Reactivity of Indazoles and Benzotriazole towards *N*-Methylation and Analysis of the ^{1}H Nuclear Magnetic Resonance Spectra of Indazoles and Benzotriazoles

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Methylation of some simple 3-, 7-, and 3,7-substituted indazoles in alkaline solution leads to mixtures of both 1- and 2-methyl compounds, in which the 1-methyl isomer predominated in all except the 7-monosubstituted cases. Steric effects are less marked in this series than in cinnolines. INDO Calculations of the electron density at the nitrogen were performed in an attempt to account for the relative reactivities. The ^{1}H n.m.r. spectra of the 1- and 2-methylindazoles are sufficiently different for this to be used as a diagnostic tool for the positions of methylation. A detailed ABCD analysis of various indazole and benzotriazole spectra has been carried out and the results assessed in terms of degree of aromatic character.

RECENTLY we reported [1] studies of the methylation of various 3- and 7-substituted cinnolines, in an attempt to test the relative importance of steric and electronic effects in the system. It was concluded that steric effects were dominant in the reaction.[1,2] In contrast von Auwers *et al.*[3,4] suggested that both isomers are formed in nearly equal amounts when indazole is methylated in alkaline solution. The contrast to the cinnolines appeared to be sharp, and worthy of re-investigation, since the indazole work [3,4] was based upon separation of the isomers by distillation or crystallisation. The virtue of studying the reactions in strongly alkaline solution is that the indazole should react as the anion, as also should benzotriazole chosen as a sterically similar species, but different electronic charge distribution (indazole and benzotriazole [5,6] have pK_a *ca.* 14 and 8.2 respectively). This avoids the problem of reaction on the neutral species being influenced by tautomeric N–H groupings.

We have recently reported [7] a number of non-empirical molecular orbital studies of the electronic structure of five-membered ring heterocycles and their benzo-derivatives. It is intended to extend these studies to the present compounds and their reactivity to methylation. However, the latter is not yet practicable in view of the large size of the computations. In these circumstances we have carried out semi-empirical studies (*cf.* ref. 2) of the electron density in the anions derived from indazole and benzotriazole.

Finally, during the course of the study it became apparent that the ^{1}H n.m.r. spectra for the 1- (1c and d) and 2-methyl- (2c and d) series showed systematic differences (Figure), and that the reported spectral analyses for some related compounds left much to be desired. We thus undertook a detailed (iterative) analysis of various compounds (1a—d) and (2a—d).

