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# Synthesis, Reactions, and Spectroscopic Properties of Benzimidazoles

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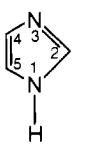
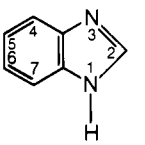
## I. Introduction

The imidazole nucleus (A) is found in a number of important natural products such as histidine, and the purines, while 5,6-dimethyl-**1**-(α-D-ribofuranosyl)benzimidazole is an integral part of the structure[1] of vitamin $B_{12}$. Consequently a massive research effort has been expended upon the chemistry of imidazoles[2] and benzimidazoles (B) with particular emphasis on the synthesis of

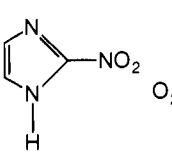


A

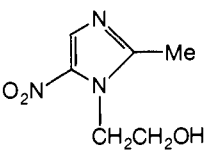


B

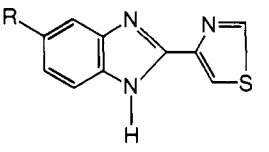
new compounds for pharmacological screening; the discovery of a new antibacterial [*viz.* 2-nitroimidazole (azomycin) (**1**)[3]], a trichomonacide [*viz.* 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole (metronidazole) (**2**)[4]], and anthelmintic agents [*e.g.*, 2-(4-thiazolyl)benzimidazole (thiabendazole (**3a**) and cambendazole (**3b**); *cf.* section IX] has added impetus to investigations in these areas.



**1**



**2**



**3a**, R = H
**b**, R = $NHCO_2$-*i*-Pr

The last systematic reviews on benzimidazoles were published in 1951[5] and 1953,[6] although subsequent surveys have appeared in articles[7-9] covering the chemistry of both imidazoles and benzimidazoles. Aspects of the chemistry of benzimidazole *N*-oxides have been covered in the texts of Ochiai[10] and of Katritzky and Lagowski[11] and also in a short review by Lettau.[12] Specific synthetic routes leading to benzimidazoles and benzimidazole *N*-oxides based on the use of ortho-substituted nitrobenzene derivatives have recently been summarized,[13] and procedures employing ortho-substituted *tert*-alkylaniline derivatives are included in a recent review article.[14]

**TABLE I. Synthesis of Benzimidazoles by the Reaction of o-Arylene Diamines with Carboxylic Acids**

| Carboxylic acid | Ref | Carboxylic acid | Ref |
|---|---|---|---|
| $HCO_2H$ | *b–q* | $HC_2C(CH_2)_2CO_2H$[a] | *m, tt, uu* |
| $CH_3CO_2H$ | *c, g, h, j, l, q–t* | $HO_2CCH=CHCO_2H$[a] (cis) | *vv* |
| $RCO_2H$: R = alkyl, aryl | *u* | $HO_2CCH_2CH(OH)CO_2H$[a] | *vv* |
| $RSCH_2CO_2H$: R = alkyl | *v* | $HO_2CCH(OH)CH(OH)CO_2H$[a] | *ww* |
| $HSCH_2CO_2H$ | *w* | $HO_2C(CH_2)_4CO_2H$[a] | *xx* |
| $ClCH_2CO_2H$ | *x, y* | $HO_2C(CH_2)_8CO_2H$[a] | *yy* |
| $Cl_2CHCO_2H$ | *z, aa* | $HO_2C(CF_2)_nCO_2H$:[a] *n* = 1, 2 | *zz* |
| $Cl_3CCO_2H$ | *aa, bb* | $ArCO_2H$: Ar = aryl | *g, h, j, l, aaa–fff* |
| $F_3CCO_2H$ | *cc–ff, nn* | $RCO_2H$: R = 5-membered ring containing N and S | *ggg, hhh* |
| $F(CF_2)_nCO_2H$: *n* = 1, 2 | *gg* | 4-Pyridinecarboxylic acid | *iii* |
| $HOC(R^1R^2)CO_2H$: $R^1$, $R^2$ = H, alkyl, or aryl | *hh, ii* | $PhCH_2CO_2H$ | *c, g, l, jjj–lll* |
| (ferrocenyl)$(CH_2)_nCO_2H$: *n* = 1–5 | *jj* | *p*-$IC_6H_4CH_2CO_2H$ | *mmm* |
| *c*-$C_6H_{11}(CH_2)_nCO_2H$: *n* = 2, 3 | *kk* | $ArOCH_2CO_2H$: Ar = aryl | *nnn, ooo* |
| *p*-$H_2H_2NO_2SC_6H_4(CH_2)_nCO_2H$; *n* = 1, 2 | *ll* | Benzimidazole-5-carboxylic acid derivatives | *qqq, rrr* |
| $HS(CH_2)_2CO_2H$ | *mm* | 2-Benzimidazolylpropionic acid | *sss* |
| $(CH_3)_2CHCO_2H$ | *nn* | 3-Fluoronaphthalene-2-carboxylic acid | *ttt* |
| $\alpha$-Amino acids | *oo–ss, ppp* | | |

[a] For a more detailed discussion of the synthesis of bisbenzimidazolylalkanes, see section II.H. [b] L. S. Elros, *Zh. Obshch. Khim.*, **23**, 842 (1953); *Chem. Abstr.*, **48**, 4524c (1954). [c] L. S. Elros, *Zh. Obshch. Khim.*, **23**, 957 (1953); *Chem. Abstr.*, **48**, 12740l (1954). [d] A. Sykes and J. C. Tatlow, *J. Chem. Soc.*, 4078 (1952). [e] F. Montarini and R. Passerini, *Boll. Sci. Fac. Chim. Ind. Bologna*, 11, 42 (1953); *Chem. Abstr.*, **48**, 6436h (1954); *Boll. Sci. Fac. Chim. Ind. Bologna*, 11, **46** (1953); *Chem. Abstr.*, **48**, 6437a (1954). [f] J. R. E. Hoover and A. R. Day, *J. Amer. Chem. Soc.*, 77, 4324, 5652 (1955). [g] L. S. Elros, *Zh. Obshch. Khim.*, **22**, 1008 (1952); *Chem. Abstr.*, 47, 12366a (1953). [h] C. A. Haley and P. Maitland, *J. Chem. Soc.*, 3155 (1951). [i] H. B. Gillespie, M. Engelman, and S. Grall, *J. Amer. Chem. Soc.*, 76, 3531 (1954). [j] L. S. Elros, *Zh. Obshch. Khim.*, **23**, 957 (1953); *Chem. Abstr.*, **48**, 8223a (1954). 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Soc.*, **78**, 2445 (1956). [u] D. W. Hein, R. J. Alheim, and J. J. Leavitt, *J. Amer. Chem. Soc.*, 79, 427 (1957); C. Hennart, *Ind. Chim. Belg.*, **31**, 547 (1966). [v] I. Sekikawa, *Bull. Chem. Soc. Jap.*, **31**, 252 (1958). [w] B. P. Fedorov and R. M. Mamedov, *Izv. Akad. Nauk. SSSR, Otd. Khim. Nauk.*, 1626 (1962); *Chem. Abstr.*, **58**, 9048g (1963). [x] O. F. Ginsberg, B. A. Porai-Koshits, M. I. Krylova, and S. M. Lotarelchik, *Zh. Obshch. Khim.*, **27**, 411 (1957); *Chem. Abstr.*, **51**, 15500d (1957). [y] W. Knobloch, *Chem. Ber.*, **91**, 2557 (1958). [z] H. R. Hensel, *ibid.*, **98**, 1325 (1965). [aa] K. H. Beuchel, *Z. Naturforsch. (B)*, **25**, 945 (1970). [bb] Fisons Pest Control Ltd., Netherlands Patent 6,603,719 (1966); *Chem. Abstr.*, 66, 85788y (1967). [cc] Shell Internationale Research Maatschappy NV, Netherlands Patent 6,705,527 (1967); *Chem. Abstr.*, 69, 10437m (1968). [dd] Fisons Pest Control Ltd., French Patent 1,522,661 (1968); *Chem. Abstr.*, 71, 61388v (1969). [ee] Q. F. Soper, U.S. Patent 3,443,015 (1969); *Chem. Abstr.*, 71, 30472p (1969). [ff] K. L. Kirk and L. A. Cohen, *J. Org. Chem.*, **34**, 834 (1969). [gg] Fisons Pest Control Ltd., Belgian Patent 659,384 (1965); *Chem. Abstr.*, **63**, 18101h (1965). [hh] W. R. Siegart and A. R. Day, *J. Amer. Chem. Soc.*, 79, 4391 (1957). [ii] S. Akihama, M. Okude, K. Sato, and S. Iwabuchi, *Yakugaku Zasshi*, **88**, 684 (1968); *Chem. Abstr.*, **69**, 96580u (1968). [jj] D. Heydenhauss and H. Schubert, *Z. Chem.*, 4, 459 (1964); *Chem. Abstr.*, **62**, 9172a (1965). [kk] C. L. Moyle and D. M. Chern, U. S. Patent 3,152,142 (1964); *Chem. Abstr.*, **62**, 566a (1965). [ll] C. L. Moyle and D. M. Chern, U. S. Patent 3,075,991 (1963); *Chem. Abstr.*, **59**, 1645h (1963). [mm] M. D. Nair, *Indian J. Chem.*, **7**, 304 (1969); *Chem. Abstr.*, 71, 3320l (1969). [nn] U. S. Borax and Chemical Corp., British Patent (Amended) 1,015,937 (1971); *Chem. Abstr.*, **75**, 151788n (1971). [oo] R. Crawlord and J. T. Edward, *J. Chem. Soc.*, 673 (1956). [pp] H. Lettré, W. Fritsch, and J. Porath, *Chem. Ber.*, **84**, 719 (1951). [qq] L. A. Cescon and A. R. Day, *J. Org. Chem.*, **27**, 581 (1962). [rr] R. Geiger and W. Seidel, German Patent 1,131,688 (1962); *Chem. Abstr.*, **57**, 16627a (1962). [ss] Y. Kanaoka, K. Tanizawa, and O. Yonemitsu, *Chem. Pharm. Bull.*, 17, 2381 (1969); *Chem. Abstr.*, **72**, 55332b (1970). [tt] J. Stanek and V. Wollrab, *Monatsh. Chem.*, 91, 1064 (1960). [uu] H. A. Dumesnil, French Patent 1,179,933 (1959); *Chem. Abstr.*, **55**, 19953g (1961). [vv] K. C. Tsou, D. J. Rabiger, and B. Sobel, *J. Med. Chem.*, **12**, 818 (1969). [ww] W. R. Roderick, German Patent 2,063,856 (1971); *Chem. Abstr.*, **75**, 76790b (1971). [xx] K. Kakimoto and I. Sekikawa, *Nippon Kagaku Zasshi*, 77, 480 (1956); *Chem. Abstr.*, **52**, 9084b (1958). [yy] C. Rai, W. E. Kramer, and R. C. Kimble, U. S. Patent 3,222,285 (1965); *Chem. 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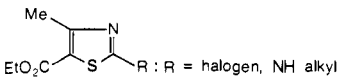
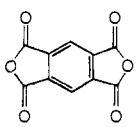
Peru*, **19**, 77 (1953); *Chem. Abstr.*, **49**, 10211 (1955). [jjj] K. Kondal Reddy, N. V. Subba Rao, and Y. C. Ratnam, *Indian J. Chem.* 1, 96 (1963); *Chem. Abstr.*, **59**, 5148h (1963). [kkk] G. M. Kharkharova, *Zh. Obshch. Khim.*, **26**, 1713 (1956); *Chem. Abstr.*, **51**, 1944a (1957). [lll] B. A. Porai-Koshits and G. M. Kharkharova, *Zh. Obshch. Khim.*, **24**, 1651 (1954); *Chem. Abstr.*, 49, 13224h (1955). [mmm] M. Covello, M. R. Mazza, N. Sacco, and F. De Simone, *Rend. Accad. Sci. Fis. Nat. Naples*, **37**, 147 (1970); *Chem. Abstr.*, 76, 34171r (1972). [nnn] C. L. Moyle and D. M. Chern, U. S. Patent 3,182,070 (1965); *Chem. Abstr.*, **63**, 4304d (1965). [ooo] C. L. Moyle and D. M. Chern, U. S. Patent 3,147,274 (1964); *Chem. Abstr.*, 61, 13319c (1964). [ppp] R. Crawlord and J. T. Edward, *J. Chem. Soc.*, 673 (1956). [qqq] B. A. Porai-Koshits, L. S. Elros, and E. S. Bolchinova, *Zh. Obshch. Khim.*, **23**, 835 (1953); *Chem. Abstr.*, **48**, 4523e (1954). [rrr] V. M. Zubarovskii and Yu. P. Makovetskii, *Ukr. Khim. Zh.*, **34**, 1151 (1968); *Chem. Abstr.*, **70**, 68251h (1969). [sss] F. Ackermann and J. Meyer, U. S. Patent 2,515,173 (1950); *Chem. Abstr.*, **45**, 666i (1951). [ttt] D. Holl and H. Peterson, French Patent 1,510,330 (1968); *Chem. Abstr.*, **70**, 77966y (1969).

In this review, a compilation of the synthesis, reactions, and spectroscopic properties of benzimidazoles is presented which incorporates material appearing in *Chemical Abstracts* between 1952 and mid-1972 (*i.e.*, Volume 76 of *Chemical Abstracts*). The chemistry of benzimidazole nucleosides[15] and of benzimidazole-containing polymers[16] is excluded since both these topics have been the subjects of recent reviews. Other aspects of benzimidazole chemistry that have been excluded are organometallic complexes containing a benzimidazole nucleus and 1,2-dihydro derivatives with the exception of the tautomeric benzimidazolin-2-ones (2-hydroxybenzimidazoles) and benzimidazoline-2-thiones (2-mercaptobenzimidazoles). It should be noted, however, that no attempt has been made to present an exhaustive review of benzimidazole chemistry. From 1953 through 1972, the number of citations in *Chemical Abstracts* on benzimidazoles and related products, e.g., benzimidazolium compounds, approximates to 13,000, and clearly a manual scan of these citations would require considerable effort and its value would be questionable; accordingly this review is based upon material appearing in *Chemical Abstracts* under the main heading of "benzimidazole" rather than within the individual compound citation index.

The review is organized primarily in relation to synthesis (section II) and reactions (section III); synthetic procedures are presented in terms of the types of starting materials employed, and the section on reactions is categorized to a large extent on a mechanistic basis rather than on product type. Since benzimidazolin-2-ones are of commercial interest (see section IX), it was felt that they, and also analogous benzimidazoline-2-thiones, should be described within individual sections (IV and V, respectively); sections have also been included on benzimidazole *N*-oxides and benzimidazolium compounds (VI and VII, respectively). The section on spectroscopic

**TABLE II. Synthesis of Benzimidazoles by the Reaction of o-Arylene Diamines with Carboxylic Acid Esters, Amides, Anhydrides, and Chlorides**

| Carboxylic acid derivative | Ref |
|---|---|
| $H_2NCH_2CO_2Et$ | *a* |
| $NCCH_2CO_2Et$ | *b, c* |
| $NCCH(R)CO_2Et$: R = alkyl | *d* |
| $CF_3(CF_2)_2CO_2Ph$ | *e* |
| $BrCH_2COCO_2Et$ | *f, g* |
| $PhCO_2Ph$ | *h* |
|  R : R = halogen, NH alkyl | *i* |
| $ArCH(CN)CO_2Et$: Ar = aryl | *j* |
| $EtO_2CCH_2CO_2Et$ | *k* |
| $(MeO_2C)_2CHCH(CO_2Me)_2$ | |
| $RCONHCH(R)CONH_2$: R = alkyl or aryl | *l* |
| $H_2NCO(CH_2)_nCONH_2$: *n* = 0, 2 | *m* |
| $RNHCO(CH_2)_nCONHR$: *n* = 0, 4, 8; R = $HOCH_2CH_2$ | |
| $PhCONH_2$ | *n* |
| $(CH_3CO)_2O$ | *o* |
|  | *p* |
| $CH_3COCl$ | *q, r* |

[a] H. Irving and O. Weber, *J. Chem. Soc.*, 2296 (1959). [b] J. Büchi, H. Zwicky, and A. Aebi, *Arch. Pharm. (Weinheim)*, **293**, 758 (1960); *Chem. Abstr.*, **55**, 5181 (1961). [c] T. Shen, A. R. Matzuk, and H. Scham, French Patent 1,580,823 (1969); *Chem. Abstr.*, **73**, 25468d (1970). [d] N. Vinot, *Bull. Soc. Chim. Fr.*, 3989 (1966); *Chem. Abstr.*, **66**, 86728d (1967). [e] G. I. Braz, I. E. Kardash, V. V. Kopylov, A. F. Oleinik, G. G. Rozantsev, A. N. Pravednikov, and A. Ya. Yakubovich, *Khim. Geterotsikl. Soedin.*, 339 (1968); *Chem. Abstr.*, **69**, 96574p (1968). [f] Chimetron S.a.r.l., French Patent 1,439,113 (1966); *Chem. Abstr.*, **65**, 18595b (1966). [g] Chimetron S.a.r.l., French Patent 1,450,505 (1966); *Chem. Abstr.*, **67**, 3092a (1967). [h] D. N. Gray, *J. Heterocycl. Chem.*, 7, 947 (1970). [i] J. M. Singh, *Indian J. Appl. Chem.*, **32**, 133 (1969); *Chem. Abstr.*, **75**, 20293z (1971). [j] Ciba Ltd., British Patent 864,131 (1961); *Chem. Abstr.*, **55**, 18776l (1961). [k] R. G. Arnold, U. S. Patent 2,697,711 (1954); *Chem. Abstr.*, **49**, 14036b (1955). [l] H. E. Johnson, U. S. Patent 3,255,202 (1966); *Chem. Abstr.*, **65**, 10595h (1966). [m] E. S. Lane, *J. Chem. Soc.*, 2238 (1953). See also section II.H. [n] S. H. Dandegaonker and G. R. Ravankar, *Karnatak Univ.*, 6, 25 (1961); *Chem. Abstr.*, **59**, 10023c (1963). [o] H. B. Gillespie, F. Spano, and S. Graal, *J. Org. Chem.*, **25**, 942 (1960). [p] B. K. Manukian, *Helv. Chim. Acta*, **47**, 2211 (1964). [q] Illord, Ltd., French Patent 1,486,322 (1967); *Chem. Abstr.*, 69, 27424c (1968). [r] V. M. Zubarovskii, R. N. Moskaleva, and M. P. Bachurina, *Zh. Obshch. Khim.*, **32**, 1581 (1962); *Chem. Abstr.*, **58**, 6952b (1963).

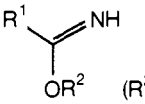
properties (VIII) is restricted to publications dealing specifically rather than incidentally with spectroscopic data and is necessarily short, while the section on commercial applications (IX) is confined to applications in the fields of pharmaceuticals, veterinary anthelmintics, and fungicides; it should be borne in mind, however, that other uses of benzimidazoles have been found, but definitive information on marketed products is rather difficult to accumulate.

## II. Synthesis of Benzimidazoles

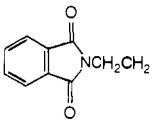
### A. From Reactions of o-Arylene Diamines with Carbonyl-Containing Compounds, Imidates, and Miscellaneous Compounds

Synthetic methods leading to benzimidazoles from the reaction of o-arylene diamines with carboxylic acids (Table I) or their derivatives (Tables II and III) are widely applicable and require little comment. In general, Phillips-type[5] reactions can be effected by heating the diamine with the carboxylic acid in hydrochloric acid, although for the case of aromatic acids this procedure is relatively difficult[17] and polyphosphoric acid is a more suitable reaction medium.[18] One problem concerning the Phillips reaction is that the diamine often competes successfully for the proton of the acid catalyst, hence inhibiting nucleophilic addition to the carbonyl group. This problem is alleviated by replacing the carbonyl group by the more basic imino group, and considerable success has been attained (Table III) using the readily available[19] imino ethers (imidates).

