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1. *The Associating Effect of the Hydrogen Atom. Part VII. The N–H–N Bond. Derivatives of Pyrazole and Indazole.*

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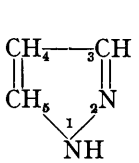
Contrasts in boiling point, solubility in donor solvents, and degree of association are shown between derivatives of pyrazole and indazole possessing a free imino-hydrogen atom and those in which this atom has been replaced by an alkyl, aryl, or acyl group. The high values of these properties of the former class of compound are attributed to hydrogen-bond formation involving the imino-hydrogen atom. Cryoscopic measurement of molecular weight of sixteen derivatives is made over a range of concentration in benzene or in naphthalene solution. A possible mechanism of pyrazole tautomerism is proposed.

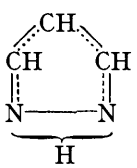
THE rarity of compounds containing the hydrogen bond connecting two nitrogen atoms is due chiefly to the comparative weakness of the N–H–N bridge. This weakness manifests itself also in the tendency shown in numerous compounds (see, *inter alia*, Part V, J., 1940, 166) in which the possibility exists of the alternative operation of various types of hydrogen bond (O–H–O, O–H–N, N–H–N), for the more stable types to assume ascendancy, and for the N–H–N bonds to contribute little, if at all, towards the structure and properties of such compounds. Again, cyclic systems which include the N–H–N bridge are more than usually sensitive to steric influences, for the bond does not survive strains which distort too greatly the normal linear distribution of the hydrogen valencies; for this reason, five-membered cyclic systems including the N–H–N bridge are extremely rare, the majority containing six, or perhaps more, members.

Almost all authentic examples of the N–H–N bridge are confined to compounds which exhibit virtual tautomerism; *i.e.*, the alternative attachment of the hydrogen atom to one nitrogen or the other can be accommodated by a suitable adjustment of valencies within the molecule. It is true that there are numerous indications of weak N–H–N bonds in systems not conforming to this condition (see, *e.g.*, the spectroscopic work of Gordy, *J. Chem. Physics*, **7**, 1939, 167; Buswell, Downing, and Rodebush, *J. Amer. Chem. Soc.*, 1939, **61**, 3252; Gordy and Stanford, *ibid.*, 1940, **62**, 497), but in these examples the bond is seldom, if ever, sufficiently stable to manifest itself in enhanced molecular weight.

In the present investigation the existence of the N–H–N bridge in derivatives of pyrazole and indazole is inferred from their physical properties, particularly their molecular weights. The virtual tautomerism of the pyrazoles follows from the researches of Knorr and v. Auwers,



(I.)



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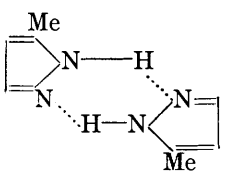
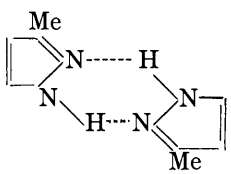


(*a*.)



(*b*.)

(III.)

who demonstrated the equivalence of the 3- and the 5-position in the pyrazole nucleus (I). As a result of this there are only two mono-*C*-substituted derivatives of pyrazole.

The symmetry (see II) of the pyrazole nucleus is immediately destroyed when the imino-hydrogen atom (position 1) is substituted; there are then three different mono-*C*-substituted isomerides [*e.g.*, 1-phenyl-3 (or 4, or 5)-methylpyrazole].

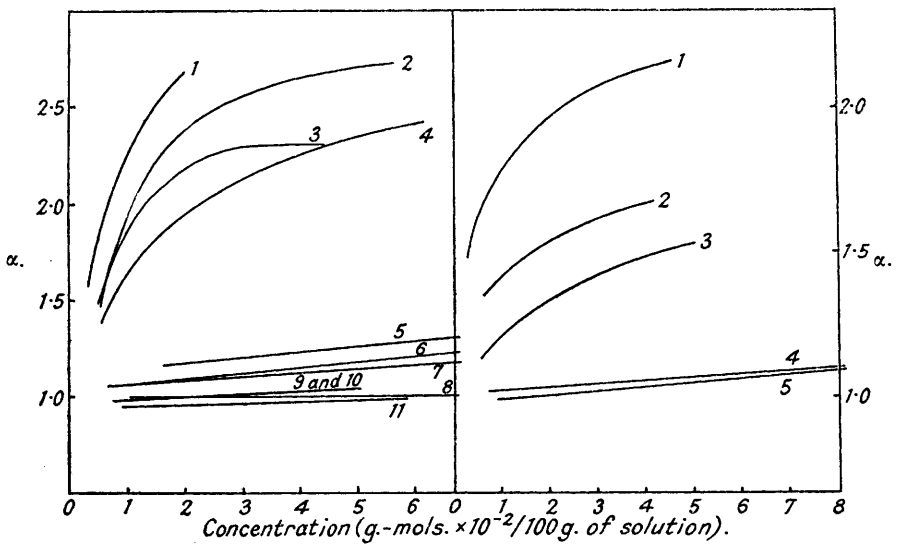
A comparison of the b. p.'s of isomeric pyrazoles (Table I) reveals the superior volatility of those isomers having substituents in the 1-position. The relatively high b. p.'s of the isomers possessing a free imino-group suggest some degree of molecular complexity in these compounds, and measurements of molecular weight of both types of pyrazole derivative over a range of concentration in benzene solution have therefore been undertaken.