EXPERIMENTAL

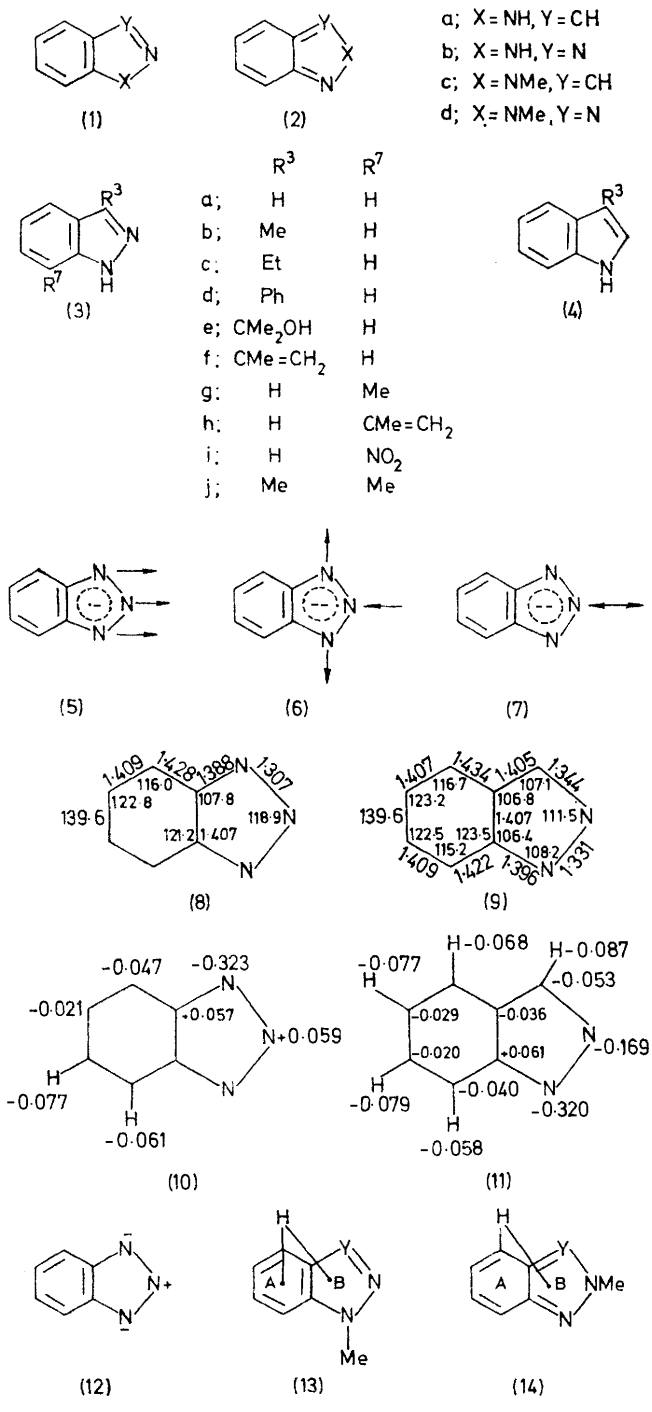
Synthetic Routes.—Indazole (3a) and its 3- and 7-methyl derivatives (3b and g) were prepared from the *o*-alkylaniline.[8] 3-Carboxyindazole was obtained by diazotisation of isatin; [9] esterification with methanol–sulphuric acid and reduction of the product with methylmagnesium iodide yielded 2-indazol-3-yl propan-2-ol (3e). The 3-isopropenyl derivative (3f) was obtained by treatment of (3e) with phosphoric oxide in benzene.[10] The indazoles (3c, d, and j) were prepared by synthesis of the corresponding 3-substituted indole; [10] periodate cleavage [11] of the latter yielded the *o*-aminophenyl ketone, which was diazotised and then reduced (sodium metabisulphite) to the hydrazine which cyclised spontaneously to the indazole.[12] 7-Ethoxycarbonylindazole was obtained from methyl 3-methyl-2-nitrobenzoate by reduction to the amine, acetylation, and nitrosation with dinitrogen trioxide.[13] The 7-isopropenyl compound (3h) was prepared from this ester, as for (3f). Attempted reduction (H_2–Pd, H_2–Ni, N_2H_4–Ni) of the isopropenyl compounds (3f and h) to the corresponding isopropyl compound led to complex mixtures which did not contain the isopropylindazoles. The indazoles and their methylation ratios are given in Table 1.

Typical Methylation Reaction.—Indazole (3.00 g), potassium hydroxide (3.00 g), methyl iodide (9.00 g), and methanol (25 ml) were boiled for 4 h, cooled, and diluted with water (100 ml). The mixture was extracted ($CHCl_3$, 3 × 50 ml) and dried ($MgSO_4$). A portion of the chloroform solution was evaporated and directly investigated by ^{1}H n.m.r. spectroscopy; the *N*-methyl resonances were generally well separated (Table 3) [14] and the mixture was analysed by integration; estimates based upon the height of the *N*-methyl resonance were inaccurate owing to long range coupling of the 2-methyl group to 3-H. N.m.r. investigation of the aqueous phase in the above separation showed

[1] M. H. Palmer and P. S. McIntyre, *Tetrahedron*, 1971, **27**, 2913.
[2] M. H. Palmer, A. J. Gaskell, P. S. McIntyre, and D. W. W. Anderson, *Tetrahedron*, 1971, **27**, 2921.
[3] K. von Auwers and K. Düesberg, *Ber.*, 1920, **53**, 1179 and later papers.
[4] L. C. Behr, R. Fusco, and C. H Jarboe, 'Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings,' ed. R. H. Wiley, Interscience, New York, 1967.
[5] A. Albert, 'Physical Methods in Heterocyclic Chemistry,' ed. A. R. Katritzky, Academic Press, New York, 1963, vol. 1.
[6] J. E. Fagel and G. W. Ewing, *J. Amer. Chem. Soc.*, 1951, **73**, 4360.
[7] M. H. Palmer, A. J. Gaskell, and R. H. Findlay, *J.C.S. Perkin II*, 1974, 1893 and references cited therein.
[8] R. Huisgen and K. Bast, *Org. Synth.*, 1962, **42**, 69.
[9] H. R. Snyder, C. B. Thomas, and R. L. Hinman, *J. Amer. Chem. Soc.*, 1952, **74**, 2009.
[10] M. H. Palmer and P. S. McIntyre, *J. Chem. Soc.* (*B*), 1969, 446.
[11] W. Dalby, *J. Amer. Chem. Soc.*, 1966, **88**, 1049.
[12] K. von Auwers and P. Stodter, *Ber.*, 1926, **59**, 529.
[13] R. Huisgen and H. Nakaten, *Annalen*, 1954, **586**, 84.
[14] J. Elguero, A. Fruchier, and R. Jacquier, *Bull. Soc. chim. France*, 1966, 2075.

it to be free of indazole derivatives, so that no loss of material by quaternisation had occurred.