**TABLE III. Synthesis of Benzimidazoles by Reaction of o-Arylene Diamines with Imino Ethers**



($R^2$ = Me or Et)

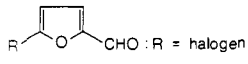
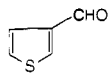
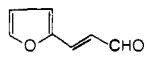
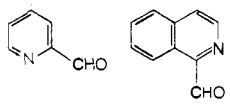
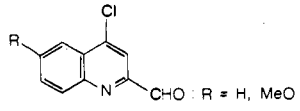
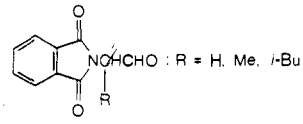
| $R^1$ | Ref |
|---|---|
| $CCl_3$ | *a-c* |
| $CH_2CH_2C(NO_2)Me_2$ | *d* |
| $CH_2CO_2Et$ | *e* |
| $CH_2CH_2NR^1R^2$ [q] | *f* |
| $EtOC(=NH)(CH_2)_n$: *n* = 4, 8 | *g* |
| $ArCH_2$ | *h* |
| $ArNHCH_2$ | *i* |
| $PhCH_2OCONHCR^1R^2-R^1$, $R^2$ = H or alkyl | *j* |
| *p*-$RO-C_6H_4-$: R = H, alkyl | *k* |
| $ArNHCH_2CH_2$ | *l* |
|  | *m* |
| $C_4H_3O$- (2-furyl) | *n* |
| $EtOC(=NH)CH_2$ | *o* |
| $(CH_2)_nBr$ | *p* |

[a] G. Holan, E. L. Samuel, B. C. Ennis, and R. W. Hinde, *J. Chem. Soc. C*, 20 (1967). [b] Monsanto Chemicals (Australia) Ltd., Netherlands Patent 6,414,890 (1965); *Chem. Abstr.*, **63**, 16357l (1965). [c] D. Floyd, U. S. Patent 3,501,492 (1970); *Chem. Abstr.*, **72**, 111469r (1970). [d] N. S. Nametkin, G. A. Shvekhgeimer, V. P. Dukhovskoi and V. D. Tyurin, *Khim. Geterotsikl. Soedin.*, 1073 (1969); *Chem. Abstr.*, **72**, 132610v (1970); V. P. Dukhovskoi, G. A. Shvekhgeimer, and V. D. Tyurin, *Tr. Mosk. Inst. Neftekhim. Gazov. Prom.*, No. 3, 7 (1969); *Chem. Abstr.*, **75**, 140761x (1971). [e] J. J. Ursprung, U. S. Patent 3,105,837 (1963); *Chem. Abstr.*, **60**, 1763g (1964); *cf.* also British Patent 935,776 (1963). [f] M. Mousseron, J. M. Kamenka, and A. Steiger, *Chim. Ther.*, **2**, 95 (1967); *Chem. Abstr.*, **68**, 21883j (1968). [g] P. R. Thomas and G. J. Tyler, *J. Chem. Soc.*, 2197 (1957). [h] A. Hunger, J. Kebrle, A. Rossi, and K. Hollmann, *Helv. Chim. Acta*, **43**, 800, 1032, 1727 (1960); German Patents 1,078,579, 1,077,666, 1,075,622, 1,079,059, 1,079,646, 1,081,019 (1960); *Chem. Abstr.*, **55**, 18776b, 19953h, 19954e, 25988i, 25989g, 25990c (1961); British Patent 870,385 (1961); *Chem. Abstr.*, **55**, 25988g (1961); Swiss Patent 361,286 (1962); *Chem. Abstr.*, **58**, 6835c (1963); F. Sparatore, U. S. Patent 3,394,141 (1968); *Chem. Abstr.*, 69, 86995n (1968); Ciba Ltd., British Patent 871,808 (1961); *Chem. Abstr.*, **57**, 4673 (1962); F. Sparatori, V. Boido, and F. Fanelli, *Farmaco, Ed. Sci.*, **23**, 344 (1968); *Chem. Abstr.*, **69**, 59157j (1968). [i] A. Hunger, J. Kebrle, A. Rossi, and K. Hollmann, U. S. Patent 3,004,982 (1959); *Chem. Abstr.*, **56**, 4772h (1962). [j] M. Mengelberg, *Chem. Ber.*, **92**, 977 (1959). [k] Farberke Hoechst A.-G., French Medicinal Patent 6681 (1969); *Chem. Abstr.*, **75**, 5898g (1971). [l] Z. F. Solomko and G. A. Polinovskii, *Khim. Geterotsikl. Soedin.*, 874 (1969); *Chem. Abstr.*, **72**, 100598l (1970). [m] M. S. Malinovskii, Z. F. Solomko, G. A. Poinovskii, and V. I. Shvets, USSR Patent 237,901 (1969); *Chem. Abstr.*, 71, 61390q (1969). [n] R. C. DeSelms, *J. Org. Chem.*, **27**, 2163 (1962). [o] Heidenheimer Chemisches Laboratium, British Patent 910,146 (1962); *Chem. Abstr.*, **58**, 9087d (1963). [p] R. C. DeSelms, *J. Org. Chem.*, **27**, 2165 (1962). [q] $NR^1R^2$ represents, *e.g.*, piperidino, morpholino, pyrrolidino, etc.

Apparently the aldehyde route to benzimidazoles is particularly suitable for the synthesis of compounds containing a heterocyclic group in the 2 position (see Table IV). A number of rather more unusual synthetic methods based on o-arylene diamines and related compounds are summarized in Table V.

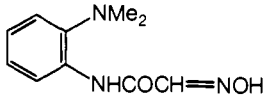
The formation of **1**-methylbenzimidazole 2-aldoxime from the reaction of *N,N*-dimethyl-*o*-phenylenediamine with chloral hydrate and hydroxylamine was first discovered by Petrov, *et al.*,[21a,b] who were actually intending to prepare *o*-(*N,N*-dimethylamino)isonitrosoacetanilide (**4**) (*cf.* the behavior[25] of aniline). The synthetic potential of such reactions has subsequently been evaluated by Garner and Suschitzky[21c] who obtained a series of oximes **5a** in ca. 60% yield from the appropriate *N*-(2-aminoaryl)-

**TABLE IV. Synthesis of Benzimidazoles by Reaction of o-Arylene Diamines with Aldehydes**

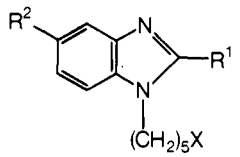
| Aldehyde | Ref |
|---|---|
| RCHO: R = alkyl, aryl, aralkyl, hetaryl | *a* |
| ArCHO: Ar = aryl | *b–h* |
|  | *i, j* |
|  | *k* |
|  | *l* |
|  | *m* |
|  | *n* |
|  | *o* |

[a] D. Jerchel, H. Fischer, and M. Kracht, *Justus Liebigs Ann. Chem.*, **575**, 162 (1952). [b] M. Schenck, H. Richter, and H. Vogel, German Patent 901,649 (1954) (Addn. to German Patent 890,644); *Chem. Abstr.*, **52**, 12926g (1962). [c] N. V. Subba Rao and C. V. Ratnam, *J. Indian Chem. Soc.*, **38**, 631 (1961). [d] O. Sues, U. S. Patent 3,050,389 (1962); *Chem. Abstr.*, **59**, 1150e (1963); [e] J. R. Bottu, French Patent 1,569,337 (1968); *Chem. Abstr.*, **72** 10073m (1970). [f] G. Hasegawa and H. Maruyama, Japanese Patent 71 09,581 (1971); *Chem. Abstr.*, **75**, 76797j (1971). [g] J. G. Smith and I. Ho, *Tetrahedron Lett.*, 3541 (1971). [h] C. M. Orlando, J. G. Wirth, and D. R. Heath, German Patent 2,064,683 (1971); *Chem. Abstr.*, **75**, 110313k (1971). [i] V. Ts. Bukhaeva, *Mater. Nauch. Konf. Aspir., Rostov.-na-Donu Gos. Univ.*, 233 (1968); *Chem. Abstr.*, 71, 13060k (1969). [j] A. F. Pozharskii, V. Ts. Bukhaeva, and A. M. Simonov, *Khim. Geterotsikl. Soedin.*, 910 (1967); *Chem. Abstr.*, **68**, 105094r (1968). [k] Merck and Co. Inc., British Patent 966,796 (1964); *Chem. Abstr.*, **62**, 2779h (1965). [l] A. F. Pozharskii, V. Ts. Bukhaeva, A. M. Simonov, L. Ya Bakhmet, and O. M. Aleksan'yan, *Khim. Geterotsikl. Soedin.*, 325 (1969); *Chem. Abstr.*, 71, 22066u (1969). [m] J. M. McManus and R. M. Herbst, *J. Org. Chem.*, **24**, 1042 (1959). [n] A. L. Gershuns and A. N. Brizitskaya, *Khim. Geterotsikl. Soedin.*, 835 (1970); *Chem. Abstr.*, **73**, 109738e (1970). [o] N. Vinot, *C. R. Acad. Sci.*, **256**, 699 (1963).

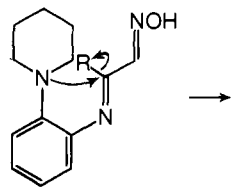
piperidines. Derivatives **5b,c**, other than 2-oximes, can be isolated by replacing hydroxylamine by analogous reagents such as semicarbazide or phenylhydrazine. The mechanism probably[21c] involves an intermediate chlorimine **6a** rather than an isonitrosoacetanilide **6b** since the latter is not converted into a benzimidazole under the reaction conditions. An additional feature of this work is that the chloro derivatives **5a** are valuable synthetic intermediates; on prolonged treatment[21c] with hot polyphosphoric acid they are converted into tricyclic derivatives [*cf.* **5a** ($R^2$ = H) → **7**; also ref 26 and **27** and section I.C].



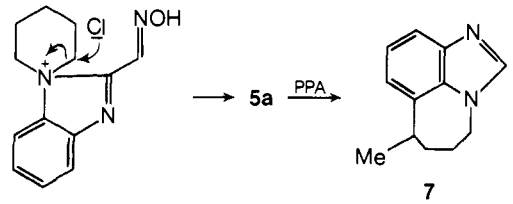
**4**



**5a**, $R^1$ = CH═NOH; $R^2$ = H, Cl or $NO_2$; X = Cl
**b**, $R^1$ = CH═NNHCONH$_2$; $R^2$ = H; X = Cl
**c**, $R^1$ = CH═NNHPh; $R^2$ = H; X = Cl

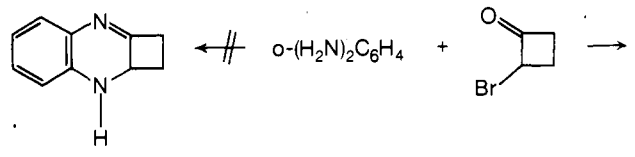


**6a**, R = Cl
**b**, R = OH

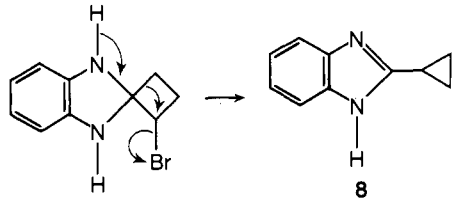


**7**

A skeletal rearrangement is probably also involved in the reaction[20] of o-phenylenediamine with 2-bromocyclobutanone which produces 2-cyclopropylbenzimidazole (**8**) and not a 1,2-dihydroquinoxaline derivative (**9**) as had been earlier suggested.[28]

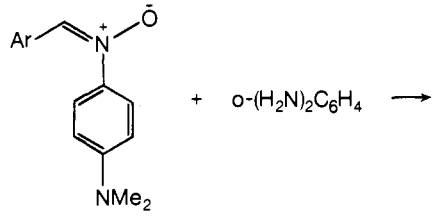


**9**

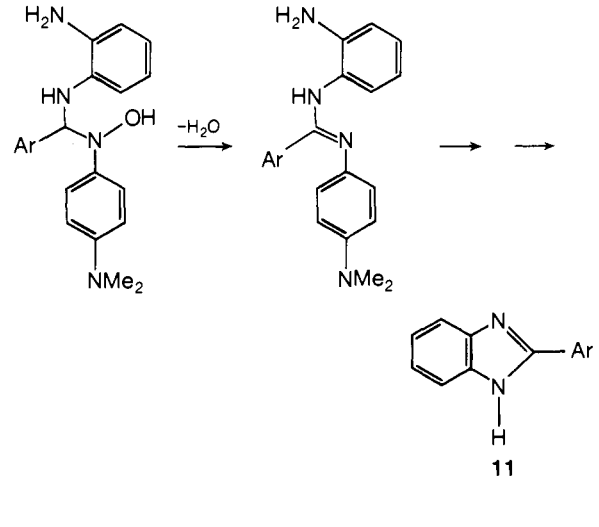


**8**

The synthesis[22,23] of 1- and 1,2-disubstituted benzimidazoles from the methoxy and cyano anil derivatives (see Table V) probably involves an addition–elimination mechanism, and a comparable route can also be envi-

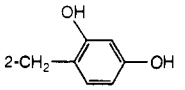
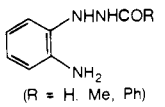
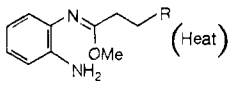
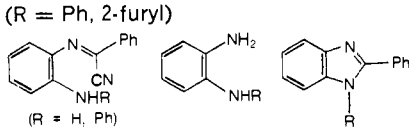
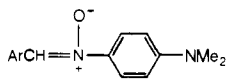


**10**



**11**

**TABLE V. Synthesis of Benzimidazoles by the Reaction of o-Arylene Diamines with Miscellaneous Compounds**

| Type of diamine deriv | Type of reagent | Type of benzimidazole product | Ref |
|---|---|---|---|
| o-Phenylenediamine | Lactone |  | a |
| o-Phenylenediamine | Lactone | 2-$(CH_2)_3OH$ | b |
| o-Phenylenediamine | $PhCOCH_2CN$ | 2-Ph | c |
| o-Phenylenediamine | $Cl_2C{=}NCO_2R$ | 2-$NHCO_2R$ (R = alkyl, aralkyl) | d |
| o-Phenylenediamine | $H_2NC(=NH)SMe/ClCOSR$ | 2-NHCOSR (R = alkyl, aryl) | e, f |
| o-Phenylenediamine | $(MeS)_2C{=}NCO_2Me$ | 2-$NHCO_2Me$ | g |
| o-Phenylenediamine | Dicyandiamides | 2-NHC(=NH)NHR (R = alkyl) | h |
| o-Phenylenediamine | 2-Bromocyclobutanone | 2-Cyclopropyl | 20 |
| o-Phenylene diamine N-Alkyl derivatives | PhN=C=NPh or PhN=C(NHMe)SMe | 1-Alkyl-2-NHPh | i |
| o-(N-Alkylamino)arylamines o-(N,N-Dialkylamino)arylamines N-(2-Aminoaryl)cycloalkylamines | $MnO_2$ or $CF_3CO_3H$ | 1-Alkyl, 1,2-dialkyl, and tricyclic derivatives | j, k |
|  (R = H, Me, Ph) | Aq m-$O_2NC_6H_4SO_3H$/heat | 1-$NH_2$-2R | l, m |
| N,N-Dimethyl-o-phenylenediamine | $Cl_3CCHO/H_2NOH$/aq HCl | 1-Me-2-CH=NOH | 21 |
| N-(2-Aminoaryl)piperidine | | 1-(5-Cl-n-pentyl)-2-CH=NOH | |
|  | | 2-$CH_2CH_2R$ | 22 |
| (R = Ph, 2-furyl)  (R = H, Ph) | | | 23 |
| o-Phenylenediamine |  | 2-Aryl | 23 |

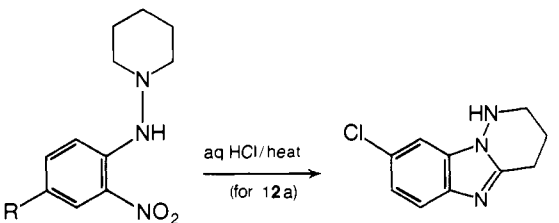
[a] F. S. Babichev and L. G. Rudchenko, *Ukr. Khim. Zh.*, **34**, 1269 (1968); *Chem. Abstr.*, **70**, 115062j (1969). [b] V. I. Shvedov, L. B. Altukhova, L. A. Cheruyshova, and A. N. Grinev, *Zh. Org. Khim.*, **5**, 2221 (1969); *Chem. Abstr.*, **72**, 66865d (1970). [c] F. Krohnke and H. Leister, *Chem. Ber.*, 91, 1479 (1958). [d] A. Widdig and E. Kuehle, German Patent 1,932,297 (1971); *Chem. Abstr.*, **74**, 76426s (1971). [e] E. H. Pommer, H. Osieka, K. H. Koenig, and G. Bolz, German Patent 2,012,589 (1971); *Chem. Abstr.*, **76**, 25294l (1972). [f] R. Aries, French Patent 2,052,901 (1971); *Chem. Abstr.*, 76, 46203r (1972). [g] M. M. Fawzi, U. S. Patent 3,562,290 (1971); *Chem. Abstr.*, **75**, 5896e (1971). [h] R. M. Acheson, G. A. Taylor, and M. L. Tomlinson, *J. Chem. Soc.*, 3750 (1958). [i] A. Hunger, J. Kebrle, A. Rossi, and K. Hollmann, *Helv. Chim. Acta.*, 44, 1273 (1961); U. S. Patent 3,000,898 (1959); *Chem. Abstr.*, **56**, 2456a (1962). [j] O. Meth-Cohn, H. Suschitzky, and M. E. Sutton, *J. Chem. Soc. C*, 1722 (1968). [k] M. D. Nair and R. Adams, *J. Amer. Chem. Soc.*, **83**, 3581 (1961). [l] R. A. Abramovitch and K. Scholield, *J. Chem. Soc.*, 2326 (1955). [m] For a superior route to 1-aminobenzimidazoles, see ref 24.

saged[23] for 2-arylbenzimidazole formation from the reaction of o-phenylenediamine with aryl-*N*-(*p*-dimethylaminophenyl)nitrones (*cf.* **10** → **11**). Yields for reactions of this type involving both anils[22,23] and nitrones[23] are often high (50–90%).

## B. From o-Nitroarylamines and o-Dinitroarenes

A number of methods have been developed in which benzimidazole syntheses are accomplished in a single step from an o-nitroarylamine or an o-dinitroarene; some examples of these direct methods are shown in Table VI. Of particular interest from a commercial aspect is the formation of benzimidazoles by thermolysis of nitroarene–alcohol mixtures in the gas phase; an assessment of the nature and scope of contact catalysts for this type of conversion could be encouraging.

Benzimidazoles have also been obtained from *N*-alkyl- and *N,N*-dialkyl-o-nitroarylamines by reduction with ferrous oxalate[29,30] or trialkyl phosphites,[31] but they can usually be obtained more efficiently by heating the amines in sand at ca. 240°; reactions of the last type together with related procedures leading to benzimidazoles and their 1-oxide derivatives have been summarized in recent reviews.[13,14] Subsequently the acid-catalyzed cyclization of *N*-(o-nitroanilino)-substituted aliphatic amines to *N*-aminobenzimidazoles (*e.g.*, **12a** → **13**) has been reported.[32] Reactions of this type give fair yields of benzimidazoles (*e.g.*, **13**) under reflux conditions in aqueous hydrochloric acid; for nitro derivatives, however (*e.g.*, **12b**), benzotriazole and benzotriazole *N*-oxide formation (*cf.* ref 13 and 14) competes successfully with benzimidazole formation, and for these cases polyphosphoric acid must be used. The mechanism of this type of reaction is considered[32] to involve a 1,5-sigmatropic rearrangement (path a, Scheme I) as a key step; such a process is thought[32] to have analogy in the thermal uncatalyzed cyclization[33] of *N*-cyclohexyl-o-nitroaniline (**14**) into the tricyclic derivative **15**, while introduction of halogen into the aryl ring has previously been noted during hydrochloric acid catalyzed cyclizations leading to benzimidazole *N*-oxides.[13,14,34]



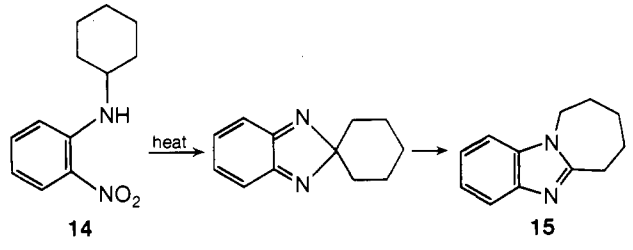

**12a**, R = H
**b**, R = $NO_2$

**13**

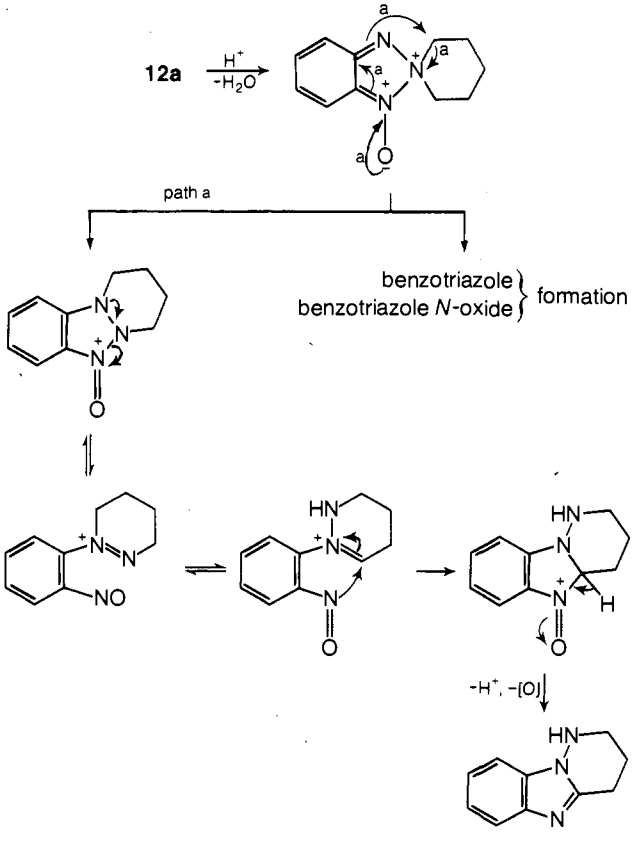
**TABLE VI. Synthesis of Benzimidazoles from o-Nitroarylamines and o-Dinitroarenes**

| Starting materials | Reductant or catalyst | Reaction conditions | Product benzimidazole | Ref |
|---|---|---|---|---|
| o-Nitroaniline/$HCONH_2$/$HCO_2NH_4$ | $NaHSO_3$ | 150°/1 hr | Unsubstituted | a |
| o-Nitroaniline/benzaldehyde | | Xylene, reflux | Unsubstituted | b |
| 2,4-Dinitro-6-methoxy-*N*-methylaniline | $BaSO_4$/Pd/$H_2$ or Sn/HCl | | 1-Me-5-$NH_2$-7-MeO | c |
| o-Nitroaniline/$HCO_2H$ | Zn | 100°/3 hr | Unsubstituted | d |
| 2-Nitro-S-isopropyloxycarbonylamino-*N*-(4-thiazolylmethyl)aniline[k] | $Na_2SO_3$ | Aq $H_2SO_4$, reflux | 2-(4-Thiazolyl)isopropyloxy-carbonylamino | e |
| o-Nitroaniline/$CH_3OH$ | $Al_2O_3$ | 320° | 1-Me | f |
| o-Nitroaniline/ROH | V/Cu/$Al_2O_3$ | 320° | 2-Alkyl | g |
| o-Dinitrobenzene/ROH | Cu/$Al_2O_3$ | 320° | 2-Alkyl | h |
| o-Dinitrobenzene/$CF_3CO_2H$ | Sn/HCl | 60–70° | 2-$CF_3$ | i |
| 2,3-Dinitroanisole/$PhCH_2NH_2$ | | Xylene reflux | 2-Ph-4-MeO | j |

[a] J. Gyurko and J. Kaloczy, Hungarian Patent 149,980 (1963); *Chem. Abstr.* **59**, 14000e (1963). [b] E. Yu. Belyaev, V. P. Kumarev, L. E. Kondrat'eva, and E. I. Shakhova, *Khim. Geterotsikl. Soedin.*, 6, 1688 (1970); *Chem. Abstr.*, 74, 53650w (1971); *Khim. Geterotsikl. Soedin.*, 7, 1293 (1971); *Chem. Abstr.*, 76, 34169w (1972). [c] L. Horner and V. Schwenk, *Justus Liebigs Ann. Chem.*, 579, 204 (1953). [d] Tanabe Drug Manulacturing Co., Japanese Patent 4728 (1952); *Chem. Abstr.*, 47, 11257i (1953). [e] R. L. Ellsworth, D. F. Hinkley, and E. F. Schoenewaldt, French Patent, 2,014,420 (1970); *Chem. Abstr.*, 74, 53799b (1971). [f] N. S. Koslov and M. N. Stepanova, *Dokl. Akad. Nauk. Belorus. SSR*, 13, 541 (1969); *Chem. Abstr.*, 71, 124337a (1969). [g] N. S. Koslov and M. N. Tovshtein, *Vestsi. Akad. Navuk Belarus. SSR, Ser. Khim. Navuk*, 89 (1967); *Chem. Abstr.*, 68, 49507p (1968). [h] N. S. Koslov and M. N. Tovshtein, *Vestsi. Akad. Navuk Belarus. SSR, Ser. Khim. Navuk*, 72 (1968); *Chem. Abstr.*, 70, 115063k (1969). [i] Shell Internationale Research Maatschappij N. V., Netherlands Patent Appl. 6,707,085 (1967); *Chem. Abstr.*, 69, 27419e (1968). [j] A. M. Simonov, V. M. Mar'yanovskii, and A. F. Pozharskii, *Zh. Org. Khim.*, 4, 534 (1968); *Chem. Abstr.*, 68, 105088s (1968). [k] S denotes that the position of the substitutent in the aryl ring is not stated.