TABLE I.

	B. p.		B. p.		B. p.
(Pyrazole	188°)	1 : 3 : 4-Trimethylpyrazole	160°	1-Phenyl-3-methylpyrazole	255°
1-Methylpyrazole	127	1 : 3 : 5-Trimethylpyrazole	170	1-Phenyl-4-methylpyrazole	266
3-Methylpyrazole	205	1 : 4 : 5-Trimethylpyrazole	177	1-Phenyl-5-methylpyrazole	263
4-Methylpyrazole	205	3 : 4 : 5-Trimethylpyrazole	233	3-Phenyl-1-methylpyrazole	281
		(1 : 3 : 4 : 5-Tetramethylpyrazole	193)	3-Phenyl-5-methylpyrazole	327
1 : 3-Dimethylpyrazole	136				
1 : 5-Dimethylpyrazole	153	1-Phenylpyrazole	246		
3 : 4-Dimethylpyrazole	222	3-Phenylpyrazole	313		
3 : 5-Dimethylpyrazole	218				

The results are represented in Figs. 1 and 2, which show the variation of the association factor (α) with concentration; a steep curve is interpreted as a high degree of association,

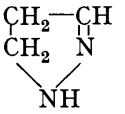
FIG. 1. FIG. 2.

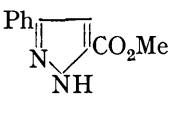


and a flat or gently sloped curve as non-association. With remarkable regularity the substances measured fall into two classes, those having a free imino-hydrogen atom being associated, whilst those substituted in position 1 are unassociated. It seems clear that the association present in the former type is due to hydrogen-bond formation between the imino-hydrogen atom of one molecule and the tertiary nitrogen atom of another. The molecular-weight data are insufficient to indicate the nature of the polymers formed, but it is reasonable to assume that they can be either the chain or the cyclic type (or both) already proposed for the diazoamino-compounds (Hunter, J., 1937, 320). In either case, treatment of the hydrogen bond as a resonance phenomenon (Sidgwick, *Ann. Reports*, 1933, **30**, 112; Pauling, " The Nature of the Chemical Bond," Cornell, 1939) will provide a satisfactory explanation of the virtual tautomerism of the pyrazoles. For example, formula (III) represents two unperturbed forms of a cyclic dimer, of which the resonance hybrid may well contribute to the structure of methylpyrazole in benzene solution; the

dissociation of (III*a*) into 5- and (III*b*) into 3-methylpyrazole may then readily account for the virtual identity of these two substances. An explanation on exactly similar lines may be put forward by use of a chain polymer. The tendency of some of the curves in Fig. 1 to attain a maximum value of α in the neighbourhood of 2 may point to a preponderance of dimers in all but very dilute solutions, although there is no evidence to show that these are cyclic. This view of the tautomerism of the pyrazoles is in direct opposition to that of Pauling (*op. cit.*, p. 427).

The close parallel between association and tautomeric character is also borne out by the behaviour of pyrazoline (IV) and its derivatives. In these compounds the conjugated


(IV.)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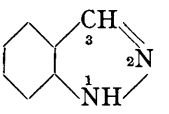

(VI.)

system is destroyed by the saturation of one double bond, thus removing the possibility of tautomerism, and it is significant that the pyrazolines possess consistently lower boiling points (Table II) than the corresponding pyrazoles. Determination of the molecular

TABLE II.

	B. p.		B. p.
Pyrazole	188°	Pyrazoline	144°
3 : 4 : 5-Trimethylpyrazole	233	3 : 5 : 5-Trimethylpyrazoline	158
3- and 4-Methylpyrazole	205	5-Methylpyrazoline	180

weights of 5-methyl- and 3 : 5 : 5-trimethyl-pyrazoline indicates that they are substantially unimolecular over a considerable range of concentration. Thus, in spite of the presence in these compounds of a free imino-hydrogen atom and a donor (tertiary) nitrogen atom, hydrogen-bond association appears to be prevented owing to the inability of the molecule to accommodate tautomeric change except by becoming a zwitterion. The case is exactly similar to that of the imino-ethers (Part I, J., 1937, 1114).