Evaporation of the bulk of the chloroform extract gave the crude methylindazole mixture. This was separated by chromatography on alumina, where the 1-isomer was eluted preferentially by light petroleum (b.p. 60—80°) followed by benzene; isomerism of 2-methyl- to 1-methylindazole was observed when in prolonged contact with alumina.

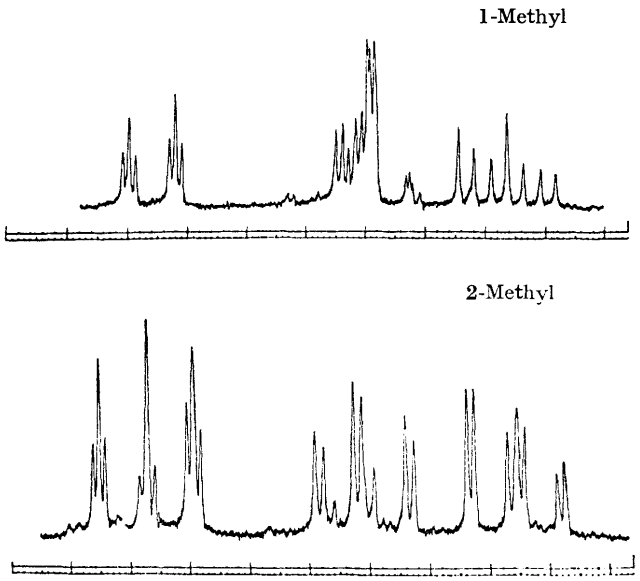


	R^3	R^7
a;	H	H
b;	Me	H
c;	Et	H
d;	Ph	H
e;	CMe_2OH	H
f;	$CMe{=}CH_2$	H
g;	H	Me
h;	H	$CMe{=}CH_2$
i;	H	NO_2
j;	Me	Me

[15] I. L. Karle, K. Britts, and P. Gunn, *Acta. Cryst.*, 1964, **17**, 496.

The physical properties of the indazoles obtained are recorded in Table 1. The assignment of structure to the isomeric *N*-methylindazoles was either by comparison with known samples [4] prepared by unambiguous methods, or by n.m.r. spectroscopy [14] (discussed in detail below) but the deshielding of the 7-H in the 2-methyl series is particularly evident (Figure).

The procedure for methylation of benzotriazole in alkaline solution was very similar. The products were again separated by chromatography after estimation of the mixture by n.m.r. spectroscopy. The characteristic AA^1BB^1 pattern of the 2-methylbenzotriazole spectrum contrasts with the ABCD type from the 1-methyl series;



^{1}H N.m.r. spectra of 1- and 2-methylindazole

although the 1H-benzotriazole form of [(1a) ⇌ (2a)] is normally predominant in solution, unsubstituted benzotriazole shows an AA^1BB^1 spectrum owing to rapid 1-H–3-H isomerism.

INDO Calculations of the Charge Distribution in the Anions.—The molecular geometry of the indazole and benzotriazole anions is not known. We started with the geometry of indole-3-acetic acid [15] for the carbocyclic system of the anions, and then proceeded to optimise the geometry of the five-membered ring. In our iterative process the total energy in the INDO semi-empirical method [16] is calculated for various geometric arrangements and allowed to achieve an optimal value by a sequence of one-dimensional parabolic minimisations. Thus certain modes of motion of the nuclei corresponding to vibrational modes, and as in (5)—(7) are performed in sequence which finally yielded (8) for the benzotriazole anion. By a similar but more lengthy process we arrived at (9) for the indazole anion.[17]

The large angle at N-2 of (8) is at first sight surprising, but is reasonable since much of the negative charge in the anion is localised in N-1 and N-3 of (10) thereby leading to substantial mutual repulsion by these centres; similarly the

[16] J. A. Pople and D. L. Beveridge, 'Approximate Molecular Orbital Theory,' McGraw-Hill, New York, 1970.

