or orange products are obtained instead;[115] these were stated [115] to be *N*-substituted, but may equally well be azo-compounds analogous to those already considered. Similar remarks apply to the products obtained with maleic anhydride.[116]

F. Reduction.—Arylhydrazones (1a) may be reduced to the (2-arylhydrazino)-alkanes (35a) and thence to the amines (35b); they are reduced less easily than



(35)

a; X = NHAr
b; X = H

oximes.[117] The most usual reagent for the reduction to the hydrazino-compound (35a) now seems to be lithium aluminium hydride, although dimeric products may also result;[118] controlled catalytic reduction[119] and sodium amalgam[120] have also been used. The lithium aluminium hydride reduction is subject to neighbouring group participation in the presence of suitably oriented neighbouring hydroxy-groups.[121]

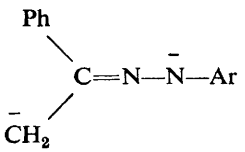
[115] J. R. Rowland and B. C. McKusick, *J. Amer. Chem. Soc.*, 1961, **83**, 1652.
[116] G. La Parola, *Gazzetta*, 1935, **65**, 624.
[117] P. Moses, R. Dahlbom, and B. Sjöberg, *Arkiv. Kemi*, 1964, **22**, 451.
[118] S. G. Cohen and C. H. Wang, *J. Amer. Chem. Soc.*, 1955, **77**, 3628.
[119] R. C. Goodwin and J. R. Bailey, *J. Amer. Chem. Soc.*, 1925, **47**, 167.
[120] E. Fischer and F. Jourdan, *Ber.*, 1884, **16**, 2241.
[121] G. J. F. Chittenden and R. D. Guthrie, *J. Chem. Soc.* (*C*), 1966, 1508.

A variety of reducing agents have been used for the reduction to the amine (35b); this is a valuable synthesis of amino-sugars[64,121,122] and amino-acids.[123,124] The starting materials for the latter compounds are α-keto-acid arylhydrazones, which are often prepared by a coupling reaction; this reduction is also used to characterise the α-keto-acid DNPs, which because of their well marked geometrical isomerism are often difficult to identify.[124,125] The method is not always quantitative, however, especially when applied to aromatic keto-acids, because of simultaneous hydrogenation of the aromatic ring.[125]

The polarographic reduction of arylhydrazones has been extensively investigated by Kitaev, Troepol'skaya, and their co-workers; the results were earlier interpreted in favour of tautomerism to azo- and ene-hydrazine forms, but this seems to have been amended in the latest paper.[126]

G. Base-catalysed Reactions and *N*-Substitutions.—The NH proton of arylhydrazones is weakly acidic; the acidity is increased by the presence of nitro-groups in the ring (the pK_a values of aromatic aldehyde DNPs are about 11[127]). Various nitro-substituted arylhydrazones are useful as indicators[128] and highly coloured alkali-metal salts may be prepared; treatment of these with alkyl halides causes *N*-alkylation.[74] The anions of the much more weakly acidic phenylhydrazones have been prepared in liquid ammonia solution; again, addition of alkyl halides leads to *N*-alkylation, and this is the best route to arylalkyl hydrazones.[129] Under the same conditions, acetophenone phenylhydrazones give rise to both mono- and di-anions (36); the monoanions undergo *N*-alkylation, whereas the dianions are preferentially alkylated at carbon.[130]

N-Acetylation,[73,131] *N*-benzoylation,[131b,132] and other related substitutions at

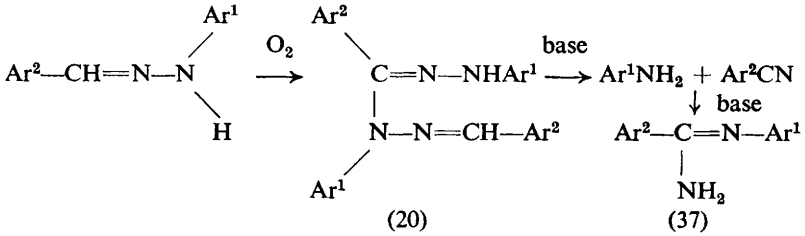


(36)