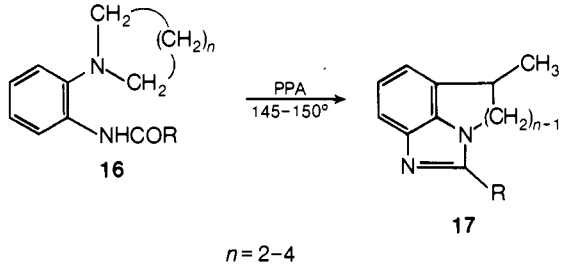



**SCHEME I**




## C. From *o*-(*N*-Acylamino and -aroylamino)arylamines and -Nitrobenzenes

Routine cyclization procedures using *o*-(*N*-acylamino and -aroylamino)arylamines and -nitrobenzenes are shown in Table VII. Formation[35] of the tricyclic derivatives **17** from N-substituted heterocycles of type **16** by heating in polyphosphoric acid is rather more interesting since a skeletal rearrangement occurs. The best yields of




*n* = 2–4
R = H, Me, Ph

benzimidazoles are obtained from piperidine derivatives (**16**, R = Me; *n* = 3) on the one hand and acetyl deriva-

**SCHEME II**

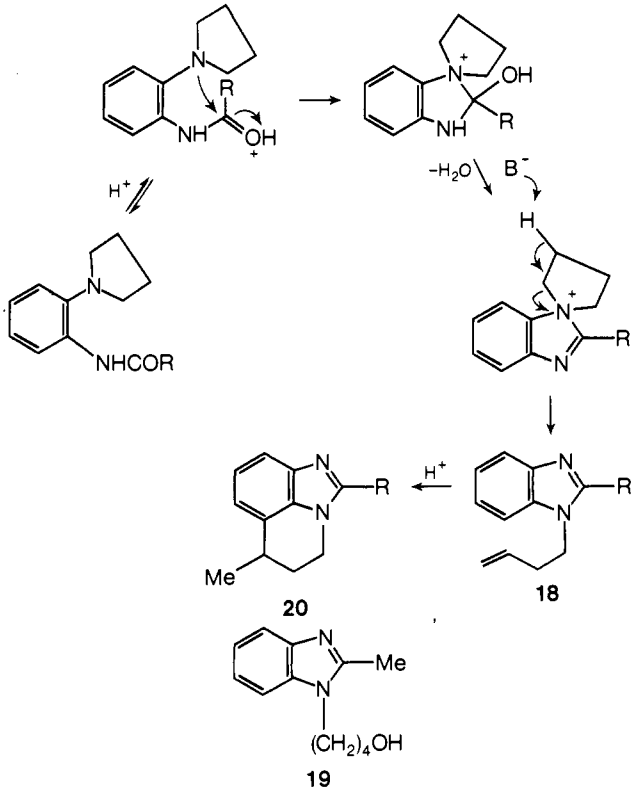
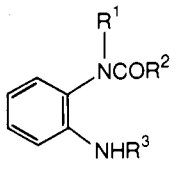
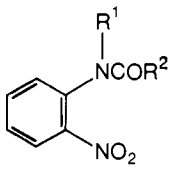


**TABLE VII. Synthesis of Benzimidazoles from o-[*N*-Acylamino- and -aroylamino]arylamines and -Nitrobenzenes**



A



B

| Starting material[a] Compound A | | | Reaction conditions | Ref |
|---|---|---|---|---|
| $R^1$ | $R^2$ | $R^3$ | | |
| H, Ac, Et $Et_2N(CH_2)_2$ | Aryl | H | Aq HCl/heat | *a* |
| H | Me | Dodecyl, dialkylamino(alkyl), hydroxyalkyl | HCl, EtOH/room temp | *b* |
| H | (Dialkylamino)alkyl | Aryl | Aq HCl/heat | *c* |
| H | Me | Aralkyl | Aq HCl/heat | *d* |
| H | Aryl | H | Aq HCl/$H_2SO_4$/heat | *e* |
| H | Carbamoyl | H | $H_2O$/heat[a] | *f* |
| H | Chloroalkyl | Chloroacyl | Heat | *g* |

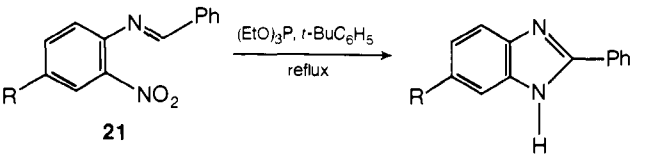
| Compound B | | Reaction conditions | Ref |
|---|---|---|---|
| $R^1$ | $R^2$ | | |
| H | Me | Sn/AcOH/heat | *h* |
| H | 4-Thiazolyl | (i) Pd/C/$H_2$ (ii) Aq HCl/heat | *i* |
| H | $CF_3$ | $H_2$/Raney Ni | *j* |
| H | Me | $Na_2S_2O_4$/heat | *k* |
| H | 4-Thiazolyl | Fe/AcOH[p] | *l* |
| H, Me | Aryl | $SnCl_2$/HCl/heat | *m* |

[a] P. Rohrbach and I. Karadavidoll, German Patent 2,049,377 (1971); *Chem. Abstr.*, **75**, 20398n (1971). [b] Ciba Ltd., British Patent 887,337 (1962); *Chem. Abstr.*, **57**, 15119g (1962). [c] D. J. Drain and J. G. B. Howes, British Patent 989,191 (1965); *Chem. Abstr.*, **63**, 609e (1965). [d] I. Ganea and R. Taranu, *Stud. Univ. Babes-Bolyai, Ser. Chem.*, 95 (1966); *Chem. Abstr.*, 67, 32648s (1967). [e] A. Baklien, Austrian Patent 257,959 (1965); *Chem. Abstr.*, **68**, 12971j (1968). [f] K. Koyamada, T. Matsui, and J. Tobitsuka, Japanese Patent 71.29,853 (1971); *Chem. Abstr.*, 75, 140859k (1971). [g] M. T. LeBris, *Bull. Soc. Chim. Fr.*, 3411 (1967). [h] Y. M. Abou-Zeid, A. A. Abou-Oul, and H. Ragab, *Bull. Fac. Pharm., Cairo Univ.*, **2**, 27 (1963); *Chem. Abstr.*, **62**, 5269b (1965). [i] H. D. Brown, Belgian Patent 613,916 (1962); *Chem. Abstr.*, **59**, 10065a (1963). [j] B. C. Bishop, A. S. Jones, and J. C. Tatlow, *J. Chem. Soc.*, 3076 (1964). [k] M. Itaya, *Yakugaku Zasshi*, **82**, 1 (1962); *Chem. Abstr.*, **57**, 9840a (1962). [l] R. L. Ellsworth, D. F. Hinkley, and E. F. Schoenewaldt, French Patent 2,014,421 (1970); *Chem. Abstr.*, 74, 76425r (1971). [m] B. A. Porai-Koshits and Ch. Frankovskii *Zh. Obshch. Khim.*, **28**, 928 (1958); *Chem. Abstr.*, **52**, 17240I (1958). [n] Substituents in the aryl ring are not included. [o] The reactions are carried out on analogous thioanilides. [p] Various reductants have been employed depending on the nature of the aryl ring substituent: e.g. $(NH_4)_2S$/aq DMF or $PtO_2/H_2$ for an isopropyloxycarbonylamino substituent and Sn/HCl, $HCO_2NH_4/HCONH_2$/$NaHSO_3$, Zn/alc $NH_4OH$, Raney Ni/DMF, or $PtO_2$/DMSO for an aryl substituent.

tives (**16**, R = Me) on the other, although unfortunately this type of reaction cannot be extended to other heterocycles such as morpholines and piperazines. The mechanism is thought[35] to involve a Friedel–Crafts cyclization of an intermediate alkene (*e.g.*, **18**; see Scheme II) since an alcohol (*viz.* **19**) has subsequently[36] been isolated from intermediate hydrolysates; significantly this alcohol **19** is converted into the appropriate benzimidazole **20** on treatment with PPA. This type of cyclization procedure (**16** → **17**) has been successfully extended[36] to *N*-acylaminonaphthyl heterocycles.

## D. From *N*-Benzylidene-2-nitro- and 2-Azidoanilines

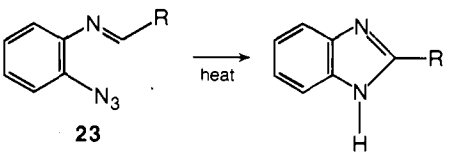
*N*-Benzylidene-2-nitroaniline derivatives (**21a,b**) are converted[37] into 2-phenylbenzimidazoles (**22a,b**) by reductive cyclization using triethyl phosphite; interestingly yields are higher than those obtained[37] using the classical Weidenhagen aldehyde method (*cf.* section II.A)



**21** **22**

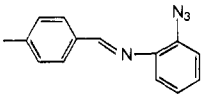
**a**, R = H (47% yield)
**b**, R = Me (33%)

A closely related mechanism may operate during formation[38,39] of 2-aryl- and 2-hetarylbenzimidazoles by thermolysis of anils derived from *o*-azidoaniline **23**; good yields have been obtained using this procedure and reaction conditions are not severe (see Table VIII).



**23** **24**

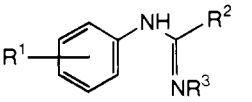
**TABLE VIII. Synthesis of Benzimidazoles from Anils of o-Azidoaniline**

| R in benzimidazole deriv **24** | Pyrolysis temp, °C | Yield of **24**, % | Ref |
|---|---|---|---|
| p-$O_2NC_6H_4$ | 130 | 48 | 38 |
| p-$NCC_6H_4$ | 130 | 56 | 38 |
| o-Pyridyl | 130 | 52 | 38 |
| 1-Quinoxalinyl | 130 | 71 | 38 |
| p-$ClC_6H_4$ | 140 | 96 | 39 |
|  | 140–145 | 85[a] | 39 |

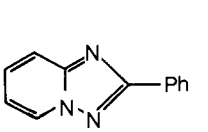
[a] The product is a bisbenzimidazole.

## E. From Amidines and Related Compounds

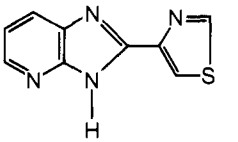
The formation of benzimidazoles from *N*-arylamidines was first reported by Partridge and Turner[40] who obtained them by allowing the hydroxy derivatives **25a** to react with benzenesulfonyl chloride in pyridine or triethylamine under anhydrous conditions. Generally yields are good (>60%), and the method can be used for the synthesis of a variety of derivatives with substituents in the aryl



**25a**, $R^1$ = alkyl, alkoxy, Cl; $R^2$ = Ph; $R^3$ = OH
**b**, $R^1$ = H; $R^2$ = 4-thiazolyl, Ph, Ph, Et; $R^3$ = H
**c**, $R^1$ = H; $R^2$ = 4-thiazolyl, Ph, Et; $R^3$ = Cl



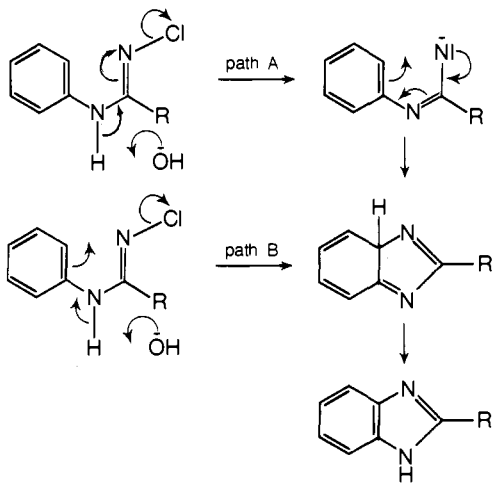
**26**



**27**

ring. Subsequently, Grenda, *et al.*,[41] showed that such products could be obtained from the parent amidines **25b** by oxidation with sodium hypochlorite under basic conditions. Using this more direct procedure, very high yields are obtained (70–98%), and this type of reaction can be applied to the synthesis of a triazole derivative **26** and an imidazopyridine **27.**

*N*-Chloro derivatives **25c** are intermediates in these reactions, but the mechanism of their conversion to benzimidazoles is in doubt; two possibilities considered[41] involve either the intermediacy of a discrete imino nitrene (path A) or a concerted process of dehydrochlorination with concomitant cyclization (path B).



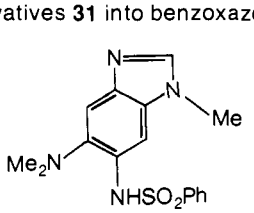

It would be interesting to carry out reactions of this type in the presence of 1,3-dipolarophiles with a view to trapping the intermediate nitrene; alternatively competition experiments involving intramolecular cycloaddition or insertion reactions with a suitable ortho side chain could be informative.

The method of Grenda, *et al.*,[41] has been subsequently employed[42] for the synthesis of 2-aryl and 2-aralkyl benzimidazole derivatives, and the process is covered by Merck patents.[43] Alternatives cyclization procedures have been developed[44] including manganese dioxide and lead tetraacetate oxidation of unsubstituted amidines (*cf.* **25b**); *N*-chloro (*cf.* **25c**), sulfonylmethyl, and *p*-tosyl derivatives (*cf.* **25**, $R^3$ = $SO_2Me$, *p*-$MeC_6H_4SO_2$) have been cyclized by thermal and photochemical reactions using benzoyl peroxide as an initiator or by the use of ferrous chloride in methanol.

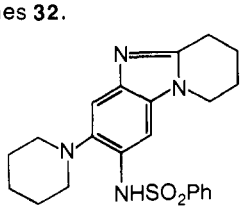
From a synthetic viewpoint the scope of these amidine cyclizations[41-44] is wide, and the formation of a variety of heterocycles can be envisaged using hetarylamidines containing one or more heteroatoms.

## F. From Quinone Derivatives

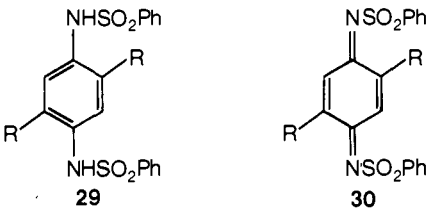
Benzimidazole derivatives **28a,b** are formed[45] together with disulfonamides **29a,b** when the quinone dibenzenesulfonimides **30a,b**, respectively, are exposed to irradiation by sunlight. The detailed mechanism of such reactions has not been elucidated, but they are probably closely related to the conversion[46] of analogous quinone derivatives **31** into benzoxazolines **32.**



**28a**

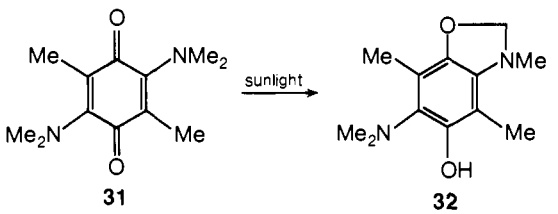


**28b**



**29** **30**

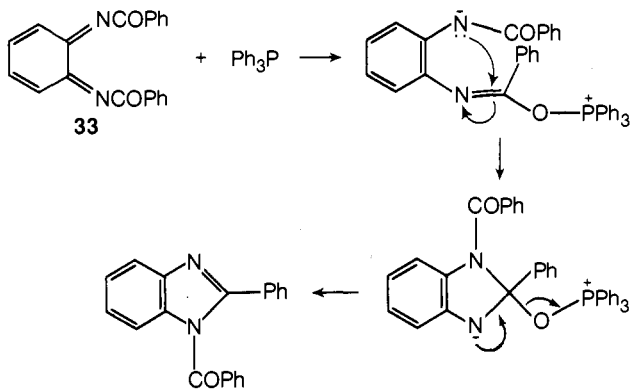
**a**, R = $NMe_2$
**b**, R = 1-piperidyl




**31** **32**

A benzimidazole derivative **34** has also been isolated[47] from reductive cyclization of o-benzoquinonedibenzimide (**33**) using triphenylphosphine, a possible[47] mechanism for which is outlined in Scheme III.

**SCHEME III**



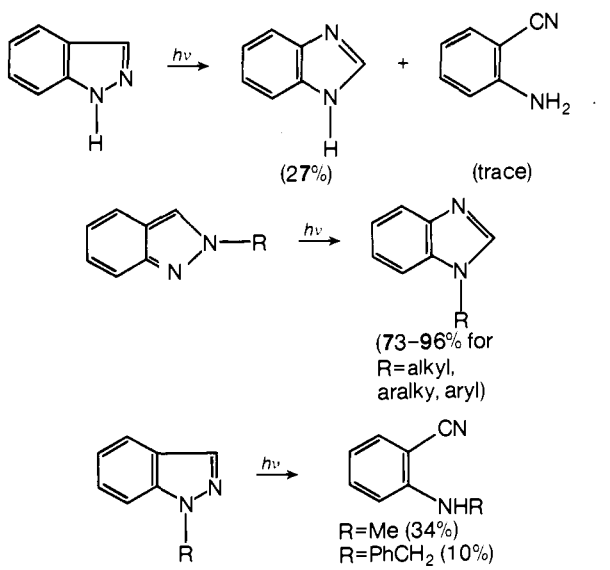
**33** **34**

## G. From Heterocyclic Compounds

### 1. From Five-Membered Ring Heterocycles

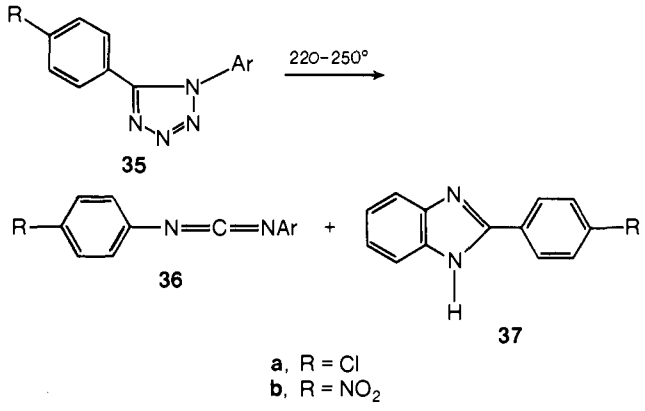
Benzimidazole and 1-alkyl derivatives are formed[48] in moderate to good yields by the photolysis of indazoles, but the course of such reactions is markedly dependent

**SCHEME IV**



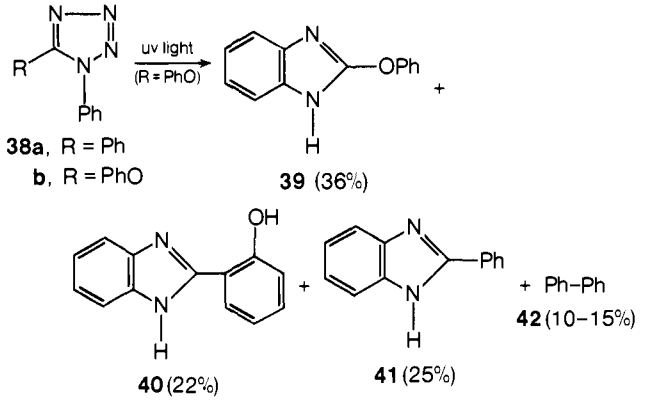
on the position of the substituent in the heterocyclic ring. Thus in the absence of a substituent, benzimidazole is formed albeit in low yield together with smaller quantities of 2-aminobenzonitrile; N(2)-alkylated indazoles are converted in good yield into 1-alkylbenzimidazoles; and N(1)-alkylated indazoles give 2-alkylaminobenzonitriles (see Scheme IV).

2-Substituted derivatives **37** are also produced,[49,50] albeit as the minor products (8–19%) accompanying carbodiimides **36** from pyrolysis of 1,5-diaryltetrazoles **35**.




The maximum yield (19%) of 2-arylbenzimidazole is provided by the *p*-chloro derivative **35a** and this is thought[50] to imply that this substituent has a retarding effect on the competing carbodiimide reaction (*cf.* its behavior[51] in the analogous Beckmann rearrangement). This type of reaction has been extended[49] using 1-(1-naphthyl)-5-phenyltetrazole (**35**, R = H; Ar = 1-naphthyl) which provides 2-phenyl-(1,2-naphth)imidazole in 25% yield but unfortunately cannot[50] be applied to heterocyclic analogs (*e.g.*, **35**, 2-pyridyl or 2-quinolyl for Ar). Investigations[50] of the effect of contact catalysts show that metallic copper lowers the temperatures required for decomposition, but complex mixtures are formed from which no pure products can be isolated.