[17] M. J. S. Dewar and G. J. Gleicher, *J. Chem. Phys.*, 1966, **44**, 759.

longer N–N distance in (9) than (8) can be accounted for in terms of charge repulsion (11). A break-down of the electron density at the nitrogen atoms, and conversion of the σ-system to radial and tangential components [2] at the ring atoms is shown in Table 3. The apparent positive charge density at N-2 in the indazole anion corresponds to a small contribution of the canonical form (12) to the overall electronic structure, and is often found in self-consistent field calculations on ions.[18]

RESULTS AND DISCUSSION

Methylation Ratios.—The comparatively small change in the 1- : 2-methylation ratio in indazole and its 3- and 7-Me derivatives (Table 1) shows only a weak steric methylation procedure; thus the preponderence of 2-methylation from the 7-nitro-compound (3i) is probably a result of steric interactions.

As with indazoles,[3,4] methylation of benzotriazole leads to various proportions of the *N*-methyl compounds depending upon the reagent (Table 2); under strongly alkaline conditions the ratio is largely independent of the reagent (MeI or Me_2SO_4) and is also independent of the base concentration; the present results are in quantitative agreement with earlier work.[20,21]

In competition for a deficiency of methyl iodide (10 mol %), a reaction with equimolar amounts of indazole (IND) and benzotriazole (BT) *after* allowance for the statistical 2 : 1 advantage at N-1 and N-3 in benzotriazole yielded the composition (*N*-Me-BT : *N*-Me-IND) 44.7 : 55.3; the relative proportions of the four products were (1c), 25.8; (2c), 19.5; (2d), 36.4; (1d), 18.3% in essential agreement with the ratios when the reactions were carried out under separate conditions. Thus we find equal reactivity at N-1 in the anions (8) and (9), which are nearly equally sterically hindered.

The steric and electronic effects raise a number of

TABLE 1

Indazoles and their methylation ratios [a]

	C-Substituent										
	None (1a)	3-Me (1b)	3-Et (1c)	3-Ph (1d)	3-(CMe_2OH) (1e)	3-($CMe{=}CH_2$) (1f)	7-Me (1g)	7-NO_2 (1i)	3,7-Me_2 (1j)	5-NO_2 (1k)	6-NO_2 (1l)
N-Substituent											
H											
M.p. (°C)	147—149 [b]	113	*c*	107—108 [d]	167 [e]	84—85 [f]	136—137 [g]	190 [b]	174 [h]	208 [b]	180 [b]
1-Me											
M.p. (b.p.) (°C)	60—61 [i]	35 [i]	(146—148 at 35 mmHg) [i]	80 [i]			52 [j]	104 [k]	51 [l]	154 [k]	126 [k]
2-Me											
M.p. (b.p.) (°C)	56 [i]	79—80 [i]	(130 at 23 mmHg) [i]				(273—275)	149 [k]	91 [m]	130 [k]	157—158 [k]
Methylation ratio (1) : (2) [a]	50 : 50	65 : 35	70 : 30	74 : 26	66 : 34	82 : 18	46 : 54	29 : 71	57 : 43	47 : 53	50 : 50

[a] Estimated accuracy ±3%. [b] Commercial samples (Koch-Light) after purification. [c] Viscous oil which failed to solidify. [d] K. von Auwers and K. Hüttenes (*Ber.*, 1922, **55**, 1112) give m.p. 107°. [e] Found: C, 68.5; H, 6.7; N, 15.1. $C_{10}H_{11}N_2O$ requires C, 68.2; H, 6.8; N, 15.1%. [f] Found: C, 75.7; H, 6.2; N, 17.5. $C_{10}H_9N_2$ requires C, 75.9; H, 6.3; N, 17.7%. [g] Found: C, 72.5; H, 6.0; N, 21.1. $C_8H_8N_2$ requires C, 72.7; H, 6.05; N, 21.2%. [h] Found: C, 73.8; H, 6.9; N, 20.0. $C_9H_{10}N_2$ requires C, 73.95; H, 6.85; N, 19.15%. [i] Ref. 4 gives the following m. or b.p.s for indazoles: 1-methyl, 61°; 2-methyl, 56°; 1,3-dimethyl, 36°; 2,3-dimethyl, 80°; 2-methyl-3-ethyl (389° at 760 mmHg); 1-methyl-3-phenyl, 80°; 1-methyl-6-nitro, 108—109°; 2-methyl-6-nitro, 159—160°. [j] Found: C, 73.95; H, 6.7; N, 19.25. $C_9H_{10}N_2$ requires C, 73.95; H, 6.85; N, 19.15%. [k] E. Noelting (*Ber.*, 1904, **37**, 2576) gives 1-(or 2-)methyl-5-nitro, m.p. 128—129°; 1-(or 2-)methyl-7-nitro, m.p. 144—145°; 1-(or 2-)methyl-6-nitro, m.p. 155°. [l] Found: C, 75.15; H, 7.4; N, 17.3. $C_{10}H_{12}N_2$ requires C, 75.0; H, 7.5; N, 17.5. [m] Found: C, 73.9; H, 6.85; N, 19.1. $C_9H_{10}N_2$ requires C, 73.95; H, 6.85; N, 19.15%.