[121] M. L. Wolfrom and J. L. Minor, *J. Org. Chem.*, 1965, **30**, 841, and earlier papers; Y. Matsushima and Y. Imanaga, *Nature*, 1953, **171**, 475.
[123] E. Fischer and R. Groh, *Annalen*, 1911, **383**, 363; V. Feofilatkov and N. K. Semenova, *Zhur. obschei Khim.*, 1953, **23**, 450 and earlier papers.
[124] G. H. N. Towers, J. F. Thompson, and F. C. Steward, *J. Amer. Chem. Soc.*, 1954, **76**, 2392.
[125] J. H. Menkes, *Nature*, 1961, **191**, 285.
[126] Yu. P. Kitaev and T. V. Troepol'skaya, *Izvest. Akad. Nauk* S.S.S.R., *Ser. khim.*, 1967, 1903 (*Chem. Abs.*, 1968, **68**, 29155u).
[127] L. A. Jones and N. L. Mueller, *J. Org. Chem.*, 1962, **27**, 2356.
[128] N. V. Chugreeva, *Zhur. analit. Khim.*, 1960, **15**, 391 and earlier papers; M. Kambe, Y. Hasegawa, and E. Shindo, *Japan Analyst*, 1964, **13**, 1218; M. Z. Barakat, S. K. Shehab and M. M. El-Sadr, *Analyst*, 1958, **83**, 695.
[129] W. G. Kenyon and C. R. Hauser, *J. Org. Chem.*, 1965, **30**, 292.
[130] F. E. Henoch, K. G. Hampton, and C. R. Hauser, *J. Amer. Chem. Soc.*, 1967, **89**, 463.
[131] (*a*) K. v. Auwers, *Ber.*, 1917, **50**, 1585; (*b*) P. Grammaticakis, *Bull. Soc. chim. France*, 1940, 527.
[132] H. El Khadem, *J. Org. Chem.*, 1964, **29**, 2073; H. El Khadem, Z. M. El-Shafei, and M. M. Mohammed Ali, *ibid.*, 1964, **29**, 1565.

nitrogen[131b] may be carried out on arylhydrazones under forcing conditions. Perbenzoylation of hexose phenylhydrazones leads to hexabenzoates containing five *O*-linked and one *N*-linked benzoyl group.[132]

The products isolated when arylhydrazones are heated with strong bases depend on the nature of the hydrazone substitution. Benzophenone[133] and tetracyclone[134] arylhydrazones gave low yields of Wolff-Kischner reduction products, but aromatic aldehyde arylhydrazones, which cannot undergo the Wolff-Kischner reduction, afford mostly aryl cyanides and arylamines.[95,135] The reaction is catalysed by air and is thought to proceed mostly by base-catalysed breakdown of the hydrazidine autoxidation product (20).[95] Amidines (37),

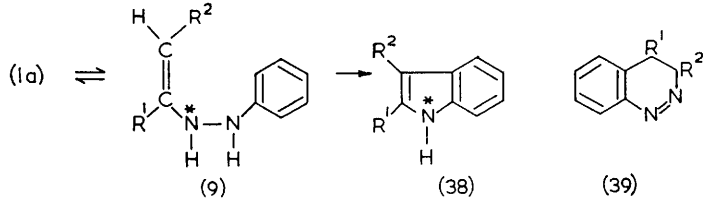


which have been isolated when aromatic aldehyde arylhydrazones are heated with anhydrous base (sodamide),[136] presumably arise by the base-catalysed condensation of the cyanide and amine products.

H. Cyclisation Reactions.—Many types of cyclisation reaction involving arylhydrazones are known. Most of these are shown only by specialised types of hydrazone, and many are not specific for arylhydrazones. For example, $\alpha\beta$-unsaturated hydrazones cyclise readily to pyrazolines, and 1,3-diketone hydrazones to pyrazoles. Another example, already mentioned, is the cyclisation of aromatic aldehyde *p*-nitrophenylhydrazones to indazoles.[53] Space precludes a full discussion of all of these reactions, for which the reader is referred to standard works.[7,137]

Only the Fischer indole synthesis,[120] which was reviewed in 1963[59] is both specific for arylhydrazones and of wide applicability. Treatment of an arylhydrazone (1a) (often prepared *in situ*) with acid, base, or merely a sufficient degree of heat, causes the formation of an indole (38), with the elimination of the nitrogen atom nearest the aryl ring. The mechanism has been extensively studied, and the ene-hydrazine form (9) of the arylhydrazone is thought to be an intermediate (*cf.* Robinson,[59] although some of his comments on the tautomer-