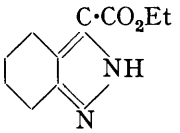
It is not surprising that the two types of pyrazole derivative show contrasts in regard to their solubility. Those which are *N*-substituted are very soluble in all organic solvents, but are insoluble in water even when hot; those possessing a free imino-group, on the contrary, are sparingly soluble in benzene and in other hydrocarbon solvents, but readily soluble in alcohol and in hot water. Similar behaviour has already been recorded for the acid hydrazides (Part VI, J., 1940, 334), the solubility in electron-donor solvents of those compounds (hydrazides and pyrazoles) possessing a free imino-group being due no doubt to hydrogen-bond formation with solvent molecules.

In a recent paper by von Auwers (*Annalen*, 1934, **508**, 51) a new aspect of pyrazole tautomerism is discussed which cannot be overlooked, for it revokes in a large measure many of the earlier conclusions. The remarkable statement is made (and accepted in other quarters; *e.g.*, Karrer, "Organic Chemistry," 1938, p. 728) that the 3- and the 5-position in the pyrazole nucleus can no longer be regarded as equivalent, and that the pyrazoles must be considered to be equilibrium mixtures of both tautomers in which the position of the equilibrium varies with the substituent groups; certain extreme cases are considered to be virtually homogeneous substances of fixed structure, *i.e.*, the imino-hydrogen atom occupies one position almost exclusively. It is to be observed that in the extreme cases quoted by von Auwers the hydrogen atom regarded as fixed is always adjacent to a substituent ester group, as in methyl 3-phenylpyrazole-5-carboxylate (V), and it appeared to us that the fixation might be a result of chelate ring formation through the imino-hydrogen atom and the carbonyl oxygen. If this were the case, it should be reflected in a much reduced degree of association. Experiment shows, however, that far from being unassociated, such esters are even more highly associated (Fig. 1, curve 1) than are pyrazoles which lack the ester group, and the increased association must clearly be due to N–H–O bonds, rendered possible by the introduction of the ester group. The

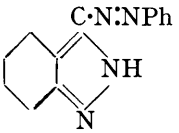
construction of models reveals no stereochemical objection to the existence of polymers containing the N–H–O bridge, and involving either one nitrogen atom or the other. Molecular-weight evidence, therefore, provides no confirmation of von Auwers's conclusions, although the isolation of chelate metallic derivatives (IX) (see below) accords them some measure of support. The behaviour of the pyrazole-5-carboxylic esters recalls the recent observation by Pratesi and Berti (*Atti X Congr. Internaz. Chim.*, 1938, III, 313) that the pyrrole-α-aldehydes are associated (dimeric) in benzene solution, and that both their molecular association and their tautomeric (aldehyde–hydroxymethine) character are destroyed by replacement of the imino-hydrogen atom.

Measurements of molecular weight have also been performed on indazole (VI) and a few of its derivatives; * the inferior solubility of the associated compounds of this series necessitated the use of naphthalene as a cryoscopic solvent. The results (Fig. 2) lead to conclusions similar to those reached for their pyrazole analogues. Indazole itself (curve 3) shows a high degree of association even in naphthalene solution, in which the high temperature (80°) of the cryoscopic determination would be expected to reduce the association owing to thermal agitation. 1-Methyl- and 1-acetyl-indazole (curves 4 and 5), on the other hand, are unassociated at the much lower temperature (5°) of melting benzene. Solubility contrasts similar to those in the pyrazole series are also apparent; indazole itself can even be recrystallised from hot water.

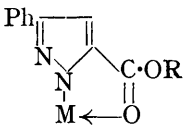
Attempts have been made to fix the imino-hydrogen atom of the indazole nucleus on the 2-nitrogen atom by substituting suitable electron-donor groups in position 3. Such fixation is not confirmed, however, in the values of α obtained (Fig. 2, curve 1) for ethyl indazole-3-carboxylate (VII), which, like its pyrazole analogue (V), is more highly



(VII.)



(VIII.)



(IX.)

associated than the parent indazole. Similarly, 3-benzeneazoindazole (VIII) shows a higher degree of association (Fig. 2, curve 2) than that of indazole, and it is clear that the high association of both (VII) and (VIII) is the result of the simultaneous operation of homogeneous and heterogeneous hydrogen-bond association (see Part V, *loc. cit.*).

The absence of chelation in pyrazole and indazole derivatives possessing donor substituents on the carbon atom adjacent to nitrogen [as in (V), (VII), and (VIII)] is probably due to steric factors connected with the strain of five-membered ring systems involving the hydrogen bond. Fixation of structure can be achieved, however, by replacing the imino-hydrogen atom by certain metallic atoms, for which the much reduced valency angle (compared with that of hydrogen) can bring about considerable relief of strain in a five-membered system. For instance, a series of metallic (copper, nickel, cobalt) derivatives of (V), (VII), and (VIII) has been prepared, the properties of which leave no doubt of their chelate nature; they must therefore contain a five-membered chelate ring as in (IX; M = 1 equiv. of metal), which represents the metallic compound derived from (V). These chelate metallic derivatives, the preparation and properties of which will be described elsewhere, are evidently derived from parent imino-compounds of the fixed structure denoted in (V), (VII), and (VIII).