TABLE 2

Methylation of benzotriazole

Reagent	CH_3I–MeOH	CH_3I–MeOH–NaOH	$(CH_3)_2SO_4$–NaOH–H_2O	CH_2N_2–EtOH
1-Methylation	100	61	65	35
2-Methylation	0	39	35	65

effect and contrasts strongly with the corresponding cinnolines.[1] However, as in the latter series (and indeed pyridazines [19]), the equal stereoelectronic effects of 3-phenyl and 3-ethyl substituents is apparent; it seems that the buttressing effect of the 4-H leads to a preferred out-of-plane conformation of the Ph group (3d) which shows an apparent size (thickness) similar to that of a CH_3 or CH_2 group. In contrast, the 3-isopropenyl group (3f) which exerts a larger effect on the alkylation ratio than (3d) must lie closer to co-planarity.

The high proportion of 2-methylation in the indazol-3-ylpropan-2-ol (3e) is curious, and suggests that stabilisation of the negative charge at N-2 may be achieved by some form of internal hydrogen bonding with the OH group. Since the N-1 : N-2 methylation ratios are little changed between the parent and 5- or 6-nitro-compounds, it seems that strongly polar groupings in the carbocyclic ring probably exert a minimal electronic effect on the

[18] L. Salem, 'Molecular Orbital Theory of Conjugated Systems,' Benjamin, New York, 1966.

[19] H. Lund, personal communication.

[20] F. Krollpfeiffer, A. Rosenberg, and C. Muhlhausen, *Annalen*, 1935, **575**, 113.

[21] N. O. Cappel and W. C. Fernelius, *J. Org. Chem.*, 1940, **5**, 40.

problems; it is pleasing to note that the calculated total electron densities at N-1 in the two systems (10) and (11)

TABLE 3

Charge distribution in the indazole and benzotriazole anions (10) and (11)

	N-1	N-2
Indazole anion		
2*s*	1.6068	1.5665
Π	1.3725	1.0772
Radial $2p_\sigma$	1.3562	1.4681
Tangential $2p_\sigma$	0.9847	1.0570
3-Methylindazole anion		
2*s*	1.6065	1.5666
Π	1.3553	1.0777
Radial $2p_\sigma$	1.3612	1.4633
Tangential $2p_\sigma$	0.9880	1.0499
7-Methylindazole anion		
2*s*	1.6065	1.5666
Π	1.3699	1.0785
Radial $2p_\sigma$	1.3574	1.4667
Tangential $2p_\sigma$	0.9848	1.0564
Benzotriazole anion		
2*s*	1.6266	1.4750
Π	1.3423	1.0195
Radial $2p_\sigma$	1.3464	1.4511
Tangential $2p_\sigma$	1.0169	0.9951

are identical, while that at N-2 in (10) and (11) is substantially less negative (Table 3). In heterocyclic analogues of the cyclopentadienyl anion [*e.g.* (10) and (11)], it is possible for the reagent to attack purely in-plane (σ), perpendicular to the ring (pure Π), or at any intermediate angle (σ–Π). There is no certain knowledge of the mechanism in the cases (10) and (11); but in a CNDO-2 investigation of the methylation of the tetrazole anion by methyl chloride we have shown [22] that at both N-1 and N-2, σ-attack is preferred to either Π or σ–Π; however, an example of the latter must of course occur in the 3-methylation of the indole anion.[23]

It is well established from non- and semi-empirical [2,7] calculations that $2s_N$ and $2s_O$ orbital densities have a heavily localised character, and that the principal bonding between the atoms is between $2p_N$, $2p_O$, and $1s_H$; this led to the earlier proposition [2] that reactivity might be associated (in reactions which are mechanistically similar and where alternative sites exist) with the radial $2p_N$ electron density in the heterocycle. For the cinnolines the reaction can unequivocally be assigned to pure σ-attack. For reaction at N-2 in both (8) and (9) again attack through the σ-system seems probable (Table 3) while for N-1 there is little to choose between pure σ- and pure Π-attack. Since of course, it is possible to re-partition the electron density into mixed σ–Π systems (equivalent to sp^3 hybridisation at N) it is possible that some at least of the N-1 reactivity occurs through either the latter or the Π-route. This would account for the still substantial amount of attack on N-1 in (3i) in particular. This possibility of more than one mechanism for reaction in the indazole and benzotriazole anions calls for further experiments to test the hypothesis. It has an additional advantage that it does not require the fortuitous balance of σ-steric and electronic factors at N-1 and N-2 in the indazole anion. It is