The formation of benzimidazoles by photolysis of tetrazoles was first noted by Moriarty and Kliegman[52] who obtained 2-phenylbenzimidazole in 42% yield by photolysis of 1,5-diphenyltetrazole (**38a**). Analogous behavior, *viz.*, formation of 2-phenoxybenzimidazole, was reported[53] for the photolysis of 5-phenoxy-1-phenyltetrazole (**38b**) in acetonitrile, but four compounds, **39–42**, are formed[54] by photolysis of the tetrazole **38b** in benzene. The formation

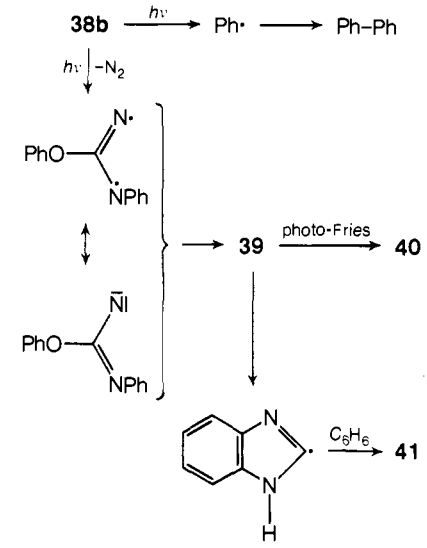



of these products, **39–42**, can be accounted for[54] (see Scheme V) in terms of initial loss of nitrogen followed by partial secondary photochemical decomposition of 2-phenoxybenzimidazole (**39**), and it has been confirmed[54] that the latter is transformed into a mixture of **40** and **41** photochemically. It is noteworthy that this is the first example of a photo-Fries rearrangement involving migration of a heterocyclic moiety, and extensions of this type of reaction to other heterocycles will be of interest from both a synthetic and a mechanistic viewpoint.

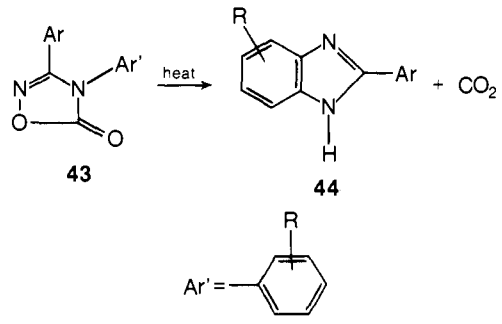
**TABLE IX. Benzimidazoles from Pyrolysis of 3,4-Diaryl-1,2,4-oxadiazol-5-ones[55b]**

| Starting material **43** | | Product benzimidazole **44** | Decomp temp, °C | Yield of **44**, % |
|---|---|---|---|---|
| Ar | Ar′ | | | |
| Ph | o-$MeC_6H_4$ | 2-Ph-4-Me | 220 | 91 |
| Ph | o-$O_2NC_6H_4$ | 2-Ph-4-$NO_2$ | 255 | 78 |
| Ph | p-$O_2NC_6H_4$ | 2-Ph-5-$NO_2$ | 230 | 75 |
| p-$O_2NC_6H_4$ | Ph | 2-(p-$O_2NC_6H_4$) | 220 | 74 |
| p-$MeOC_6H_4$ | Ph | 2-(p-$MeOC_6H_4$) | 190 | 14 |

**SCHEME V**




A method[55] closely related to the tetrazole studies described above involves the pyrolysis of 3,4-diaryl-1,2,4-oxadiazol-5-ones (**43** → **44**); this is a superior procedure since yields are generally high (Table IX) and the starting materials are easily synthesized.[55b] A more recent modification[56] of this method involves peroxide-initiated thermolysis, or photolysis of the oxadiazolones **43** or analogous thiones in dioxane solution; such procedures have been used[56] successfully for the synthesis of a number of 2-(4-thiazolyl) ("thiabendazole") derivatives (*cf.* section IX).




A wide range of 1-benzyl-2-substituted benzimidazoles have been prepared[57] by pyrolysis of 1,3-dibenzyl-2-substituted benzimidazolines at 200°.

## 2. *From Six-Membered Ring Heterocycles*

Benzimidazole and its 1-methyl derivative have been obtained[58] in 100 and 50% yields, respectively, by allow-

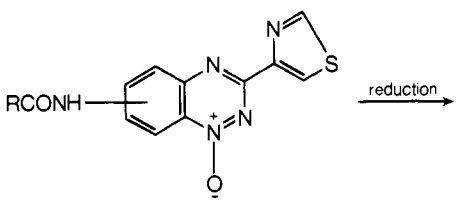
**TABLE X. Synthesis of Bis(benzimidazolyl)alkane Derivatives from the Reaction of *o*-Arylene Diamines with Dicarboxylic Acids**

| Type of benzimidazole product[k] (*cf.* X in **48**) | Ref |
|---|---|
| $(CH_2)_n$: $n = 2, 4, 6, 8$ | *a* |
| $[CH(OH)]_2$ | |
| $(CH_2)_2S(CH_2)_2$ | |
| $[CH(OH)]_4$ | *b* |
| $(CH_2)_2$ | *c* |
| $[CH(OH)]_n$: $n = 2, 4$ | |
| 2,5-Furyl | *d* |
| $CH(OH)CH_2$ | *e* |
| $(CH_2)_n$: $n = 2$-4, 6 | *f* |
| $[CH(OH)]_n$: $n = 2, 4$ | |
| $CH(CH_3)CH_2$ | |
| $(CH_2)_2S(CH_2)_2$ | |
| $CH(OH)CH_2$ | |
| CH(OH)CH(R): R = H, OH | *g* |
| $CF_2$ | *h* |
| $-C_6H_4-$ | *i* |
| CH(OH)CH(OH) | *j* |

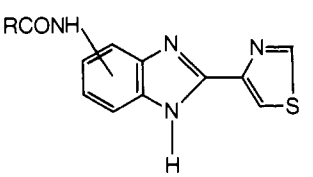
[a] L. Li-Yen Wang and M. M. Jouillé, *J. Amer. Chem. Soc.*, 79, 5706 (1957). [b] A. E. Siegrist and M. Duennenberger, U. S. Patent 2,901,408 (1959); *Chem. Abstr.*, 55, 1658c (1961). [c] J. Stanek and V. Wollrab, *Monatsh. Chem.*, 91, 1064 (1960). [d] M. Duennenberger and A. E. Siegrist, German Patent 1,086,37 (1960); *Chem. Abstr.*, 56, 4774g (1962). [e] Ciba Ltd., British Patent 861,431 (1961); *Chem. Abstr.*, 55, 22342i (1961). [f] K. H. Talls, L. V. Prosser, F. B. Wigton, and M. M. Jouille, *J. Org. Chem.*, 26, 462 (1961). [g] D. G. O'Sullivan and A. K. Wallis, *Nature (London)*, 198, 1270 (1963). [h] B. C. Bishop, A. S. Jones, and J. C. Tatlow, *J. Chem. Soc.*, 3076 (1964). [i] S. Chatterjee and J. Wolski, *J. Indian Chem. Soc.*, 43, 660 (1966). [j] T. Shen and T. A. Maag, German Patent, 2,013,910 (1970); *Chem. Abstr.*, 73, 120626n (1970). W. R. Roderick, German Patent 2,063,856 (1971); *Chem. Abstr.*, 75, 76790b (1971). [k] The nature of substituents in the aryl rings are not indicated here.

ing *o*-phenylenediamine or *N*-methyl-o-phenylenediamine to react with *s*-triazine at temperatures just over the melting point of the diamine. The scope of this approach has not been assessed, but generally reactions of this type are efficient and have been used for the synthesis of a variety of heterocycles including other benzazoles, imidazolines, tetrahydropyrimidines, and purines.

2-(4-Thiazolyl)benzimidazoles (**46**) are formed[59] by reduction of the benzotriazine 1-oxides (**45**) using a number of methods including zinc/acetic acid or platinum oxide in ethanol. Reactions of this type are unique in the chemistry of benzo-**1**,2,4-triazines, and mechanistic studies in this area would be valuable.




**45**




**46**

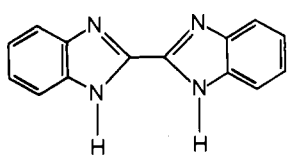
R = $Me_2CHO$, aryl

## H. Synthesis of Bibenzimidazolyls and Related Compounds

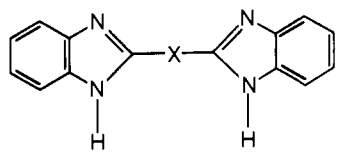
The synthesis of bibenzimidazolyls (*e.g.*, **47**) can be achieved by allowing *o*-phenylenediamine to react with oxalic acid diamide[60] or preferably with 2-(trichloromethyl)benzimidazoles;[61,62] in the latter case, the trichloro derivative is utilized[62] *in situ* and the dimer **47** can be isolated in 90% yield. Other approaches include indirect methods using *N*-(1,1,2-trifluoro-2-chloroethyl)benzimidazole[63] (see section III.A.2), organometallic intermediates[64,65] (see section III.F), *o*-nitrophenylalanine,[66] **1**-methylbenzimidazole 3-oxide[67] (see section IV.A.2.a), and benzimidazolium salts[68,69] (see section VII.A).

**TABLE XI. Relative Rates of Reactions of 2,4-Dinitrofluorobenzene and 4-Fluorobenzimidazoles with Alanylglycine at pH 7.95**

| Compound | Rel rate |
|---|---|
| 2,4-Dinitrofluorobenzene | 1 |
| 4-Fluoro-5,7-dinitrobenzimidazole | 84.2 |
| 4-Fluoro-2-methyl-5,7-dinitrobenzimidazole | 37.3 |
| 4-Fluoro-1,2-dimethyl-5,7-dinitrobenzimidazole | 22.5 |



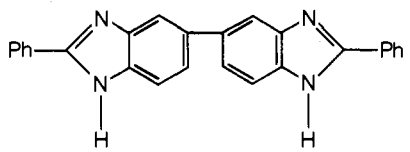
**47**




**48**

Bis(benzimidazolyl)alkane derivatives (**48**) can be prepared routinely by the reaction of *o*-arylene diamines with diacids (see Table X), diesters,[70-72] diimidoates[72,73] diamides,[72] and benzimidazolyl acetic acid ester derivatives.[74,75]

5,5′-Bibenzimidazolyls (*e.g.*, **49**) have been synthesized by thermal reactions of tetraminobiphenyls with monoesters.[76,77]




**49**

# III. Reactions of Benzimidazoles

## A. With Nucleophiles

### 1. Substitution in the Aryl Ring

Very little use has been made of nucleophilic aromatic substitution in the benzimidazole series; hence the influence of the imidazole ring on such processes is not well established. A 4-chloro substituent in 2-trifluoromethyl-5,7-dinitro derivatives can be displaced[78] by secondary amines, whereas 5- or 6-bromo substituents in 5-bromo-**1**-ethyl, 5-bromo-**1**-ethyl-6-nitro, or 6-bromo-**1**-ethyl-5-nitro derivatives are not displaced[79] by various amines at 190°. Only one report of quantitative work has been published;[80] apparently a fused imidazole ring has a marked activating effect on nucleophilic aromatic substitution compared with 2,4-dinitrofluorobenzene (*cf.* Table XI). Relative retardations due to methyl substituents at the 1 and/or 2 positions are in accord with the behavior expected from inductive effects while the overall rate enhancements in the benzimidazole series are ascribed to electronic activation by the imidazole ring rather than to intramolecular interactions within the Meisenheimer complex. As might be expected, 4-fluoro-**1**,2-dimethyl-5,6-dinitrobenzimidazole is considerably less reactive than the 5,7-dinitro analog.

**TABLE XII. Synthesis of 2-Aminobenzimidazoles by the Chichibabin Reaction[j]**

| Benzimidazole deriv | Ref | Benzimidazole deriv | Ref |
|---|---|---|---|
| 1-Me | *a* | 1-*i*-Pr | *f* |
| 1-Me-5-MeO | *a*, *b* | 1-Et-5-MeO | *e*, *g* |
| 1-Me-5-MeS | *c* | 1-Cyclohexyl | *h* |
| 1,5-$(Me)_2$ | *d* | 1-PhI | |
| 1-Me-5-EtO | e | 1-R-5-R'[k] | *i* |

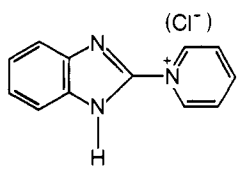
[a] A. M. Simonov and N. D. Vitkevich, *Zh. Obshch. Khim.*, **30**, 590 (1960); *Chem. Abstr.*, 54, 24677i (1960). [b] A. M. Simonov and P. A. Uglov, *Zh. Obshch. Khim.*, **21**, 884 (1951); *Chem. Abstr.*, 46, 498c (1952). [c] A. M. Simonov, V. G. Sayapin, and V. I. Siderman, *Zh. Vses. Khim. Obshchest.*, **15**, 232 (1970); *Chem. Abstr.*, **73**, 45414m (1970). [d] A. M. Simonov and A. N. Lomakin, *Zh. Obshch. Khim.*, **32**, 2228 (1962); *Chem. Abstr.*, **58**, 7923g (1963). [e] A. N. Lomakin, A. M. Simonov, and V. A. Chigrina, *Zh. Obshch. Khim.*, **33**, 204 (1963); *Chem. Abstr.*, **58**, 13936l (1963). [f] A. M. Simonov and A. F. Pozharskii, *Zh. Obshch. Khim.*, **31**, 3970 (1961); *Chem. Abstr.*, **57**, 8559h (1962). [g] N. D. Vitkevich and A. M. Simonov, *Zh. Obshch. Khim.*, **29**, 2614 (1959); *Chem. Abstr.*, **54**, 11002h (1960). [h] A. M. Simonov and A. F. Pozharskii, *Zh. Obshch. Khim.*, **33**, 2350 (1963); *Chem. Abstr.*, **59**, 13967h (1963). [i] A. N. Lomakin, *Mater. Nauchn. Konf. Aspir. Rostov-na-Donu Univ., 4th, 1962*, 108 (1962); *Chem. Abstr.*, **60**, 10670e (1964). [j] The reactions are usually carried out using sodium amide under rellux in either xylene or *N,N*-dimethylaniline. [k] Substituent (R, R') combinations are 1-Me, -Et, $-(CH_2)_2NEt_2$ and $-(CH_2)_3NEt_2$, and 5-OEt, $-OCH_2Ph$ and -H.

## 2. *Nucleophilic Substitution in the Imidazole Ring*

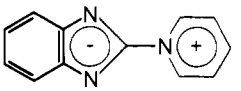
The Chichibabin reaction has been used routinely for the synthesis of a number of 2-aminobenzimidazole derivatives. The reaction appears to have wide applicability (*cf.* Table XII), although there is a need for kinetic studies in this area in relation to substituent effects.

Apart from the displacement of a 2-hydrazino group by sulfonyl chloride[81] and the rather less common substitution of a 2-nitro group by ethoxide ion,[82] other nucleophilic reactions are confined to 2-chloro substituents (see Table XIII).

A number of the reactions shown in Table XIII are noteworthy. For example, conversion[83] of 2-chlorobenzimidazole by pyridine into the pyridinium salt **50** provides a precursor for synthesis of a diaza analog **51** of pyridinium cyclopentadienide.[84] The chemistry of compounds of this type (**51**) has not been explored, and investigations on their reactivity could be interesting.




**50**




**51**

An extensive kinetic study has been made of the nucleophilic displacement of chloride ion from 2-chlorobenzimidazole by piperidine and by methoxide ion. Apparently[85] the reactivity of the 2-chloro derivative is comparable to that of 2-chloro-1-methylbenzimidazole but is lower than that of 2-chlorobenzothiazole and 2-chlorobenzoxazole. As might be anticipated, such reactions are facilitated[86-88] by electron-withdrawing substituents (*e.g.*, $NO_2$, Cl) in the aryl ring.

An important general principle in connection with the design of nucleophilic substitution reactions has been pointed out by Harrison and Ralph:[89] for unsubstituted 2-halogenobenzimidazoles a competition exists between proton abstraction by the nucleophile at the 1 position with concomitant retardation of 2-substitution, and nucleophilic substitution at the 2 position. Accordingly, chloride ion is not displaced from 2-chlorobenzimidazole by the powerful nucleophiles $RO^-$ (R = Me, Et, or *t*-Bu),

**TABLE XIII. Nucleophilic Substitution Reactions Involving 2-Chlorobenzimidazoles**

| Nucleophile | Ref |
|---|---|
| $NH_4OH$, morpholine, $PhCH_2NH_2$ | *a* |
| Ethylenediamine derivatives | *b* |
| Piperidine[l] | 85–88 |
| Alkoxide ion[j] | 85,86,88–90 |
| Aminothiazole, aminothiadiazole | *c* |
| Pyridine[j] | 83 |
| Thiazole, 2-methylthiazole | *d* |
| $N_2H_4$ | e, *f* |
| Alkylamines,dialkylamines, arylalkylamines,etc. | *f* |
| $ArS^-$ | *g*, *h* |
| Thiourea,[k] benzimidazoline-2-thione | *h* |
| $RS^-$ | *i* |

[a] A. M. Simonov and A. N. Lomakin, *Zh. Vses. Khim. Obshchest.*, **8**, 234 (1963); *Chem. Abstr.*, **59**, 5150c (1963). [b] E. L. Engelhardt, U. S. Patent 2,971,005 (1961); *Chem. Abstr.*, **55**, 13449b (1961). [c] Chimetron S.a.r.l., French Patent 4,761 (1967); *Chem. Abstr.*, **69**, 67383v (1968). [d] Chimetron S.a.r.l., French Patent 1,439,224 (1966); *Chem. Abstr.*, **65**, 18594h (1966). [e] N. P. Bednyagina and I. Ya Postovskii, *Zh. Obshch. Khim.*, **30**, 1431 (1960); *Chem. Abstr.*, **55**, 1586h (1961). [f] A. Hunger, J. Kebrle, A. Rossi, and K. Hollmann, *Helv. Chim. Acta*, **44**, 1273 (1961). [g] Taisho Pharmaceutical Co. Ltd., French Patent 1,438,607 (1966); *Chem. Abstr.*, **65**, 18596e (1966). [h] D. Harrison and J. T. Ralph, *J. Chem. Soc.*, 3132 (1965). [i] Chimetron S.a.r.l., French Patent 4,806 (1967); *Chem. Abstr.*, 69, 6786y (1968). [j] See discussion in this section. [k] The product is benzimidaazoline-2-thione which is presumably[h] formed via an intermediate isothiourea derivative.

whereas 2-chloro-1-methylbenzimidazole reacts readily with sodium methoxide or ethoxide; interestingly, even this process is susceptible to steric effects since 2-chloro-1-isopropylbenzimidazole reacts only slowly with sodium methoxide or ethoxide, and 2-chloro-1-methylbenzimidazole gives no alkoxy derivative with sodium *tert*-butoxide. Despite these limitations, 2-alkoxybenzimidazoles are accessible[90] *via* nucleophilic displacement of chloride ion from 2-chloro-1-isopropenyl derivatives by alkoxide ion followed by oxidative cleavage of the isopropenyl group.

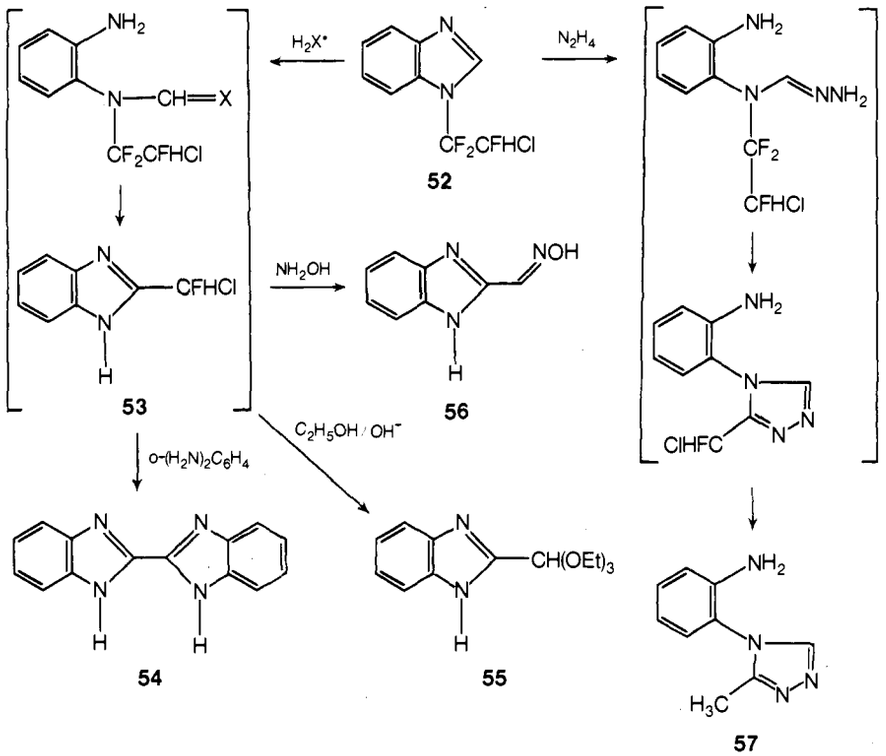
The reactivity of the 2 position toward nucleophilic addition is enhanced by the presence of a strongly electron-withdrawing substituent in the 1 position. The preparative value of this behavior has been demonstrated[91] by allowing the readily accessible *N*-(1,1,2-trifluorochloroethyl)-benzimidazole (**52**) to react with a variety of nucleophiles (see Scheme VI). Opening of the imidazole ring followed by ring closure *via* the very reactive difluoromethylene group can produce 2-(chlorofluoromethyl)-benzimidazole (**53**) which may undergo subsequent transformations (*cf.* **54–56**). Using hydrazine as the nucleophile, the preferred pathway involves triazole formation followed by Wolff–Kisher reduction to give a 3-methyltriazole derivative **57** in 73% yield in a single-step process. The facile conversion[92] of benzimidazole into the butadiene derivative **59** by reaction with ethoxymethylenemalononitrile is considered[92] to be another example of a process in which the 2 position of benzimidazole is activated toward nucleophilic attack; in this case, however, the adduct **58** is thought to rearrange as shown in Scheme VII.