[133] W. Seibert, *Chem. Ber.*, 1948, **81**, 266.
[134] N. O. V. Sonntag, S. Linder, E. I. Becker, and P. E. Spoerri, *J. Amer. Chem. Soc.*, 1953, **75**, 2283.
[135] L. Wolff, *Annalen*, 1912, **394**, 86; Yu. A. Naumov, A. N. Kost, and I. I. Grandberg, *Vestnik Moskov. Univ.*, 1965, **20**, 46 (*Chem. Abs.*, 1965, **62**, 14447b).
[136] S. Robev, *Compt. rend. Acad. bulg. Sci.*, 1961, **14**, 353; S. Robev, *Chem. Ber.*, 1958, **91**, 244.
[137] R. C. Elderfield (ed.), 'Heterocyclic Compounds', Wiley, New York, 1950.



(9) (38) (39)

ism of arylhydrazones are now out of date). Cyclisation of cyclohexanone arylhydrazones affords tetrahydrocarbazoles (38; $R^1R^2 = [CH_2]_4$), which may be dehydrogenated to carbazoles (the Borsch carbazole synthesis).

An interesting illustration of the way in which the tautomerism of an arylhydrazone may influence its chemical properties is given by the 1,2-diketone monoarylhydrazones, which on treatment with strong acid may cyclise in the Fischer manner to acylindoles, or to tetrahydrocinnolines (39); the direction of cyclisation depends on the preponderance of normal and azo-enol (6b) forms, and hence on the nature of R^1 and R^2.[61]

I. Reconversion into the Carbonyl Compound.—Finally, some mention should be made of the methods which have been employed to convert arylhydrazones into the parent carbonyl compound, a reaction of obvious practical importance in the analytical field. Regeneration from arylhydrazones is less easy than from certain other derivatives, notably semicarbazones. Straightforward acid hydrolysis is not usually practicable unless the equilibrium is forced in some way, although if strong enough acid is used the equilibrium may be forced by protonation of the free arylhydrazine. Thus Fischer and Hirschberger[138] employed the acid hydrolysis of mannose phenylhydrazone in their classical synthesis of mannose from mannitol, and on the micro-scale, DNPs are instantly hydrolysed by cold concentrated sulphuric acid.[139]

The most useful way of forcing the equilibrium is to employ a catalytic amount of acid, together with an excess of a second carbonyl compound as an arylhydrazine acceptor. Aromatic aldehydes,[140] α-keto-acids,[141] α-diketones,[32a] and β-diketones[142] are frequently recommended as acceptors, but almost every type of carbonyl compound has been used. The addition of copper(II) carbonate to DNP solutions functions by oxidising the free arylhydrazine.[143] There are few reports of base-catalysed hydrolysis, but some acid-sensitive, volatile carbonyl compounds, *e.g.* citronellal, have recently been obtained in 35–60% yield by distillation of their DNPs from alkali.[144]

[138] E. Fischer and J. Hirschberger, *Ber.*, 1888, **21**, 1805.
[139] R. Bassette and E. A. Day, *J. Amer. Oil Chemists' Soc.*, 1960, **37**, 482.
[140] H. Rupe and A. Gassmann, *Helv. Chim. Acta*, 1936, **19**, 569; J. C. Sowden and H. O. L. Fischer, *J. Amer. Chem. Soc.*, 1947, **69**, 1963.
[141] M. Keeney, *Analyt. Chem.*, 1957, **29**, 1489; H. R. Harrison and B. J. Eisenbraun, *J. Org. Chem.*, 1966, **31**, 1294.
[142] W. Ried and G. Mühle, *Annalen*, 1962, **656**, 119.
[143] R. Robinson, *Nature*, 1954, **173**, 541.
[144] G. W. O'Donnell, *Austral. J. Chem.*, 1968, **21**, 271.

A different method sometimes used for DNPs involves reduction with stannous chloride,[145–146] chromous chloride,[147] or sodium hyposulphite;[145] a 2,4-diaminophenylhydrazone is formed, and is readily hydrolysed. Ozonolysis also splits arylhydrazones in preparatively useful yields;[32b,148] from acetone DNP the products were acetone, nitrogen, and *m*-dinitrobenzene.[148] The reaction is probably an electrophilic attack by ozone at the C:N double bond of the hydrazone.[149]

I thank Dr. R. D. Guthrie and Professor Dr. H. Zollinger.

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