TABLE 4

Coupling constants (Hz) of indazoles

	$J_{3,7}$	$J_{4,5}$	$J_{4,6}$	$J_{4,7}$	$J_{5,6}$	$J_{5,7}$	$J_{6,7}$
Indazoles (1a and c)							
Substituents							
None (0.08) [a]	0.89	8.22	1.00	1.12	6.97	1.04	8.48
None (0.10) [b]	0.99	8.15	0.95	1.04	6.89	0.82	8.36
1-Me (0.04)	0.85	8.81	0.89	0.97	6.87	0.86	8.38
3-Me (0.06) [c]		8.24	0.96	1.01	7.01	0.79	8.34
1,3-Me (0.07) [c]		8.29	1.02	1.08	6.96	0.85	8.46
7-Me (0.05) [c,d]		8.28	0.66		6.75		
3,7-Me_2 (0.10) [c,d]		8.11	0.91		6.99		
1,3,7-Me_3 (0.05) [c,d]		8.36	0.68		6.99		
3-Et (0.10)		8.26	0.91	1.01	6.97	0.90	8.44
1-Me, 3-Et (0.30)		8.13	1.05	0.84	7.14	0.80	9.17
1-Me, 5-NO_2 (0.40)	0.84		2.15	0.68			9.42
1-Me, 6-NO_2 (0.03)	0.95	8.83		0.76		1.97	
1-Me, 7-NO_2 (0.05)		8.02	0.91		7.87		
Indazoles (2a and c)							
Substituents							
2-Me (0.04) [e]	0.89	8.35	1.14	1.04	6.71	0.85	8.52
2,3-Me_2 (0.07) [b]		8.44	1.00	1.02	6.86	0.72	8.53
2,7-Me_2 (0.10) [c,d]		8.72	0.78		6.83		
2,3,7-Me_3 (0.05) [c,d]		8.39	1.00		6.71		
2-Me, 3-Et (0.09)		8.37	1.03	1.16	6.79	0.88	8.68
2-Me, 5-NO_2 (0.09)	0.84		2.15	0.75			9.65
2-Me, 6-NO_2 (0.07) [f]	0.84	9.23		0.80		2.03	
2-Me, 7-NO_2 (0.06)		8.02	0.91		7.87		

[a] Standard deviations in parenthesis. [b] Ref. 24. [c] Spin decoupling of 3- and 7-substituents in this analysis. [d] Order of coupling constants $J_{4,5} > J_{5,6}$ assigned by analogy with other members of the series where no 7-substituent present. [e] $J_{2\text{-Me},3}$ 0.5, $J_{3,6}$ 0.11 Hz. [f] $J_{3,4}$ 0.12, $J_{3,5}$ 0.12 Hz.

[22] M. H. Palmer and K. Mallen, to be published.

[23] M. H. Palmer, 'Structure and Reactions of Heterocyclic Compounds,' Arnold, London, 1967, p. 317.

of course clear that the 6/5 fusion in these bicyclic systems leads to lower steric effects in plane than the 6/6 fusion of the cinnolines.

N.m.r. Spectra of the Indazole and Benzotriazoles.—(i) *Assignments.* As mentioned above the mixtures (1c) and (2c) and (1d) and (2d) were separated and subjected to detailed n.m.r. analyses. Of the present compounds only indazole [24] and benzotriazole and its 1- and 2-methyl derivatives [25–27] have been studied by iterative analyses; for indazole only the value of $J_{5,7}$ lies outside the combined probable errors of the two analyses,[24] and in the light of the values for the other compounds (Tables 4 and 5) it seems that the earlier value may be more reliable, although the overall error in the present analysis is better. The results for benzotriazole (Table 6) and its 1- and 2-methyl derivatives are in good agreement with some of the previous analyses [25,26] but not others.[27]

In the 3- and 7-unsubstituted indazoles the ABCD analysis was assigned to the hydrogen atoms shown on the basis of the inter-ring coupling ($J_{3,7}$) which is well known in bicyclic aromatic [28] and heterocyclic compounds.[24,29] In the 2-methyl series this was also consistent with assignment of the 7-H to the low-field position by analogy with early work on quinolines [29] and other heterocycles.[14] The assignments of the 3- and 7-substituted compounds then followed on the assumption that a methyl substituent had an insignificant or small effect upon coupling constants,* but led to a