Clearly these investigations[91,92] highlight an area where a number of novel compounds should be accessible by careful choice of the alkylating or acylating agent and the entering nucleophile.

## 3. *Substitution and Addition at Side-Chain Substituents*

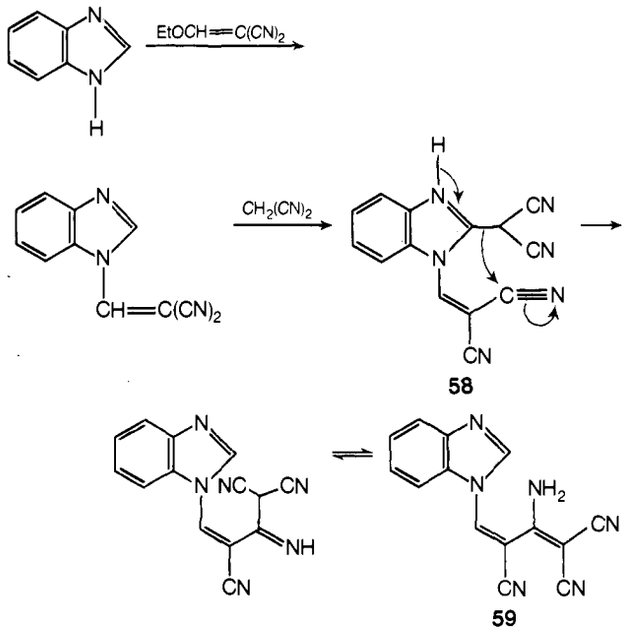
A number of conventional nucleophilic substitution reactions occur in which side-chain substituents are involved; most of the reported examples incorporate chloride ion displacement in 2-chloromethyl derivatives by

**SCHEME VI**[a]



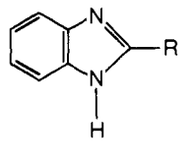

[a] $H_2X$ is a general representation of the nucleophile.

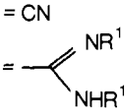
**SCHEME VII**

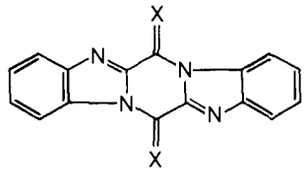



amines or alcohols (see Table XIV). The investigations of Holan, *et al.*,[93-97] on the mode of reactivity of 2-trichloromethylbenzimidazoles with nucleophiles are especially interesting. There is considerable evidence[98] that the benzimidazole nucleus is significant in relation to purine antimetabolite behavior which suggests that benzimidazoles may act biologically by competitive inhibition in nucleic acid synthesis. With this in mind, Holan, *et al.*,[93-97] have investigated 2-trichloromethyl derivatives as model systems with a view to providing substrates which might react irreversibly at nucleophilic enzyme sites.

Reaction of 2-trichloromethylbenzimidazole (**60a**) with aqueous ammonia gives a mixture of 2-cyanobenzimidazole (**60b**, 50%) and the pyrazine diimine (**61a**, 30%), although with anhydrous ammonia the cyano derivative is the sole product in 86% yield. With primary alkyl- and arylamines, the trichloro compound **60a** is converted into amidine derivatives **60c** although in the absence of an additional base or in an acidic medium the reaction of arylamines produces amides **60d**; with secondary amines the appropriate anilides **60e** are formed.



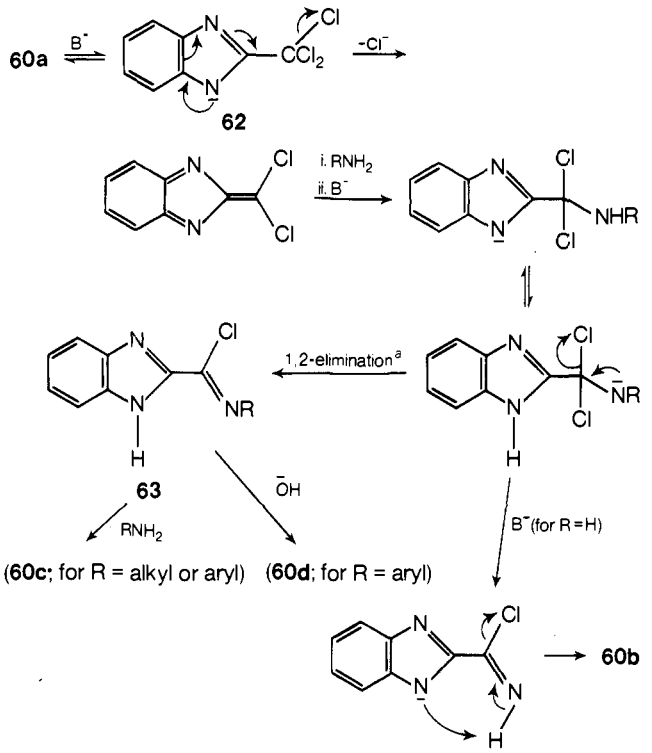

**60a**, R = $CCl_3$
**b**, R = CN
**c**, R =  (R' = alkyl or aryl)
**d**, R = CONHAr
**e**, R = $CONR^1R^2$ ($R^1$ = alkyl; $R^2$ = alkyl or aryl)




**61a**, X = NH
**b**, X = O

Interestingly, 1-methyl-2-trichloromethylbenzimidazole is considerably less susceptible to nucleophilic attack which suggests[94] that the anion **62** is a probable intermediate in transformations of the trichloromethyl derivative **60a** (*cf.* Scheme VIII and also the reactivity[99] of analogous trichloromethylpurine derivatives). An alternative[94] route to the nitrile **60b** could involve the intermediacy of

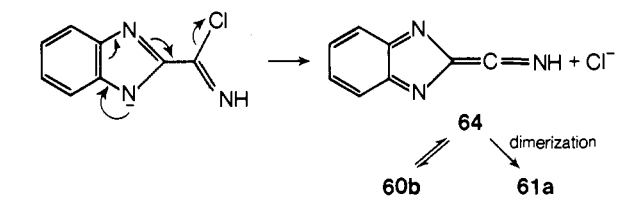
**SCHEME VIII**[94]



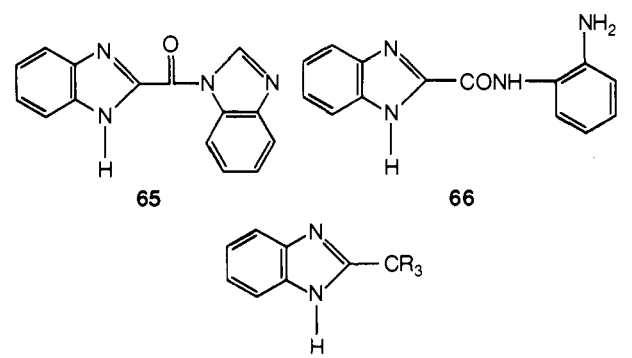

[a] An alternative 1,6-elimination mechanism can be envisaged[94] for formation of the imidoyl chloride.

a ketenimine **64**, and indeed such a pathway is an attractive one in relation to formation of the pyrazinediamine **61a** (*cf.* Scheme IX). Although the mechanisms depicted in Schemes VIII and IX are speculative, it is noteworthy that reaction of the trichloromethyl derivative **60a** with 2-amino-5-chloropyridine provides[94] an isolable imidoyl chloride intermediate (*cf.* **63**).

**SCHEME IX**

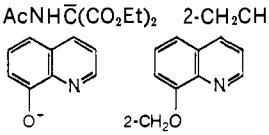



A wider investigation[96,97] of this type of reaction using a variety of mono- and difunctional nucleophiles indicates considerable synthetic potential. Carefully controlled basic hydrolysis[96] of **60a** can lead to the pyrazine dione **61b** or its decomposition products (*e.g.* **65**, **66**) while




**67a**, R = OMe
**b**, R = SMe
**c**, R = $SC_6H_4Cl(p)$

**TABLE XIV. Reactions Involving Nucleophilic Displacement within Side Chains**

| Type of benzimidazole side chain | Nucleophile | Type of benzimidazole product[v] | Ref |
|---|---|---|---|
| $2\text{-}CH_2Cl$ | Dialkylamines | $2\text{-}CH_2NR_2$ | *a–d* |
| | Cyclic amines | $2\text{-}CH_2N(CH_2)_n$ | |
| $2\text{-}CH_2Cl$ | Arylamino | $2\text{-}CH_2NHAr$ | *e* |
| $2\text{-}CH_2Cl$ | $HN(CH_2CH_2OH)_2$ | $2\text{-}CH_2N(CH_2CH_2OH)_2$ | *c, f, g* |
| $2\text{-}CH_2Cl$ | $p\text{-}H_2NC_6H_4COG$[w] | $2\text{-}CH_2NHC_6H_4COG(p)$ | *h* |
| $2\text{-}CH_2Cl$ | Trialkylamines | Quaternary salts | *i, j* |
| $2\text{-}CH_2Cl$ | $SCN^-$ | $2\text{-}CH_2SCN$[y] | *k* |
| $2\text{-}CH_2Cl$ | $AcNH\bar{C}(CO_2Et)_2$ | $2\text{-}CH_2CH(NH_2)CO_2H$ | *l* |
| $2\text{-}CH_2Cl$ |  | | *m* |
| $2\text{-}CH_2Cl$ | $HOCH_2CH_2O^-$ | $2\text{-}CH_2OCH_2CH_2OH$ | *n* |
| | $Et_2NCH_2CH_2O^-$ | $2\text{-}CH_2OCH_2CH_2NEt_2$ | |
| $1\text{-}CH_2Cl$ | $NH_3$ | $1\text{-}CH_2NH_2$ | *o* |
| $1\text{-}CH_2Cl$ | $RO^-$ | $2\text{-}CH_2OR$ | *p* |
| $1\text{-}CH_2CH_2Cl$ | Cyclic amines | $1\text{-}CH_2CH_2N(CH_2)_n$ | *q* |
| $2\text{-}COCH_2Cl$ | $NH_2CS_2^-$ | 2-(2-Mercapto-4-thiazolyl) | *r* |
| $2\text{-}CHCl_2$ | $H_2O$ | 2-CHO | *s* |
| 2-(5-Halogeno-furyl) | $NO_2^-$ | 2-(5-Nitrofuryl) | *t* |
| $2\text{-}CCl_3$ | $NH_3$ | 2-CN[x] | *u*, 93, 94 |

[a] Schering A.-G., British Patent 703,272 (1954); *Chem. Abstr.*, 49, 18162e (1955). [b] Schering A.-G., British Patent 703,723 (1954); *Chem. Abstr.*, 49, 1816e (1954). [c] W. Knobloch, *Chem. Ber.*, 91, 2562 (1958). [d] H. Richter, German Patent 1,078,132 (1960); *Chem. Abstr.*, 55, 17654a (1961). [e] P. Cheosakul, R. Parker, and H. E. Skipper, *Thai Sci. Bull.*, 10, 14 (1959); *Chem. Abstr.*, 59, 3906l (1963). [f] W. Knobloch, *Chem. Ber.*, 91, 2557 (1958). [g] O. F. Ginzburg, B. A. Porai-Koshits, M. I. Krylova, and S. M. Lotareichik, *Zh. Obshch. Khim.*, 27, 411 (1957); *Chem. Abstr.*, 51, 15500d (1957). [h] W. R. Siegart and A. R. Day, *J. Amer. Chem. Soc.*, 79, 4391 (1957). [i] M. Schenck, U. S. Patent 2,728,776 (1955); *Chem. Abstr.*, 50, 15593c (1956). [j] J. M. Sprague, U. S. Patent 2,567,912 (1951); *Chem. Abstr.*, 46, 2583c (1952). [k] D. R. Haugwitz and L. V. Narayanan, German Patent 2,110,440 (1971); *Chem. Abstr.*, 75, 151786k (1971). R. D. Haugwitz, B. V. Maurer, and V. L. Narayanan, *Chem. Commun.*, 1100 (1971); R. D. Haugwitz and V. L. Narayanan, *J. Org. Chem.*, 37, 2776 (1972). [l] S. Tatsuoka and H. Hitomi, Japanese Patent 3780 (1952); *Chem. Abstr.*, 48, 4004i (1954). [m] Chimetron S.a.r.l. French Patent 1,503,697 (1967); *Chem. Abstr.*, 70, 11701a (1969). [n] J. Buchi, H. Zwicky, and A. Aebi, *Arch. Pharm. (Weinheim)*, 293, 758 (1960); *Chem. Abstr.*, 55, 5181 (1961). [o] A. F. Pozharskii, A. M. Simonov, E. A. Zvezdina, and N. K. Chub, *Khim. Geterotsikl. Soedin.*, 889 (1967); *Chem. Abstr.*, 68, 105096t (1968). [p] V. M. Pechenina, N. A. Mukhina, K. A. Abaturova, L. P. Grebenshchikova, T. V. Mikhailova, V. M. Kurilenko, and A. P. Gilev, *Khim.-Farm. Zh.*, 5, 13 (1971); *Chem. Abstr.*, 76, 14430w (1972); USSR Patent 319,597 (1971). [q] W. J. Welstead and C. G. Helsley, German Patent 2,017,265 (1970); *Chem. Abstr.*, 74, 3627y (1971). [r] Chimetron S.a.r.l., French Patent 88,775 (1967); *Chem. Abstr.* 67, 73607w (1967). [s] H. Baganz, *Angew. Chem.*, 68, 151 (1956). [t] A. F. Pozharskii, V. Ts. Bukhaeva, A. M. Simonov, and R. A. Savel'eva, *Khim. Geterotsikl. Soedin.*, 183 (1969); *Chem. Abstr.*, 71, 3323j (1969). [u] P. McCloskey and R. A. Sizeland, German Patent 2,014,293 (1970); *Chem. Abstr.*, 74, 3619x (1971). [v] R and Ar denote alkyl and aryl substituents, respectively. [w] G = $-NHC(CO_2Et)HCH_2CH_2CO_2Et$. [x] See text for a detailed discussion of the reaction of 2-trichloromethyl derivatives with nucleophiles. [y] The product 2-thiocyanatomethyl derivatives have been used[k] for the synthesis of new fused benzimidazole ring systems.

reactions with methanol, methanethiol, and *p*-chlorothiophenol under basic conditions lead to the ortho esters **67a–c**, respectively.

Reactions with difunctional nucleophiles[97,100] are especially versatile and afford an effective method for the synthesis of benzimidazoles containing a variety of heterocyclic substituents in the 2 position; some examples of this type of process are shown in Scheme X.

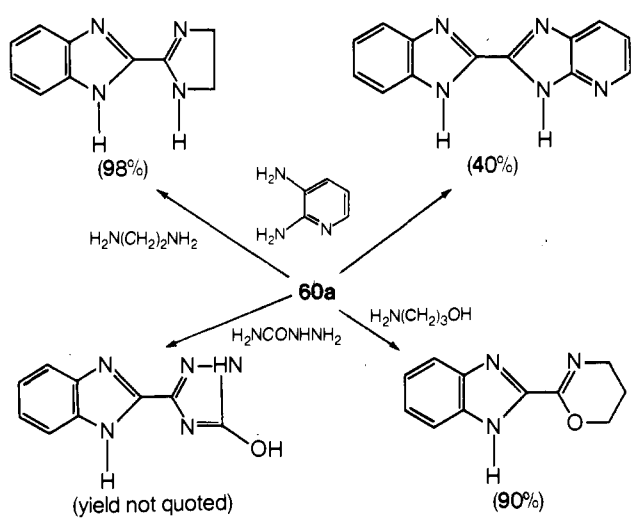
Very little attention has been paid to intramolecular nucleophilic substitution reactions in the benzimidazole series: Knobloch and Lietz[101] reported the synthesis of the tricyclic derivatives **68–70** by interaction of **7**-amino or **7**-thiol substituents with a **1**-haloalkyl side chain. It would be of interest to extend this synthetic approach using in-

**TABLE XV. Electrophilic Aromatic Substitution Reactions of Benzimidazoles**

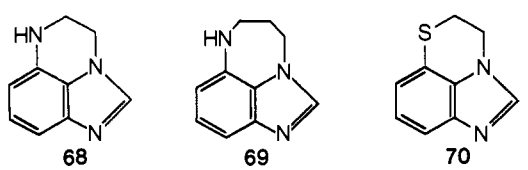
| Substituents in the benzimidazole | Reagent | Product | Ref |
|---|---|---|---|
| None | $H_2SO_4$ | 5-$SO_3H$ | *a* |
| 2-OH | Phthalic anhydride/$AlCl_3$ | 5-(2-Carboxybenzoyl) derivatives | *b* |
| 2-OH-6-Me | | | |
| 2-OH-1,3-$(Me)_2$ | | | |
| 2-$NMe_2$ | | | |
| 2-Me-4-AcNH | $H_2SO_4/HNO_3$ | 2-Me-4-AcNH-7- (and -5-) $NO_2$ | *c* |
| 4-NHCHO | $H_2SO_4/HNO_3$ | 4-$NH_2$-5- (and -7-) $NO_2$ | |
| 4-$NH_2$ | $PhN_2^+Cl^-$ | 4-$NH_2$-7-N=NPh | |
| 2-Me-4-$NH_2$ | $PhN_2^+Cl^-$ | 2-Me-4-$NH_2$-7-N=NPh | |
| 2-$CH_2Ph$ | $H_2SO_4/HNO_3$ | 5-$NO_2$-4′-$NO_2$ | *d* |
| 1-Me-2-$NH_2$ | $H_2SO_4/KNO_3$ | 1-Me-2-$NH_2$-5- (and -6-) $NO_2$ | *e* |
| 1-Me-2-$NH_2$ | $H_2SO_4$/excess $KNO_3$ | 1-Me-2-$NH_2$-5,6-$(NO_2)_2$ | |
| 1,3-$(Me)_2$-2-(=NH) (nitrate) | $H_2SO_4$ | 1,3-$(Me)_2$-2-(=NH)-5-$NO_2$ | |
| 1,3-$(Me)_2$-2-(=NH)-5-$NO_2$ | $H_2SO_4/KNO_3$ | 1,3-$(Me)_2$-2-(=NH)-5,6-$(NO_2)_2$ | |
| 2-Me | $Br_2$ | 2-Me-4,5-$(Br)_2$ | *f* |
| None | $Cl_2$ | 4,5,6-$(Cl)_3$ | |
| 2-Me | $Cl_2$ | 2-Me-4,5,6-$(Cl)_3$ | |
| 2-CHO | $Cl_2$ | 2-CHO-4,5-$(Cl)_2$ | |
| None | $ClSO_3H$ | 5-$SO_3H$ and/or 5-$SO_2Cl$ deriv | *g* |
| 2-Alkyl | | | |
| 2-Aryl | | | |
| 5-$NO_2$ | $HNO_3/H_2SO_4$ | 5,6-$(NO_2)$ (+4,6-$(NO_2)_2$) | 110 |
| 2-Me-5-$NO_2$ | $HNO_3/H_2SO_4$ | 2-Me-5,6-$(NO_2)_2$ (+2-Me-4,6-$(NO_2)_2$) | |
| 4-F | $H_2SO_4/HNO_3$ | 4-F-7-$NO_2$ | *h* |
| 2-$CF_3$-4-F | $H_2SO_4/HNO_3$ | 2-$CF_3$-4-F-7-$NO_2$ | |
| 2-Me-4-F | $H_2SO_4/HNO_3$ | 2-Me-4-F-5,7-$(NO_2)_2$ | |
| 1,2-$(Me)_2$-4-F | $H_2SO_4/HNO_3$ | 1,2-$(Me)_2$-4-F-5-$NO_2$ | |
| 1,2-$(Me)_2$-4-F-5-$NO_2$ | $H_2SO_4/HNO_3$ | 1,2-$(Me)_2$-5,7- (and -5,6-) $(NO_2)_2$ | |

[a] L. S. Elros, *Zh. Obshch. Khim.*, **23**, 842 (1953); *Chem. Abstrs.* **48**, 4524c (1954). [b] L. S. Elros, B. A. Poral-Koshits, and S. G. Farbenshtein, *Zh. Obshch. Khim.*, **23**, 1691 (1953); *Chem. Abstr.*, **48**, 13686e (1954). [c] L. S. Elros, *Zh. Obshch. Khim.*, **23**, 951 (1953); *Chem. Abstr.*, **48**, 8222b (1954). [d] A. F. Casey and J. Wright, *J. Chem. Soc.*, 1511 (1966). [e] A. M. Simonov, Yu. M. Yutinov, and V. A. Anisimova, *Khim. Geterotsikl. Soedin. Akad. Nauk. Latv. SSR*, 913 (1965); *Chem. Abstr.*, 64, 12661a (1966). [f] H. R. Hensel, French Patent, 1,403,128 (1965); *Chem. Abstr.*, 64, 2094l (1966). [g] V. G. Sayapin, A. M. Simonov, and V. V. Kuz'menko, *Khim. Geterotsikl. Soedin.*, 681 (1970); *Chem. Abstr.*, **73**, 45409p (1970). [h] K. L. Kirk and L. A. Cohen, *J. Org. Chem.*, **34**, 384 (1969).

**SCHEME X**[97]




teraction of a 1-haloalkyl side chain with a nucleophilic site (*e.g.*, $NH_2$) at the 2 rather than the 7 position.




Examples of nucleophilic addition of benzimidazole side-chain substituents are restricted to reactions of 2-formylbenzimidazoles with a variety of compounds including toluene derivatives,[102] Grignard and organolithium reagents,[103] nitroalkanes,[104] hydantoirs,[105] and thiazolidinones.[106]

## B. With Electrophiles

### 1. Substitution in the Aryl and Imidazole Rings

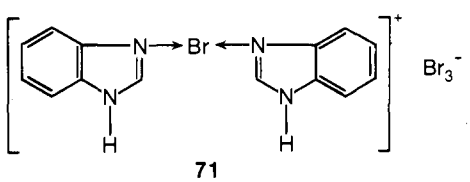
Very little use has been made of electrophilic substitution reactions since publication of the review by Wright.[5] In general, it appears (*cf.* Table XV) that electrophiles preferentially attack benzimidazoles in the 5 position. If a C-5 substituent does not influence the course of subsequent substitution (*e.g.*, methyl[107] and methoxy[108] groups), the second substituent normally enters the 6 position. However, if the C-5 substituent is powerfully electron releasing, *e.g.*, amino or hydroxy groups, the second substituent enters at the 4 position;[109] on the other hand, an electron-withdrawing substituent at the 5 position directs the entering electrophile to the 4 as well as to the 6 position.[110] Aspects of such directive effects have been rationalized on theoretical grounds by Brown and Heffernan[111] although it should be noted that their work was completed a number of years ago and a more elaborate treatment is required in this area.