In the following tables concentrations are expressed as g.-mols. $\times 10^{-2}$/100 g. of solution, the formula weights appearing in parentheses; M is the apparent molecular weight deduced according to the ideal-solution laws; and the association factor (α) is calculated as the ratio of M to the formula weight. The cryoscopic solvent is benzene except where otherwise stated. Conclusions as to molecular association are based, not on the absolute

* The old distinction between indazole and *iso*indazole is now invalid, the imino-hydrogen atom not being definitely located on either nitrogen atom; but two isomeric *N*-substituted indazoles are distinguishable, according as the substituent is attached at position 1 or 2 (see VI).

values of α, which may have no quantitative significance, but rather on the slope of the association–concentration curves. By comparing the slopes of these curves for substances of similar constitution, errors arising from departures from the ideal laws are very much diminished.

Fig. 1.

	Concn.	*M.*	α.
Ethyl 3-phenylpyrazole-5-carboxylate (216) (Curve 1)	0·33	341	1·58
	0·65	425	1·965
	1·28	522	2·42
	1·89	578	2·68
5-Phenyl-3-methylpyrazole (158) (Curve 2)	0·495	233	1·47
	1·575	371	2·35
	2·72	400	2·53
	4·00	419	2·65
	5·59	434	2·74
5-Ethoxy-3-methylpyrazole (126) (Curve 4)	0·545	176	1·39
	1·61	231	1·83
	2·63	257	2·04
	4·13	284	2·25
	6·06	305	2·42
3 : 5 : 5-Trimethylpyrazoline (112) (Curve 5)	1·685	131	1·17
	3·82	136	1·21
	5·67	142	1·27
	7·51	147	1·31
	9·27	153	1·36
5-Ethoxy-1-phenyl-3-methylpyrazole (202) (Curve 9)	0·72	198	0·98
	1·88	201	0·99
	2·87	200	0·99
	3·84	204	1·01
	5·05	207	1·02
5-Benzoyloxy-1-phenyl-3-methylpyrazole (278) (Curve 10)	0·53	266	0·96
	1·05	265	0·95
	1·80	268	0·96
	2·74	272	0·98
	3·85	276	0·99
	5·09	281	1·01
3 : 5-Dimethylpyrazole (96) (Curve 3)	0·47	143	1·485
	1·83	206	2·145
	3·145	221	2·30
	4·42	221	2·30
5-Methylpyrazoline (84) (Curve 6)	1·61	90	1·07
	3·62	94	1·12
	5·65	100	1·19
	7·65	104	1·23
	10·40	110	1·31
1 : 3 : 5-Trimethylpyrazole (110) (Curve 7)	0·76	115	1·04
	2·22	120	1·09
	4·22	122	1·11
	6·12	125	1·14
	8·23	126	1·15
1-Phenyl-3 : 5-dimethylpyrazole (172) (Curve 8)	1·05	173	1·01
	2·49	171	1·00
	4·22	170	0·99
	6·00	171	1·00
	7·74	174	1·01
1 : 5-Diphenyl-3-methylpyrazole (234) (Curve 11)	0·91	225	0·96
	2·38	228	0·97
	3·41	227	0·97
	4·62	228	0·975
	5·94	231	0·99

Fig. 2.

	Concn.	*M.*	α.
Ethyl indazole-3-carboxylate (190) (*in naphthalene*) (Curve 1)	0·35	281	1·48
	0·70	317	1·67
	1·37	343	1·80
	2·35	382	2·01
	3·29	398	2·09
	4·49	409	2·15
Indazole (118) (*in naphthalene*) (Curve 3)	0·55	137	1·16
	1·09	139	1·18
	1·63	153	1·30
	2·41	158	1·33
	3·45	167	1·42
	4·94	180	1·52
3-Benzeneazoindazole (222) (*in naphthalene*) (Curve 2)	0·59	300	1·35
	1·16	319	1·44
	1·715	328	1·48
	2·53	351	1·58
	3·31	362	1·63
	4·06	372	1·67
1-Methylindazole (132) (Curve 4)	0·81	133	1·01
	2·13	137	1·03
	4·10	137	1·03
	6·38	140	1·06
	9·16	147	1·11
1-Acetylindazole (160) (Curve 5)	0·93	157	0·98
	2·70	161	1·01
	4·37	166	1·085
	6·34	170	1·065
	8·17	174	1·09

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