TABLE 5

Chemical shifts (δ) of indazoles

	N-Me	3-H	4-H	5-H	6-H	7-H
Indazoles (1a and c) Substituents						
None (0.06) [a,b]		8.1030	7.7686	7.1163	7.3374	7.5886
1-Me (0.03) [c]	3.95	7.9335	7.7071	7.0954	7.3374	7.5886
3-Me (0.03) [c,d]		(2.63)	7.6436	7.0976	7.3167	7.3990
1,3-Me_2 (0.07) [c,d]	3.90	(2.53)	7.5682	7.0452	7.2865	7.2048
7-Me (0.03) [c,d]		8.110	7.5599	7.0385	7.1033	(2.56)
1,7-Me_2 (0.03) [c,d]	4.18	7.850	7.550	6.950	7.000	(2.62)
3,7-Me_2 (0.08) [c,d]		(2.54)	7.4805	7.0349	7.110	(2.47)
1,3,7-Me_3 (0.03) [c,d]	4.15	(2.55)	7.3770	6.9020	6.9615	(2.73)
3-Et (0.05) [c]		3.05, 1.42	7.6924	7.0928	7.3171	7.3940
1-Me, 3-Et (0.07) [c]	3.95	2.98, 1.30	7.6607	7.0771	7.3363	7.2944
5-NO_2 (0.03) [b]		8.370	8.810		8.260	7.770
1-Me, 5-NO_2 (0.03) [c]	4.15	8.1526	8.6662		8.2345	7.4362
6-NO_2 (0.03) [b]		9.200	8.000	8.960		9.270
1-Me, 6-NO_2 (0.03) [c]	4.18	8.0931	7.8128	7.9787		8.3581
7-NO_2 (0.03) [b]		9.250	9.320	8.290	9.190	
1-Me, 7-NO_2 (0.03) [c]	4.18	8.0600	7.9376	7.1436	8.0076	
Indazoles (2a and c) Substituents						
2-Me (0.04) [c]	3.80	7.672	7.5591	7.0203	7.2251	7.6807
2,3-Me_2 (0.08) [c]	3.85	(2.33)	7.5841	6.9336	7.1883	7.4014
2,7-Me_2 (0.09) [c,d]	4.10	(7.70)	7.4183	6.9508	6.9972	(2.62)
2,3,7-Me_3 (0.06) [c,d]	3.96	(2.42)	7.3092	6.8907	6.9763	(2.58)
2-Me, 3-Et (0.08) [c]	3.99	2.91, 1.30	7.5326	6.9702	7.2107	7.6096
2-Me, 5-NO_2 (0.08) [c]	4.26	8.2080	8.6663		8.0690	7.7160
2-Me, 6-NO_2 (0.06) [c]	4.30	8.0350	7.7308	7.8551		8.6320
2-Me, 7-NO_2 (0.06) [c]	4.16	8.2220	8.0339	7.1537	8.2817	

[a] Standard deviations in parentheses. [b] In $(CD_3)_2CO$, concentration 200 ± 50 g l^{-1}. [c] In $CDCl_3$, concentration 200 ± 20 g l^{-1}. [d] Spin decoupling of the 3- or 7-substituent included in present analysis.

TABLE 6

Chemical shifts (δ) and coupling constants (Hz) for benzotriazoles

	4-H	5-H	6-H	7-H
Substituent				
None (0.04) [a]	7.8728	7.3210	7.3210	7.8728
1-Me (0.03)	8.0127	7.3356	7.4565	7.4751
2-Me (0.03)	7.8306	7.3328	7.3328	7.8306

	$J_{4,5}$	$J_{4,6}$	$J_{4,7}$	$J_{5,6}$	$J_{5,7}$	$J_{6,7}$
Substituent						
None (0.07) [a]	8.34	1.17	0.88	7.08	1.17	8.34
1-Me (0.02)	8.20	0.77	0.93	6.61	1.18	8.36
2-Me (0.05)	8.65	1.03	1.04	6.79	1.03	8.65

[a] Standard deviations in parentheses.

* In studies of polycyclic hydrocarbons two steric factors resulting from *peri*-interactions have been identified,[30] namely naphthalene (S_N +0.08 Hz) and phenanthrene (S_{Ph} 0.30 Hz). In fused 5,6-bicyclic systems the effect of a 3-methyl group is likely to lie between these two figures. Although comparison of (3a) with (3b), and their 1- and 2-methyl corresponding pairs does disclose an increase in $J_{4,5}$ (*ca.* 0.10 Hz) this is not observed with all pairs when a 3-methyl substituent is introduced, particularly in the 7-methylindazole series.