Two aspects concerning halogenation of benzimidazoles are of interest: firstly, the compound obtained from the reaction of iodine with an alkaline solution of benzimidazole is actually[112] the 1-iodo, and not the 2-iodo derivative, as had been assumed;[113] and secondly the bromination of benzimidazole and its 1-methyl derivative in chloroform at room temperature provides a dicoordinate complex and an n-donor complex that are formulated[114] as **71** and **72**, respectively.

**TABLE XVI. Alkylation of Benzimidazoles Using Alkyl Halides in the Presence of Base**

| Organic halide | Base | Ref |
|---|---|---|
| $R_2N(CH_2)_2$– | $NaNH_2$ | *a–d* |
| $Et_2NCH_2C(CH_3)H$– | $NaNH_2$ | *e* |
| $Et_2N(CH_2)_2$– | NaOEt | *f, g* |
| $RCOCH_2$– | NaOMe | *h* |
| $ArCOCH_2$– | | |
| $MeO_2C$– | NaOEt | *i* |
| $CH_2$=$CHCH_2$– | NaOEt, NaOMe | *j, k* |
| $CH_2$=$C(CH_3)CH_2$– | NaOEt | *j* |
| $ArCH_2$– | Na | *l* |
| $RO_2C$– | Na | *m* |
| $CH_2CH_2CH_2CH_2CH_2N(CH_2)_2$– | Na | *n* |
| $CH_2$=$CHCH_2$– | NaH | *k* |
| *n*-$C_6H_{13}$–, $ArCH_2$–, –$(CH_2)$– | NaH | 123 |
| Hydroxyalkyl | NaH | *o* |
| MeO—C(=S)– | $NaHCO_3$ | *p* |
| $R(CH_2)_n$– | KOH | *q* |
| $R_2N(CH_2)_n$– | NaOH | *r* |
| $HO_2CCH_2$– | NaOH | *s* |
| $CH_3$–, $PhCH_2$– | $K_2CO_3$ | 119 |
| $CH_2$=$CHCH_2O_2C$–, $PhCH_2O_2C$ | $K_2CO_3$ | *t* |
| –$(CH_2)_2$– | KOH | *u* |
| 2,4-$(NO_2)_2C_6H_3$ | NaOAc | *v* |
| $EtS_2C$– | $Et_3N$ | *t* |

[a] J. Sawlewicz, L. Bukowski, and M. Rogaczewska, *Diss. Pharm.*, **14**, 297 (1962); *Chem. Abstr.*, **59**, 5149d (1963). [b] K. Hollmann and A. Hunger, Swiss Patent 363,657 (1962); *Chem. Abstr.*, **59**, 11504a (1963). [c] K. Hollmann, A. Hunger, J. Kebrle, and A. Rossi, Swiss Patent 361,286 (1962); *Chem. Abstr.*, **58**, 6835c (1963). [d] A. Hunger, J. Kebrle, A. Rossi, and K. Hollmann, *Helv. Chim. Acta*, **43**, 800 (1960). [e] A. F. Casy and J. Wright, *J. Chem. Soc. C*, 1511 (1966). [f] K. Hollmann, A. Hunger, J. Kebrle, and A. Rossi, Swiss Patent 362,081 (1962); *Chem. Abstr.*, **59**, 8758l (1963). [g] Y. M. Abou-Zeid, A. A. Abou-Oul, and B. Abdel-Fattah, *U. A. R. J. Pharm. Sci.*, 11, 29 (1970); *Chem. Abstr.*, **75**, 129723r (1971). [h] A. N. Krasovskii, P. M. Kochergin, and L. V. Samoilenko, *Khim. Geterotsikt. Soedin.*, 827 (1970); *Chem. Abstr.*, **73**, 109740z (1970). [i] H. Roechling and K. H. Buechel, *Z. Naturforsch. B*, **25**, 1103 (1970); *Chem. Abstr.*, **74**, 13062z (1971). [j] Farbenlabriken Bayer A.-G., British Patent 849,793 (1960); *Chem. Abstr.*, **59**, 7535d (1963). [k] E. L. Ringwald and A. B. Craig, U. S. Patent 2,623,879 (1952); *Chem. Abstr.*, 47, 9367c (1953). [l] S. Herrling, H. Keller, and H. Muckter, German Patent 1,000,384 (1957); *Chem. Abstr.*, **54**, 1550b (1960). [m] Fisons Pest Control, French Patent 1,459,782 (1966); *Chem. Abstr.*, 67, 54129a (1967); *cf.* French Addn. 93,257; *Chem. Abstr.*, **72**, 21691c (1970). [n] T. Seki, *Yakugaku Zasshi*, **87**, 301 (1967); *Chem. Abstr.*, 67, 82159d (1967). [o] Chimetron, French Patent 1,450,541 (1966); *Chem. Abstr.*, 66, 85792v (1967). [p] H. L. Klopping, French Patent 1,523,597 (1968); *Chem. Abstr.*, **72**, 21692d (1970). [q] K. Hideg, H. O. Hankovsky, G. Mehes, L. Decsi, and M. Varszegi, Hungarian Patent, 152,439 (1965); *Chem. Abstr.*, 64, 8195d (1966). [r] K. Hideg and O. H. Hankovsky, *Acta Chim. Acad. Sci. Hung.*, **49**, 303 (1966); *Chem. Abstr.*, 66, 65425z (1967). [s] H. Irving and O. Weber, *J. Chem. Soc.*, 2269 (1969). [t] Fisons Pest Control, Netherlands Appl. 6,609,19 (1967); *Chem. Abstr.*, 67, 73609y (1967). [u] A. M. Simonov and A. F. Pozharskii, *Zh. Obshch. Khim.*, **31**, 3970 (1961); *Chem. Abstr.*, **57**, 8559h (1962). [v] A. M. Simonov and N. D. Vitkevich, *Zh. Obshch. Khim.*, **29**, 2404 (1959); *Chem. Abstr.*, **54**, 9896b (1960).



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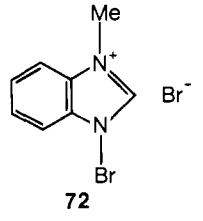

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**TABLE XVII. Alkylation of Benzimidazoles by Addition to Alkenes, Epoxide Ring Opening, and Mannich Reactions**

| Reactant(s) | Reaction conditions | Ref |
|---|---|---|
| 2-Vinylpyridine | AcOH/120° | *a, b* |
| 4-Vinylpyridine | *i*-PrOH/reflux | *c* |
| $CH_3CH$=$CHNO_2$ | EtOH/room temp | *d* |
| $CH_2$=$CHCN$ | Aq dioxane/$Et_3N^+CH_2Ph(OH^-)$/ 45–60 | *e* |
| Ethylene oxide | EtOH/trace pyridine/heat | *f* |
| Propylene oxide | EtOH/trace pyridine/65° | *g* |
| Styrene oxide | | *h* |
| $ArOCH_2$–CH(–$CH_2$–O)– | | *i* |
| $H_2N(CH_2)_2$-2-pyridyl/$CH_2O$ | EtOH/reflux | *j* |
| $Et_2NH/CH_2O$, Morpholine/$CH_2O$, Piperidine/$CH_2O$ | EtOH/HCl/reflux | *k* |
| $HN(CH_2CH_2OH)_2/CH_2O$ | EtOH/reflux | *l* |
| Morpholine/$CH_2O$ | MeOH | *m* |

[a] T. Hisano and M. Ichikawa, *Yakugaku Zasshi*, 91, 1136 (1971); *Chem. Abstr.*, 76, 14432y (1972). [b] E. Prollt and W. Georgi, *Justus Liebigs Ann. Chem.*, **643**, 136 (1961). [c] A. P. Gray, H. Kraus, and D. E. Heitmeier, *J. Org. Chem.*, **25**, 1939 (1960). [d] V. P. Dukhovskoi, V. D. Tyurin, and G. A. Shvekhgeimer, *Tr., Mosk. Inst. Neftekhim. Gazov. Prom.*, No. 3, 12 (1969); *Chem. Abstr.*, **75**, 151728t (1971). [e] V. N. Syutkin, A. M. Elros, and S. N. Danilov, *Zh. Prikl. Khim.*, **43**, 1367 (1970); *Chem. Abstr.*, **73**, 87843l (1970). [f] J. Sawlewicz, L. Bukowski, J. Jasinska, D. Polaczek, J. Purzycka, Z. Sznigir, and D. Wesolowska, *Acta Pol. Pharm.*, 17, 85 (1960); *Chem. Abstr.*, 54, 17381g (1960); J. Sawlewicz and Z. Sznigir, *Acta Pol. Pharm.*, **18**, 1 (1961); *Chem. Abstr.*, **55**, 27277i (1961); J. Sawlewicz and M. Wasowska, *Acta Pol. Pharm.*, 17, 113 (1960); *Chem. Abstr.*, 54, 21056i (1960). [g] J. Sawlewicz, D. Kajoto, J. Purzycka, and D. Wyzinska, *Rozpr., Gdansk. Tow. Nauk. Wydz. 3*, No. 1, 175 (1964); *Chem. Abstr.*, 64, 15869e (1966). [h] G. Cooper and W. J. Irwin, *private communication*. [i] I. I. Chizhevskaya and V. I. Pansevich-Kolyada, *Zh. Obshch. Khim.*, **27**, 1495 (1957); *Chem. Abstr.*, **52**, 3720g (1958). [j] K. Hideg and H. O. Hankovsky, *Acta Chim. (Budapest)*, **53**, 271 (1967); *Chem. Abstr.*, 69, 59156h (1968). [k] T. Okuda, *Yakugaku Zasshi*, **80**, 205 (1960); *Chem. Abstr.*, **54**, 13141g (1960). [l] G. R. Revankar and S. Siddappi, *Monatsh. Chem.*, **98**, 169 (1967). [m] A. Novelli, *Bol. Soc. Quim. Peru*, 19, 77 (1953); *Chem. Abstr.*, **49**, 10211 (1955).

## 2. *Alkylation and Related Reactions*

The mechanism of imidazole and benzimidazole alkylation together with complications concerning benzimidazolium compound formation have been discussed by Simonov, *et al.*[8] Alkylation can be successfully achieved using a number of procedures including substitution reactions of alkyl halides (Table XVI), addition reactions to alkenes, epoxide ring-opening and Mannich procedures (Table XVII), and also by the use of dialkyl sulfates[115-117] and diazomethane.[81,118] Procedures leading to acyl, sulfonyl, and sulfenyl derivatives are listed in Table XVIII, while reactions leading specifically to benzimidazole nucleosides have been discussed in a recent review.[15]

A number of the procedures outlined in Table XVI are interesting. The mechanistic problem concerning product orientation from the alkylation of asymmetrically substituted benzimidazoles remains unclear: the recent literature has been summarized by Reddy and Subba Rao in connection with their investigations[119] on the methylation and benzylation of 5-nitrobenzimidazole. Alkylation with diethyl sulfate[115] gives a higher proportion of the 1,6 isomer, whereas alkylation by dimethyl sulfate[120] in the presence or absence of base gives a mixture containing approximately equal quantities of the 1,5 and 1,6 isomers. On the other hand, alkylation by alkyl halides[119] (MeI, $PhCH_2Cl$) in the presence of base gives predominantly the 1,5 isomer. The original results of Ridd and Smith[120] were interpreted[120] in terms of $S_E2'$ and $S_E2CB$ mechanisms and the product isomer ratio was considered to be a consequence of the tautomer ratio in the starting material. Clearly further studies of the effect of

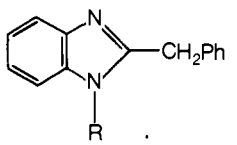
**TABLE XVIII. Acylation, Sulfonylation, and Sulfenylation of Benzimidazole Derivatives**

| Reagent | Reaction conditions | Ref |
|---|---|---|
| $RS(CH_2)_2NCO$ | Pyridine/40° | *a* |
| $NC(CH_2)_{11}NCO$ | Picoline/40° | *b* |
| RCONCO[o] | $CHCl_3$/room temp | *c* |
| RCOCl, ArCOCl | $NaH/C_6H_6$ | *d* |
| $COCl_2$ | THF/room temp | *e* |
| $COCl_2$/2,6-dimethylmorpholine | $Et_3N/C_6H_6$ | *f* |
| $RSO_2Cl$, $ArSO_2Cl$ | $NaHCO_3$ or $Et_3N$ or NaH/$Me_2CO$ | *g–l* |
| $Cl_3CSCl$ | NaOMe/MeOH/PhMe | *m* |
| $Cl_3CSH$ | $Et_3N/C_6H_6$ | *n* |

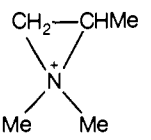
[a] E. H. Pommer, H. Osieka, K. H. Koenig, and G. Bolz, German Patent 2,012,589 (1971); *Chem. Abstr.*, 76, 25294l (1972). [b] W. Daum, H. Scheinpflug, P. E. Frohberger, and F. Crewe, British Patent 1,228,108 (1971); *Chem. Abstr.*, 75, 36053g (1971). [c] A. Widdig, K. Sasse, F. Grewe, H. Scheinpflug, P. E. Frohberger, and H. Kaspers, German Patent 1,936,130 (1971); *Chem. Abstr.*, 74, 87980u (1971). [d] H. D. Brown and L. H. Sarett, Belgian Patent 621,596 (1963); *Chem. Abstr.*, 59, 11504h (1963); U. S. Patent 3,055,907 (1962); *Chem. Abstr.*, 58, 2456c (1963). [e] H. A. Staab and G. Seel, *Justus Liebigs Ann. Chem.*, 612, 187 (1958). [f] R. Aries, French Patent 2,054,799 (1971); *Chem. Abstr.*, 76, 25292d (1972). [g] Chimetron, French Patent 1,439,128 (1966); *Chem. Abstr.*, 65, 20135d (1966). [h] G. T. Newbold and A. Percival, U. S. Patent 3,430,259 (1969); *Chem. Abstr.*, 70, 96797j (1969). [i] Fisons Pest Control, Netherlands Appl. 6,610,554 (1967); *Chem. Abstr.*, 67, 73610s (1967). [j] J. Sawlewicz and J. Jasinska, *Rocz. Chem.*, 38, 1073 (1964); *Chem. Abstr.*, 61, 16062e (1964). [k] Chimetron, French Patent, 1,439,129 (1966); *Chem. Abstr.*, 65, 18594c (1966). [l] P. E. Wittreich, K. A. Folkers, and F. M. Robinson, U. S. Patent 3,056,777 (1963); *Chem. Abstr.*, 58, 9087g (1963). [m] C. Hennart, *Bull. Soc. Chim. Fr.*, 4286 (1967). [n] R. Aries, French Patent 1,565,347 (1969); *Chem. Abstr.*, 73, 25466b (1970). [o] R = O-alkyl, O-aryl, SPh, and S-alkyl.

various aryl ring substituents as well as the type of alkylating agent used are desirable before definitive mechanistic conclusions can be drawn.

The work of Casey and Wright[121] is important in connection with the synthesis of analgesically active branched chain 1-(2-aminoethyl)-2-benzylbenzimidazoles (*cf.* section IX). Thus the desired 1-(2-aminopropyl) derivative **73a** predominates over the isomer **73b** in the product from reaction of the sodium salt of 2-benzylbenzimidazole with 2-chloro-1-dimethylaminopropane. The product orientation is rationalized on the basis of an intermediate imonium ion **74**,[122] ring-opening of which is subject to steric control.



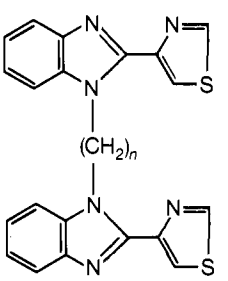
**73a**, R = $CH_2C(CH_3)HNMe_2$
**b**, R = $C(CH_3)HCH_2NMe_2$



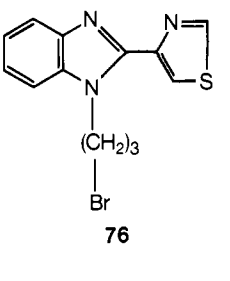
**74**

The work of Maynard, *et al.*,[123] on the alkylation of 2-(4-thiazolyl)benzimidazole ("thiabendazole"—*cf.* section IX) is also of commercial interest in that it highlights the surprisingly little information available on the chemistry of this important anthelmintic agent. 1-Alkylation of thiabendazole occurs in normal[124] fashion with *n*-hexyl and benzyl halides in the presence of sodium hydride; analogous procedures with $\alpha,\omega$-dihalides produce a series of bisbenzimidazolylalkanes **75**, but in the absence of a base the bromo derivative **76** gives rise to formation of a thiazolium salt **77**. Investigations of the scope of such reactions using benzimidazoles containing a variety of heterocyclic substituents in the 2 position are desirable.

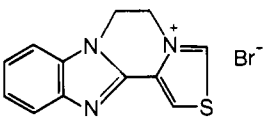
A number of alkylated benzimidazoles containing a $\gamma$-carbonyl function (*e.g.*, **78**a.b) have been synthesized[125,126] by the amine exchange procedure[127] using benzimidazoles and the appropriate Mannich base.



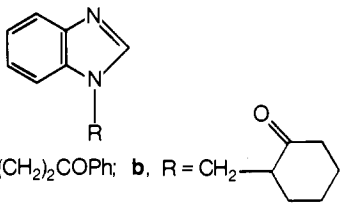
**75**, *n* = 1, 3, 6, 12



**76**



**77**

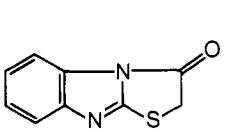


**78a**, R = $(CH_2)_2COPh$; **b**, R = $CH_2$-

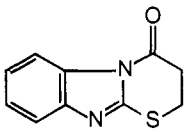
This special case of alkylation, *viz.*, 1-trimethylsilylation, can be achieved[128,129] very efficiently by allowing benzimidazole to react with hexamethyldisilazane at 150°.

### 3. *Intramolecular Alkylation and Acylation*

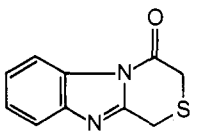
Little attention has been paid to assessment of the synthetic use of intramolecular alkylation and related processes involving the 1-nitrogen position. Derivatives of thiazolo[3,2-a]benzimidazol-3(2*H*)-one (**79**)[130,131] and the tetrahydrothiazinobenzimidazolones **80** and **81**[131] have been obtained by base-catalyzed cyclization of the appropriate 2-substituted thioacid derivatives. However, further studies are required in connection with seven-membered ring annellation. An attempt[132] to extend the



**79**

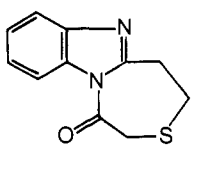


**80**

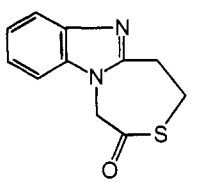


**81**

above type of reaction using 2-(benzimidazol-2-ylethylthio)acetic acid gave a product that has not been definitely formulated (*cf.* **82** or **83**); indeed, doubt exists con-



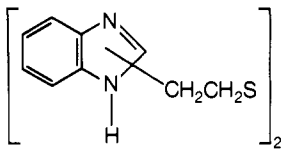
**82**



**83**

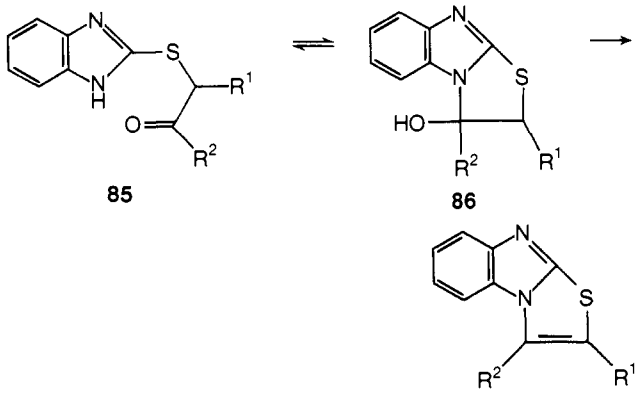
cerning the nature of the alkylation process during synthesis of the starting material from benzimidazol-2-ylethylthiol and chloroacetic acid (*cf.* conflicting reports[132,133] in relation to S- or N-alkylation during reaction of benzimidazol-2-ylmethanethiol with alkyl or aralkyl halides). The product from the reaction of 1,2-dichloroethane with 2-benzimidazol-2-ylethanethiol does not result from a cyclization process, but analyses agree with the structure eth-

ylenebis(thiomethylene)bisbenzimidazole (**84**); however, its exact structure also requires evaluation.



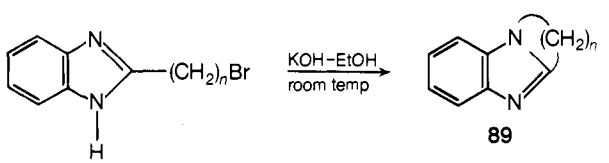
**84**

Intramolecular acylation of the series of ketones **85** produces[134] a series of potentially tautomeric carbinolamines **86**, dehydration of which provides a convenient entry into the thiazolo[3,2-a]benzimidazole series **87**. Infrared and nmr studies indicate that the position of the tautomeric equilibrium **85** ⇄ **86** is dependent on the substituents in the thiazolidine ring. In the solid phase and in solution, the unsubstituted compound (**85**, $R^1 = R^2 = H$) exists entirely in the carbinolamine form **86**; the methyl derivative (**85**, $R^1 = H$; $R^2 = Me$) is in the cyclic form in the solid state, but in solution a 2:1 equilibrium mixture is established in which the open-chain form predominates; and the phenyl derivative (**85**, $R^1 = H$; $R^2 = Ph$) exists only as the ketone in both the solid phase and in solution. Interestingly the latter situation is unaffected[135] by the presence of a variety of substituents (*e.g.*, MeO, Ph, Cl, Br, $NO_2$) in the aryl ring—an effect in marked contrast to the behavior of cis-β-aroylacrylic acids in which the presence of electron-withdrawing substituents assists formation of the lactone tautomer.[136]



**85** **86** **87**

Intramolecular alkylation of benzimidazoles can be achieved[137] in high yield at room temperature by base-catalyzed cyclization of 2-(ω-haloalkyl)benzimidazoles **88**; the starting materials **88** are readily accessible by the imidate method (see section II.A and Table III), and this route to the tricyclic derivatives **89** presents an alternative to methods involving the use of *N*-(*o*-aminoaryl)heterocycles (*cf.* ref 14).