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slight upfield shift on *ortho*-H or downfield shift with *peri*-H.[29] Coupling between the 7-methyl substituent (3g and j) and 4-, 5-, and 6-H was observed and the iterative analysis was assisted by spin decoupling of this substituent. The effects of a nitro-group on the adjacent coupling constants in the indazoles follow earlier studies of quinolines [29,31] and naphthalenes.[32]

(ii) *Comparison of the* 1- *and* 2-*methyl series* (1) *and* (2). (a) Chemical shifts. Although the spectra (Figure) appear very different, this largely arises from the deshielding effect on the N-1 lone pair on H-7 in the 2-methyl series (1) and the consequent change in pattern from ABCD towards ABCX. Thus the 2-methyl series often show non-overlapping multiplet spectra (Table 5), in contrast to the 1-methyl series. It is well established that chemical shifts are more dependent upon solvent and concentration than the coupling constants; in the present work we used comparatively strong solutions in $CDCl_3$, which were chosen to be similar in strength in all cases, especially within 1- and 2-methyl isomeric pairs. Over five pairs of the 1- and 2-methyl series, the latter give signals *upfield* from these of the former in all cases, the differences being small and varying with the nucleus: 9.0 (4-H), 6.0 Hz (5-, 6-H). The 7-H difference is omitted owing to the change in environment noted above. At the present concentration range in $CDCl_3$ the naphthalene resonances are at 782 (1-H, α) and 746 Hz (2-H, β) respectively; whilst these are downfield of the position for the 4-(α), 5-, and 6-H(β) in all the methylindazoles, the shift differences between the naphthalene and indazole resonances are small when the latter are compared [30] with those of cyclohexadiene (1-H; 568.3; 2-H, 582.9 Hz in C_6H_6) even when possible differences in solvent are allowed for. The chemical shifts of the 3- and 5-H of 1-methylpyrazole are similar (730 and 736 Hz respectively); [33] by comparison the 3-H signals of the indazoles, which lie in the range 765—800 Hz, are significantly downfield in both 1- and 2-methyl series. Thus in the light of these effects upon both protons in the carbocyclic and heterocyclic rings we conclude that the shifts indicate ring current contributions from both rings (13) rather than from one (14) or no rings.

(b) Coupling constants. Comparison of the coupling constants $J_{a,b}$ (Table 4) between the 1- and 2-methyl series (five pairs of compounds) shows that $J_{4,5}$ and $J_{5,6}$ are larger in the 2-methyl series by *ca.* 0.20 and 0.23 Hz respectively; while $J_{4,5}$ and $J_{6,7}$ are also larger in the latter series the difference on average is much smaller (0.10 Hz). When interpreted through the well established vicinal coupling–π-bond order relationships [30,31] these suggest that the 4,5-bond order is slightly higher in the 2-methyl (1) series than the Kekulé-like series (2). However, the average values of the coupling constants in the quinonoid series $J_{4,5}$ 8.45 and $J_{5,6}$ 6.78 Hz are closer to those of the Kekulé-series heterocycles and naphthalene than to cyclohexa-1,3-dienes: some relevant figures ($J_{4,5}$ and $J_{5,6}$) are: indole: 7.84, 7.07; [34] benzofuran: 7.89, 7.27; [34] benzothiophen: 8.09, 7.22; [35] naphthalene: 8.30 ($J_{1,2}$), 6.83 ($J_{2,3}$); [30] cyclohexa-1,3-diene: 9.64, 5.04; [30] *cis*-5,6-dimethylcyclohexa-1,3-diene: 9.46, 4.95 Hz,[36] respectively. These similarities again suggest considerable aromatic character in both the 1- and 2-methyl series.

Conclusions.—Methylation of some simple 3- and 7-substituted indazoles in alkaline solution leads to mixtures of both 1- and 2-methyl compounds. In most cases the 1-isomer is predominant and even when large 7-substituents are present, the 1-isomer is still formed in significant amounts. The electron density calculations on the indazole and benzotriazole anions explain the electronic preference for N-1, but in 7-substituted cases it seems probable that reaction at that centre occurs *via* an out-of-plane attack, in contrast to N-2 where σ-attack seems probable under all conditions.

The n.m.r. spectra of the simple indazoles show generally only very small differences between the Kekulé-like 1-methyl series and the quinonoid 2-methyl series. Detailed analyses suggest that the *additional* dienic character of the C-4—C-7 system of the latter is quite small, and that both series are much closer to naphthalene than to cyclohexa-1,3-diene.

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