**88**, $n = 3$–5 **89**

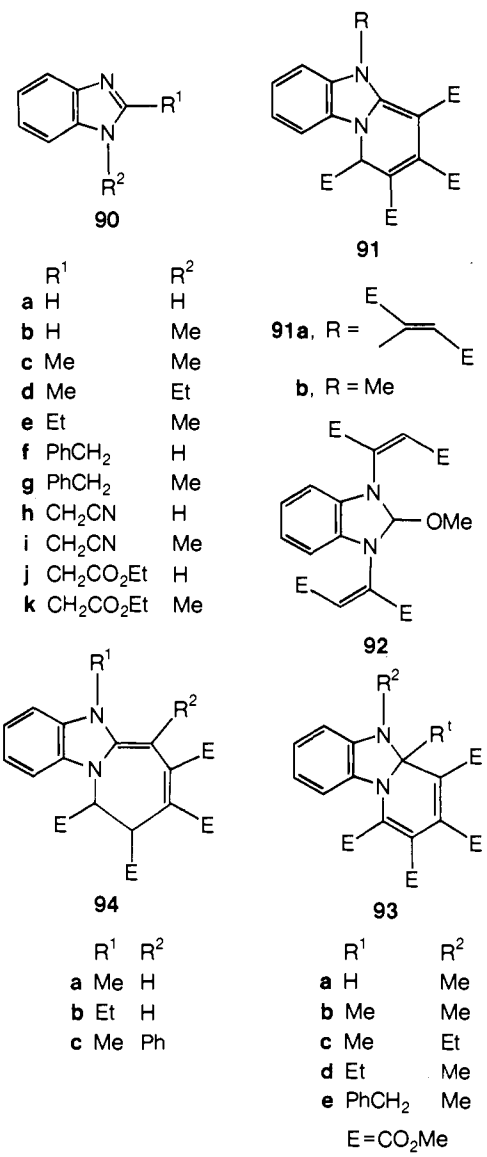
## 4. Electrophilic Attack by Alkynes

1-Vinylbenzimidazole[138] and 1,3-divinylbenzimidazolone[139] are formed by the nucleophilic addition of benzimidazole or benzimidazolone to acetylene in aqueous dioxane at 160 or 200°, respectively. The situation with activated alkynes is rather more complex: addition of benzimidazole derivatives **90** to dimethyl acetylenedicarboxylate provides an interesting variety of tricyclic derivatives (*e.g.*, **91**, **93–95**, **97**, **98**), among other products; some examples of this type of transformation are shown in Table XIX. Analogous procedures have found application on a wider basis in heterocyclic synthesis[140] and have been extensively investigated. The products can often arise by initial Michael addition followed by internal proton transfer (see Scheme XI).

**TABLE XIX. Reaction of Benzimidazole Derivatives with Dimethyl Acetylenedicarboxylate**

| Starting material **90** | Reaction conditions | Products | Ref |
|---|---|---|---|
| **a** | Excess diester/$C_6H_6$/reflux | **91a**,[a] **92**[b] | 142 |
| **b** | MeCN/reflux | **91b**,[a] **93a**[b] | 142 |
| **c** | MeCN/0° | **94a** | 142 |
| **c** | THF/0° | **94a**, **93b** | 142 |
| **d** | THF/room temp | **94b**, **93c** | 142 |
| **e** | MeCN/room temp | **93d** | 142 |
| **e** | THF/0° | **93d**,[a] **95**[b] | 142 |
| **f**[c] | $C_6H_6$/reflux | **96** | 143 |
| **g**[c] | MeCN/reflux | **95**, **93e**, **94c**, **97**, **98** | 143 |

[a] Major product. [b] Minor product. [c] For a related investigation on 2-$CH_2CN$ and 2-$CH_2CO_2Et$ derivatives, see ref 144.



**90**

| | $R^1$ | $R^2$ |
|---|---|---|
| **a** | H | H |
| **b** | H | Me |
| **c** | Me | Me |
| **d** | Me | Et |
| **e** | Et | Me |
| **f** | $PhCH_2$ | H |
| **g** | $PhCH_2$ | Me |
| **h** | $CH_2CN$ | H |
| **i** | $CH_2CN$ | Me |
| **j** | $CH_2CO_2Et$ | H |
| **k** | $CH_2CO_2Et$ | Me |

**91** **91a**, R = **b**, R = Me **92**

**94** **93**

| | $R^1$ | $R^2$ |
|---|---|---|
| **a** | Me | H |
| **b** | Et | H |
| **c** | Me | Ph |

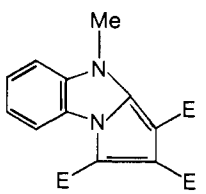
| | $R^1$ | $R^2$ |
|---|---|---|
| **a** | H | Me |
| **b** | Me | Me |
| **c** | Me | Et |
| **d** | Et | Me |
| **e** | $PhCH_2$ | Me |

E = $CO_2Me$

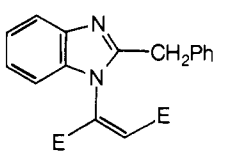
**TABLE XX. Electrophilic Attack at Benzimidazole Side-Chain Substituents**

| Position and type of substituent nucleophile | Electrophilic reagent | Ref |
|---|---|---|
| 2-$NH_2$, 2-NHPh | $Me_2SO_4$ | 146 |
| 2-$NH_2$ | $ClCO_2$-2-thienyl | *a* |
| | $ClCO_2$-4-thiazolyl | |
| 2-$NH_2$ | $ClCO_2Et$ | *b* |
| 1-$CH_2CH_2OH$ | $Ph_2CHCl$ | *c* |
| 1-$CH_2CH_2OH$ | RCOCl | *d* |
| | ArCOCl | |
| 2-$CH_2CH_2NH_2$ | $CS_2/NH_2NH_2$ | *e* |
| 2-$NH_2$ | RNCO | *f* |
| 2-$NH_2$ | ArCHO | *g*, *h* |
| 2-$NH_2$ | Furan-2-carboxaldehyde | *i* |
| 2-$NH_2$ | 1,4-Benzodioxan-2-carbonyl chloride | *j* |
| 2-$NH_2$ | OHCNHNHCHO | 149 |
| 2-$NH_2$ | $NCCH_2CO_2Et$ | |
| | $CH_3COCH_2CO_2Et$ | 148 |
| | $PhCOCH_2CO_2Et$ | |
| 5-$NH_2$ | ArCN | *k* |
| 2-Me | ArCHO | *l* |

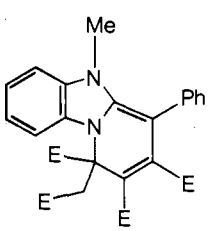
[a] Dyanchim S.a.r.l., French Patent 2,046,114 (1971); *Chem. Abstr.*, **75**, 151800k (1971). [b] R. J. Stedman, U. S. Patent, 3,480,642 (1969); *Chem. Abstr.*, **75**, 118314g (1971). [c] V. M. Pechenina, N. A. Mukhina, K. A. Abaturova, L. P. Grebenshchikova, T. V. Mikhailova, V. M. Kurilenko, and A. P. Gilev, *Khim.-Farm. Zh.*, **5**, 13 (1971); *Chem. Abstr.*, **76**, 14430w (1972). [d] V. M. Pechenina, N. A. Mukhina, K. A. Abaturova, V. K. Gorshkova, and A. P. Gilev, *Khim.-Farm. Zh.*, **3**, 18 (1969); *Chem. Abstr.*, **71**, 13062n (1969). [e] V. S. Misra and N. S. Agarwal, *J. Prakt. Chem.*, **311**, 697 (1969). [f] J. R. E. Hoover and R. J. Stedman, U. S. Patent 3,399,212; *Chem. Abstr.*, **70**, 11697d (1969). [g] H. O. Hankovsky and K. Hideg, *Acta Chim. Acad. Sci. Hung.*, **53**, 405 (1967); *Chem. Abstr.*, **68**, 19642a (1968). [h] A. M. Simonov and N. D. Vitkevich, *Zh. Obshch. Khim.*, **30**, 590 (1960); *Chem. Abstr.*, **54**, 24677i (1960). [i] A. M. Simonov and A. F. Pozharskii, *Khim. Geterotsikl. Soedin., Akad. Nauk. Latv. SSR*, 203 (1965); *Chem. Abstr.*, **63**, 8343g (1965); Zh. Obshch. Khim., **31**, 3970 (1961). [j] J. Koo, S. Avakian, and G. J. Martin, *J. Amer. Chem. Soc.*, **77**, 5373 (1955). [k] V. S. Misra and I. Husain, *J. Indian Chem. Soc.*, **37**, 710 (1960); *Chem. Abstr.*, **55**, 12390f (1961). [l] W. R. Sullivan, *J. Med. Chem.*, **13**, 784 (1970).




**95**




**96**

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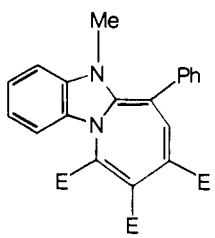
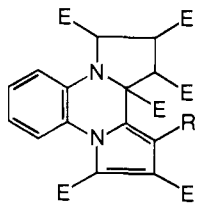



**98**

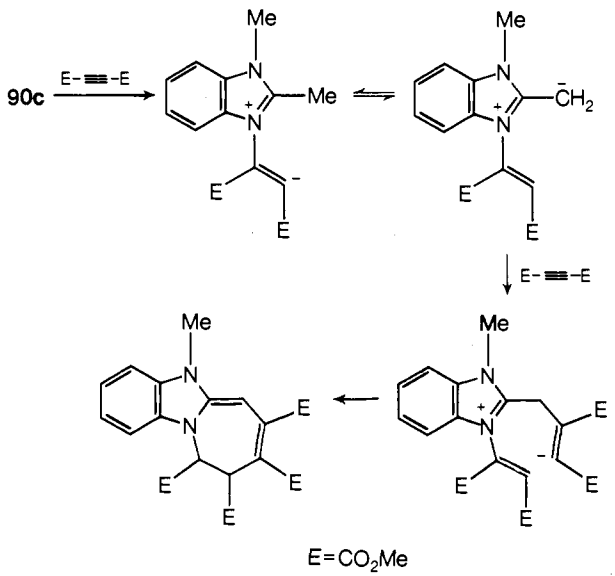



**99a**, R = $PhCH_2$
**b**, R = CN
**c**, R = $CO_2Et$

E=$CO_2$Me

Very recently[144] reactions of benzimidazole-2-acetonitrile (**90h**) and ethyl benzimidazole-2-acetate (**90j**) and their 1-methyl derivatives **90i,k** with methyl propiolate and dimethyl acetylenedicarboxylate have been examined. A number of products have been isolated including pyrrolo-, pyrido-, and azepino[1,2-a]benzimidazoles. Formation of the quinoxalines **99**[144,145] from the benzimidazole derivatives **90f,h,i** provides a remarkable example of a ring expansion that is probably unprecedented in benzimidazole chemistry; unfortunately, yields are very low (<7%) in this type of reaction although attempts to elucidate the mechanism will clearly be of some interest.

**SCHEME XI**[a]



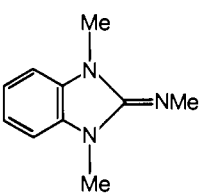

[a] *Cf.* ref 141 and 142.

From a general viewpoint addition reactions of this type are of synthetic value despite the low yields obtained. It will be of interest to elaborate upon the synthetic utility in relation to the nature of the 2-substituent; a wider investigation of solvent effects will also be informative in view of the conversions **90c** → **94a** and **90c** → **93b** + **94a** in methyl cyanide and tetrahydrofuran, respectively (see Table XIX).

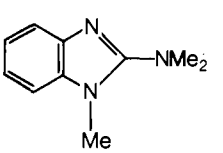
### 5. *Electrophilic Attack at Side-Chain Substituents*

Reactions in this category include substitution and addition processes and are confined mainly to amino derivatives (*cf.* Table XX).

The N-trimethylation[146] of 2-aminobenzimidazole is noteworthy since of the two possible products **100** and **101**, only the imino derivative **100** is formed; this mode of alkylation is in accord with the behavior of 5-aminotetrazoles.[147] Interestingly, the ultraviolet spectrum of 2-aminobenzimidazole is similar to the benzimidazole derivative **101** which indicates that it exists in solution mainly in the amino form.

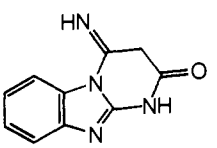



**100**

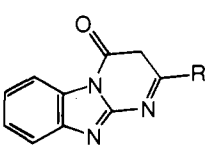



**101**

The synthetic value of nucleophilic addition reactions of 2-amino derivatives is nicely demonstrated[148] by the reaction of 2-aminobenzimidazole with ethyl cyanoacetate, ethyl acetoacetate, and ethyl benzoylacetate in




**102**




**103a**, R = Me
**b**, R = Ph

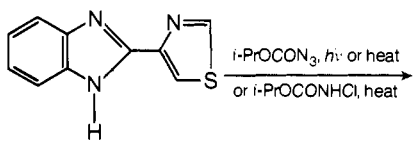
which subsequent cyclization of the addition products leads to the pyrimidobenzimidazole derivatives **102**, **103a**, and **103b**, respectively.

The reaction of aminohetarenes with diformylhydrazine has been used[149] to prepare a number of **4**-substituted 1,2,4-4*H*-triazoles. For the case of 2-aminobenzimidazole, however, the reaction affords a solid, mp 200–202°, in high yield, the structure of which has not been elucidated.

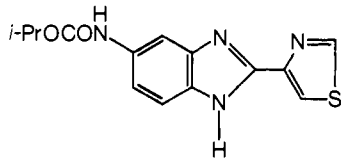
## C. Reactions Involving Arynes, Nitrenes, Carbenes, and Free Radicals

Benzimidazole reacts[150] as a nucleophile with benzyne in conventional fashion[151] to give 1-phenylbenzimidazole (29%) together with polymeric materials. The failure[152] of *N*-[(2-azido-1-benzimidazolyl)carbonyl]glycine isopropyl ester to react with benzyne has been rationalized[152] on the grounds that this azide is abnormal because of interaction of the azido group with the heterocyclic nitrogen atom (but *cf.* ref 153 and section III.H). The generation and reactions of 5,6-dehydrobenzimidazole[154] have been described elsewhere (see section III.D).

Nitrene intermediates generated from azides and from haloimines have been used[155] for the synthesis of the carbamate ester **105**, although its formation, **104** → **105**,



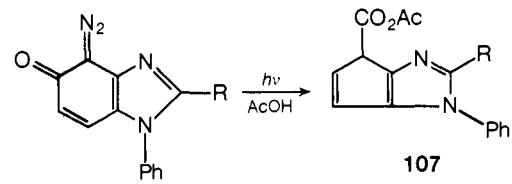

**104**



**105**

is unusual since nitrenes normally[156] react with aromatic compounds by cycloaddition followed by ring expansion of an intermediate azanorcaradiene to an azepine. The behavior of benzimidazolyl nitrenes is an unexplored field despite the fact that 2-azidobenzimidazoles have been reported[153] (*cf.* section III.H); cyclic iminonitrenes which might be expected from thermal or photochemical decomposition of such azides would be of interest in relation to their potential as 1,3-dipoles. Related investigations on 4- and 5-azidobenzimidazoles might also prove useful for the synthesis of imidazoazepines (*cf.* ref 157).

Apparently only two examples of reactions involving carbene intermediates have been reported. Diazotization of 2-substituted 4-amino-5-hydroxy-1-phenylbenzimidazole provides the diazo ketones **106** which can be transformed[158] into the imidazocyclopentene derivatives **107** by photochemical Wolff rearrangement in acetic acid. The structures of these products, **107**, have not been definitively elucidated but are assigned[158] on the basis of the behavior[158] of benzotriazole analogs (*cf.* also ref 159 for related procedures on other heterocyclic compounds).

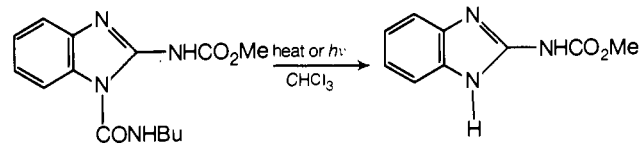



**106** R=H, Ph

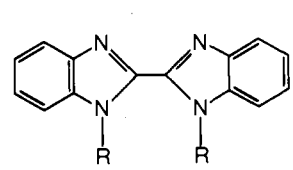
**107**

Evidence[160,161] for the intermediacy of carbenes in reactions of benzimidazolium salts with nucleophiles has been described elsewhere (see section VII).

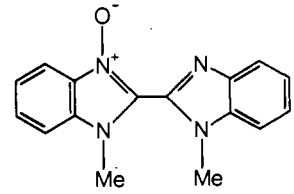
Very little has been reported on free radical reactions in benzimidazole chemistry although three definitive esr studies have been carried out (see section VIII.B). Other reactions that may involve free radical intermediates are the bromination[162] of 5,6-dimethylbenzimidazole with *N*-bromosuccinimide, deamidation[162a] of the carbamate ester (**108** → **109**) by thermal or photochemical methods, and the formation of bibenzimidazolyls [**110a** and (**110b** and **111**)] by pyrolysis of o-nitrophenylalanine[66] and 1-methylbenzimidazole 3-oxide,[67] respectively.




**108** **109**



**110a**, R = H
**b**, R = Me



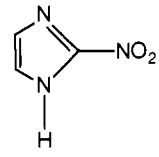
**111**

## D. Oxidation

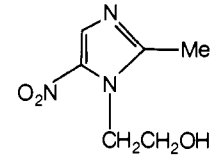
Imidazole-4,5-dicarboxylic acids can be prepared in practicable yields by oxidation of benzimidazole and its 2-alkyl derivatives with chromic acid,[163] although this method cannot be applied to **1**-substituted benzimidazoles. The oxidation has also been achieved[164,165] using 30–35% hydrogen peroxide at 100–160°. A number of routine procedures for the oxidation of side-chain substituents are indicated in Table XXI.

Two of the procedures illustrated in Table XXI are of interest: oxidation of the 2-(4-thiazolyl) derivatives with organic peracids provides[166] a series of thiazole *N*-oxides rather than benzimidazole *N*-oxides which is in accord with previous reports describing the difficulty in effecting N-oxidation of benzimidazoles (*cf.* ref 167–169).

Approaches directed[170,171] toward the synthesis of 2-nitrobenzimidazole derivatives (see Table XXI) stemmed from the commercial success of two nitro derivatives of imidazole, *viz.* azomycin (**112**)[3] and metronidazole (**113**).[4] The proposed[170] mechanism of oxidation of the



**112**



**113**

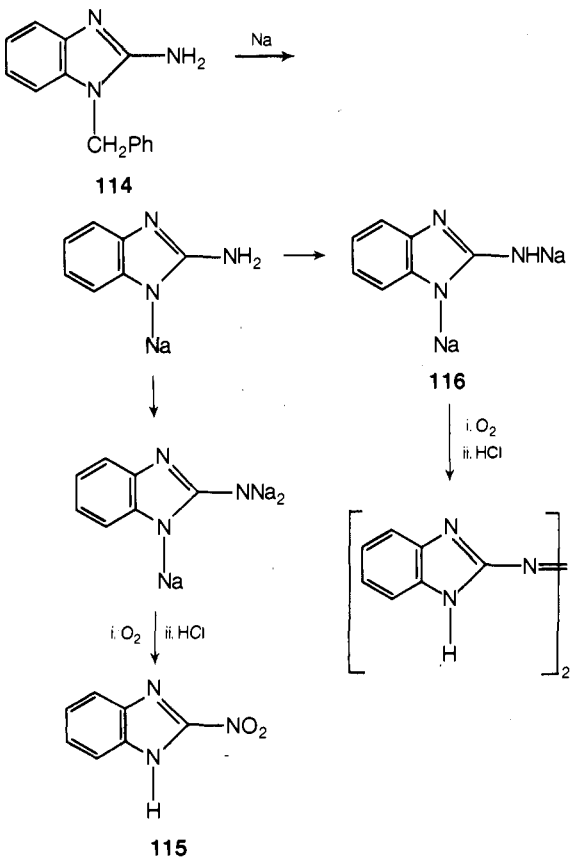
2-amino derivatives shown in Table XXI is indicated in Scheme XII and is based on the following circumstantial evidence: the 1-methyl and 1-ethyl analogs of **114** are not converted[170] into 2-nitro derivatives under comparable reaction conditions; sodio derivatives from the **1**-alkyl analogs of **114** are converted to the corresponding azo compounds only after extended contact with air;[170] and formation of the nitro compound **115** from 2-aminobenzimidazole requires the presence of **1**-benzylbenzimidazole in 3 molar excess.[171] It has been deduced[171] from the last observation that benzylsodium is significant in

**TABLE XXI. Oxidation of Benzimidazoles**

| Substituents | Oxidant | Products | Ref |
|---|---|---|---|
| 4,7-Dihydroxy derivatives[l] | $FeCl_3$ or $K_2Cr_2O_7$ or $Na_2O_3$ or $FeCl_3$ | 4,7-Quinones | *a, b* |
| 6,7-Dihydroxy derivatives | $FeCl_3$ | 6,7-Quinones | *c* |
| 5,6-Dihydroxy derivatives | $Ag_2O$ | 5,6-Quinones | *d* |
| 5,6-Dimethoxy | $HNO_2$ | 5,6-Quinones | *e* |
| 1,5-Dimethyl derivatives | Aq $KMnO_4$ | 1-Me-5-$CO_2H$ deriv | *f* |
| 1-Me-2-$CH_2OH$ | $AgNO_3/H_2SO_4/K_2S_2O_8$ | 1-Me-2-CHO | *g* |
| 1,2-$(Me)_2$ | $SeO_2$ | 1-Me-2-CHO | *g* |
| 1-$Et_2NCH_2CH_2$-2-CH(OH)aralkyl | Various oxidants, *e.g.*, $CrO_3$, $Pb(OAc)_4$ | 1-$Et_2NCH_2CH_2$-2-CO-aralkyl | *h, i* |
| 2-$CH_2CHPh_2$ | $SeO_2$ | 2-$COCHPh_2$ | *i* |
| 2-(4-Thiazolyl)-5-carboxamido | $CF_3CO_3H$ or $Cl_2CHCO_3H$ | 2-(3-Oxo-4-thiazolyl)-5-carboxamido | 166 |
| 1-R-2-$NH_2$[m] | Aq NaOCl | 2,2′-Azobenzimidazole deriv[j] | |
| 1-$PhCH_2$-2-$NH_2$ | (i) Na (2 mol)/$NH_3$ (ii) Autoxidation | 2-Aminobenzimidazole 2,2′-Azobenzimidazole | 170, 171 |
| 1-$PhCH_2$-2-$NH_2$ | (i) Na (4 mol)/$NH_3$ (ii) Autoxidation | 2-Nitrobenzimidazole[n] 2,2′-Azobenzimidazole | 170, 171 |

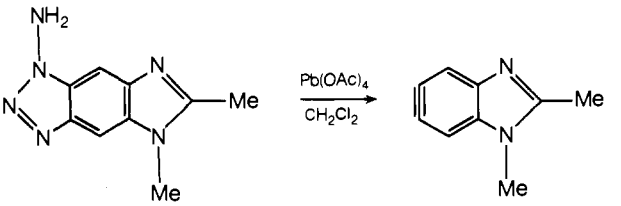
[a] L. Weinberger and A. R. Day, *J. Org. Chem.*, **24**, 1451 (1959). [b] E. R. Zakhs and L. S. Elros, *Zh. Org. Khim.*, **2**, 1095 (1966); *Chem. Abstr.*, **65**, 15365l (1966). [c] E. R. Zakhs and L. S. Elros, *Zh. Obshch. Khim.*, **34**, 1633 (1964); *Chem. Abstr.*, 61, 5636h (1964). [d] L. C. March and M. M. Joullié, *J. Heterocycl. Chem.*, 7, 39 (1970). [e] A. V. El'tsov and L. S. Elros, *J. Gen. Chem. USSR*, **30**, 3319 (1960); *Chem. Abstr.*, **55**, 18711g (1961). [f] A. M. Simonov and A. N. Lomakin, *Zh. Obshch. Khim.*, **32**, 2228 (1962); *Chem. Abstr.*, **58**, 7923g (1963). [g] D. D. Dalgatov and A. M. Simonov, *Zh. Obshch. Khim.*, **33**, 1007 (1963); *Chem. Abstr.*, **59**, 10024d (1963). [h] Donau-Pharmazie G.m.b.H., Austrian Patent 227,693 (1963); *Chem. Abstr.*, **59**, 11503g (1963). [i] Donau-Pharmazie G.m.b.H., French Medicinal Patent 1627 (1963); *Chem. Abstr.*, **59**, 6415c (1963). [j] A. F. Pozharskii, E. A. Zvezdina, and A. M. Simonov, *Khim. Geterotsikl. Soedin.*, 184 (1967); *Chem. Abstr.*, 67, 64302r (1967). [k] A. F. Pozharskii and E. A. Zvezdina, *Zh. Org. Khim.*, **3**, 2251 (1967); *Chem. Abstr.*, **68**, 59494w (1968). [l] Type of oxidant used depends on nature of substituents. [m] R = alkyl, aralkyl, and aryl. [n] 2-Nitrobenzimidazoles can also be prepared [k] by oxidation of 2-azido derivatives in the presence of $Na/NH_3$ or $K/NH_3$.

**SCHEME XII**

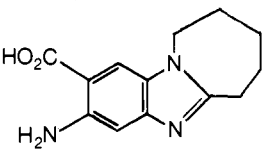



relation to formation of the disodio derivative (*cf.* **116**). It would be interesting to examine such reactions by esr spectroscopy with a view to assessing the possible intermediacy of radical anions; investigations of this unique type of oxidation process on other aminoheterocyclic compounds are also desirable.

Oxidation[172] of the *N*-aminotriazolobenzimidazole derivatives **117** by the lead tetraacetate method[173] provides a 5,6-dehydrobenzimidazole **118** as evidenced by trapping reactions using furan, tetracyclone, and phenylazide; this type of reactive intermediate is also accessible by allowing the carboxylic acid derivative **119** to react with isopentyl nitrite in chloroform (*cf.* the aprotic diazotization procedure of Friedman and Lagullo[174]).

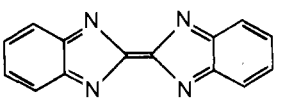



**117** **118**




**119**

In contrast to the oxidation of benzimidazole with chromic acid[163] and hydrogen peroxide,[164,165] prolonged treatment[175] with lead dioxide in benzene gives $\Delta^{2,2'}$-biisobenzimidazolylidine (**120**). The reaction is slow and inefficient, and the product **120** is more easily accessible by a similar oxidation of 2,2′-bibenzimidazolyl.



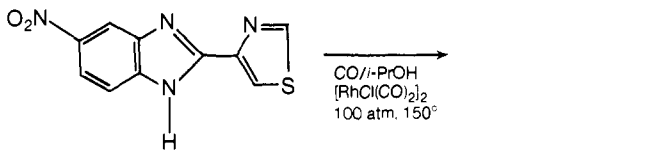
**120**

The mechanism of formation of this tetraazadibenzofulvene analog **120** is unclear, but Hill[175] has tentatively suggested that an intermediate 2,2′-bibenzimidazole is formed by dimerization of a 2-benzimidazolyl free radical which could arise by isomerization of a 1-benzimidazolyl radical; a rearrangement of this type could have precedent in the thermally induced isomerization[176] of 1-trityl- to 2-tritylimidazole derivatives.

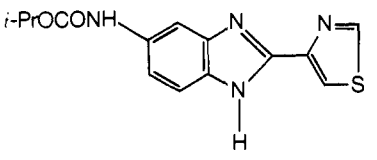
## E. Reduction

The standard method for the synthesis of 4,5,6,7-tetrahydrobenzimidazoles involves hydrogenation in the presence of a platinum catalyst in acetic acid (*cf.* ref 5), although more recently rhodium,[177] palladium,[178] and platinum oxide[179] catalysts have been used; reduction of the imidazole ring can be achieved[180] using lithium aluminum hydride.

One new method[181] involving side-chain reduction deserves comment: when 5-nitro-2-(4-thiazolyl)benzimidazole (**121**) is allowed to react with carbon monoxide in isopropyl alcohol in the presence of rhodium chlorocarbonyl, the carbamate ester **122** is formed in a single step. A wider investigation of the scope of this reaction in




**121**




**122**

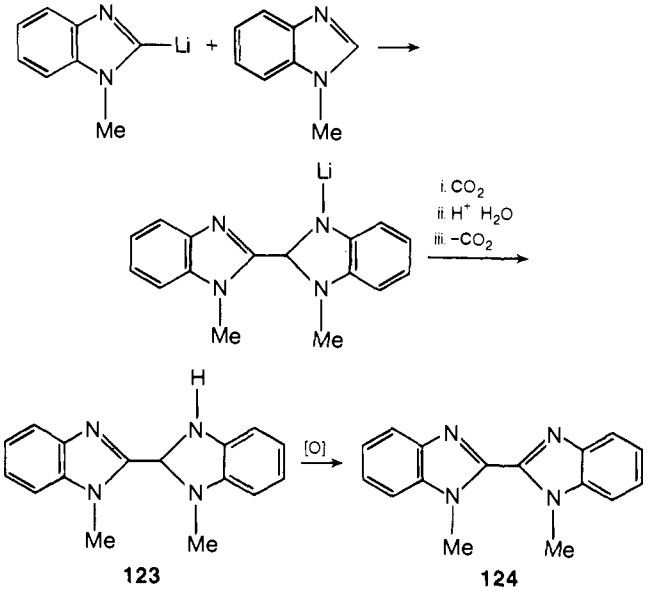
nitroaromatic and heteroaromatic chemistry would be interesting, and indeed this highlights the general requirement for further work in the field of nitro group reduction using transition metal carbonyl catalysts (*cf.* ref 182).

## F. Metalation

Metalation of benzimidazoles was first achieved by Alley and Shirley[183] who obtained **1**-methylbenzimidazole-2-carboxylic acid in 45% yield by carbonation of the reaction product from **1**-methylbenzimidazole and *n*-butyllithium at −60°. If the metalation is carried out at room temperature, a mixture containing a 3:1 molar ratio of the compounds **123** and **124** is formed[183] (see Scheme XIII).

Metalation of 1-alkylbenzimidazoles can also be achieved by the use of phenylsodium at low temperature[184,185] although for **1**-arylbenzimidazoles this procedure can give rise[185] to mixtures of the desired 2-sodio derivative together with 3-sodio addition products; however, metalation of **1**-phenylbenzimidazole can be effected[186] by phenyllithium. An alternative method[187,188] of metalation of 1-alkyl derivatives involves the use of sodium or potassium in a mixture of benzene and isoamyl alcohol although application of this type of reaction at room temperature gives rise to dimer formation[188] (*cf.* ref 183 and compound **124**).

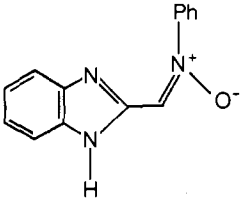
**SCHEME XIII**



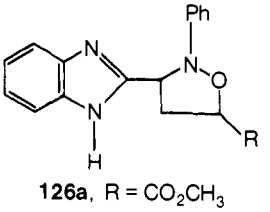

**123** **124**

## G. Electrocyclic Reactions

2-(Benzimidazolyl)-*N*-phenylnitrone (**125**) reacts[189] with methyl acrylate or styrene in conventional fashion[190,191] to give isoxazolidines **126a,b** in moderate yield (40 and 50%, respectively); the orientation of addition is in accord with previous reports[190a] of nitrone–alkene 1,3-dipolar cycloaddition reactions. Typically,[192] the nitrone **125** is photosensitive[189] although the structures of the decomposition products have not been elucidated; possibly 2-amidobenzimidazole derivatives may be accessible by this route (*cf.* ref 192).

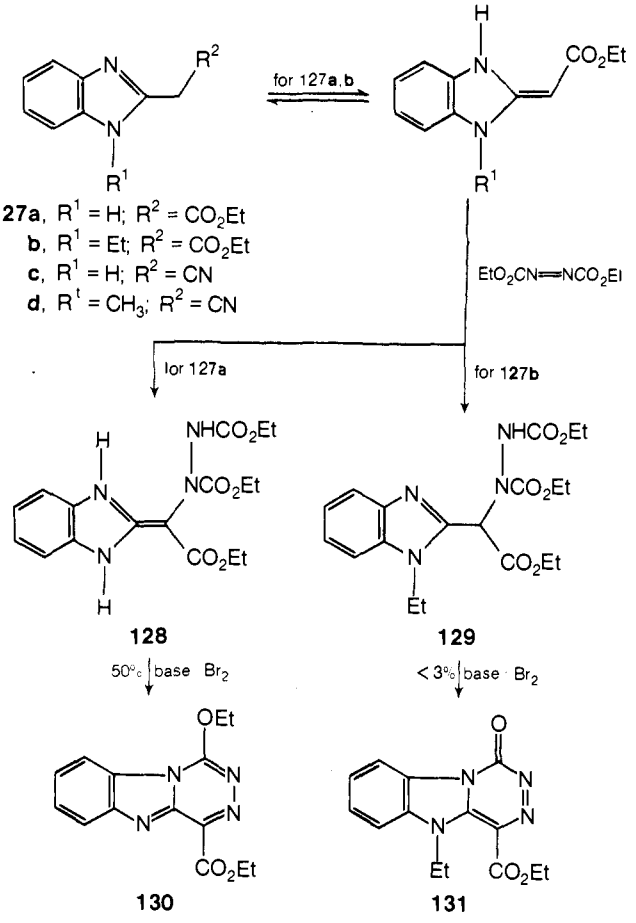



**125**




**126a**, R = $CO_2CH_3$
**b**, R = Ph

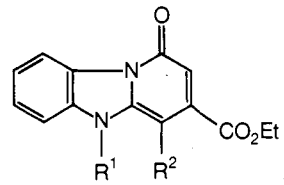
Reactions of the esters **127a,b** with diethyl azodicarboxylate give good yields of the adducts **128** and **129**, respectively;[193] inclusion of these processes in this section



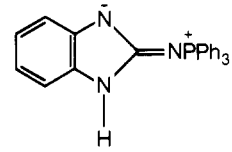

**127a**, $R^1$ = H; $R^2$ = $CO_2Et$
**b**, $R^1$ = Et; $R^2$ = $CO_2Et$
**c**, $R^1$ = H; $R^2$ = CN
**d**, $R^t$ = $CH_3$; $R^2$ = CN

**128** **129**

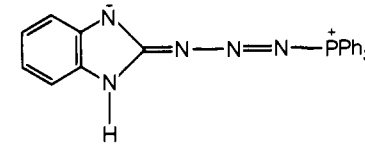
**130** **131**



**132a**, $R^1 = H$; $R^2 = CO_2CH_3$ (from **127a**)
**b**, $R^1 = H$; $R^2 = CN$ (from **127c**)
**c**, $R^1 = CH_3$; $R^2 = CN$ (from **127d**)

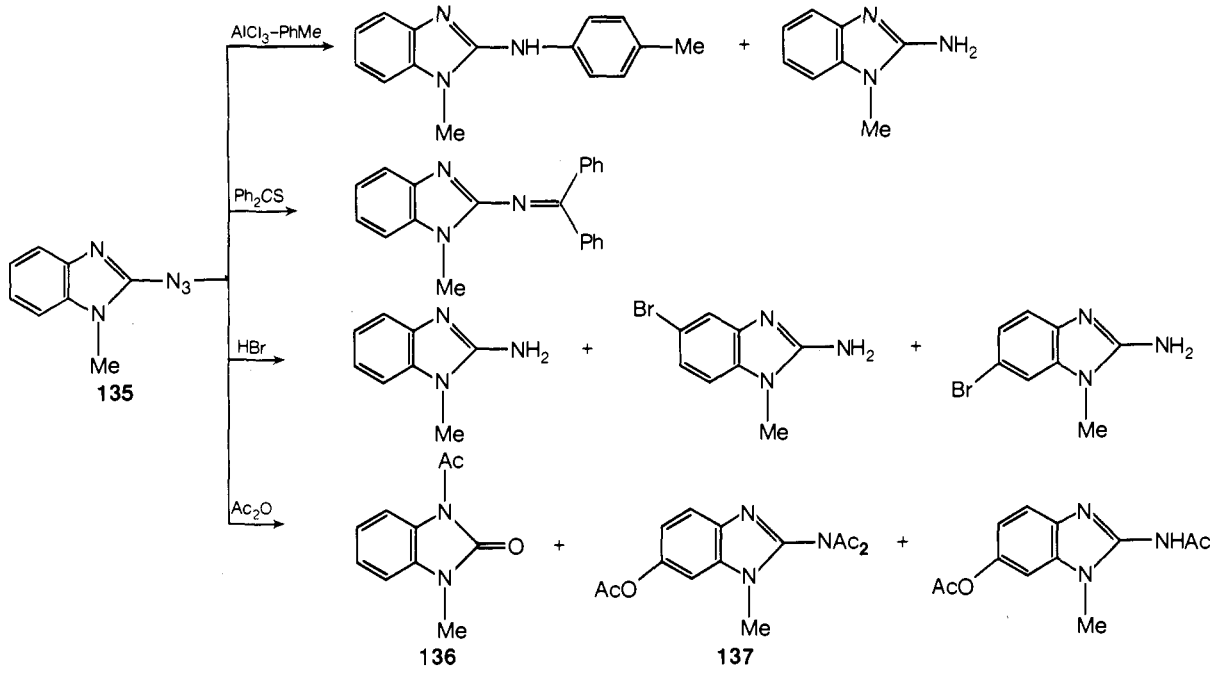


**133**



**134**

**SCHEME XIV**



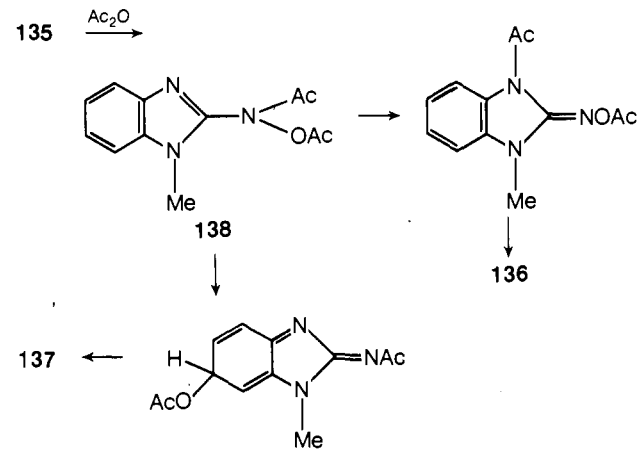
is based on the assumption of the authors[193] that they are hetero examples of the ene reaction[194] rather than Michael reactions. Formation of the adduct **128** is useful since it can be converted by oxidative cyclization into an *as*-triazinobenzimidazole (**130**) in moderate yield; *cf.* the formation of **131** from **129**, however, which can be isolated in only 3% yield. Tricyclic derivatives **132a-c** are also obtained when the ester **127a** or the nitriles **127c,d** are allowed to react with dimethyl acetylenedicarboxylate, although for these cases intermediate adducts are not isolated since spontaneous cyclization occurs.

1,3-Dipolar cycloaddition reactions involving benzimidazolium tetrafluoroborates[195] are described in section VII.

## H. Reactions of Azides, Azo Compounds, and Formazans

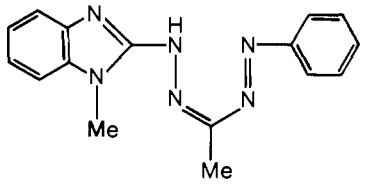
The existence of certain 2-azidobenzimidazole derivatives in the azido rather than the tetrazole form has been established by spectroscopic methods.[196] Investigations on the reactivity of 2-azidobenzimidazoles are limited in number: a phosphinimine, **133**, has been obtained[197] by thermolysis of a stable triphenylphosphine adduct, **134**, and other reactions[198] are summarized in Scheme XIV. Product formation from reaction of the azide **135** with acetic anhydride has been rationalized[198] on the basis of an intermediate O,*N*-diacetyl-2-benzimidazolylhydroxylamine derivative (**138**) which could arise by interaction of a 2-nitrene moiety with acetic anhydride (*cf.* Scheme XV and the mechanism proposed[199] for phenyl azide decomposition in acetic anhydride).

**SCHEME XV**



Diazotization of amino substituents in the aryl ring of benzimidazoles proceeds normally,[200a-c] and a number of coupled products have been prepared.[200a,b] On the other hand, diazotization of 1-alkyl-2-amino derivatives with nitrous acid proceeds only slowly in the presence of sulfuric acid and not at all in hydrochloric acid. For these cases, diazotization can be effected[201] by nitrosylsulfonic acid in the presence of a mixture of sulfuric and phosphoric acids.

A number of benzimidazole-substituted formazans (*e.g.*, **139**) have been prepared[202-206] by the usual[207,208] procedure although their chemical reactivity has not been examined.



139

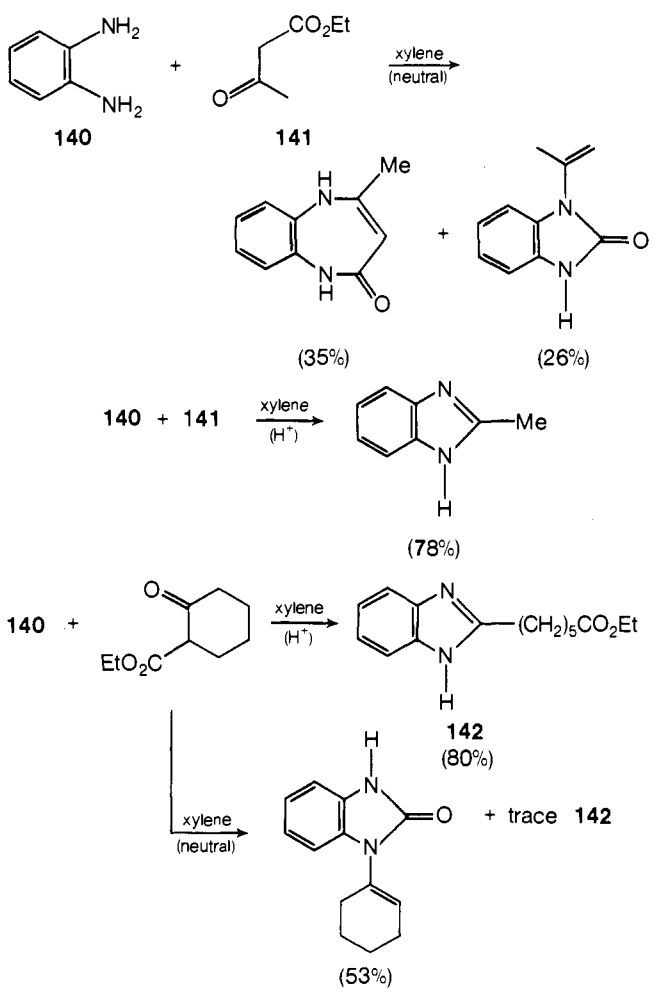
## IV. Synthesis and Reactions of Benzimidazolones

### A. Synthesis

#### 1. From Arylamine Derivatives

A detailed study[209a] has been made of the conditions necessary for formation[209b] of benzimidazolones from the reaction of β-keto esters with o-phenylenediamine. Satisfactory results are achieved by heating the reactants in neutral solutions in xylene, and this type of reaction can be extended to β-keto esters derived from cycloalkanones (see Scheme XVI); a possible route[209a] to the benzimidazole products is outlined in Scheme XVII.

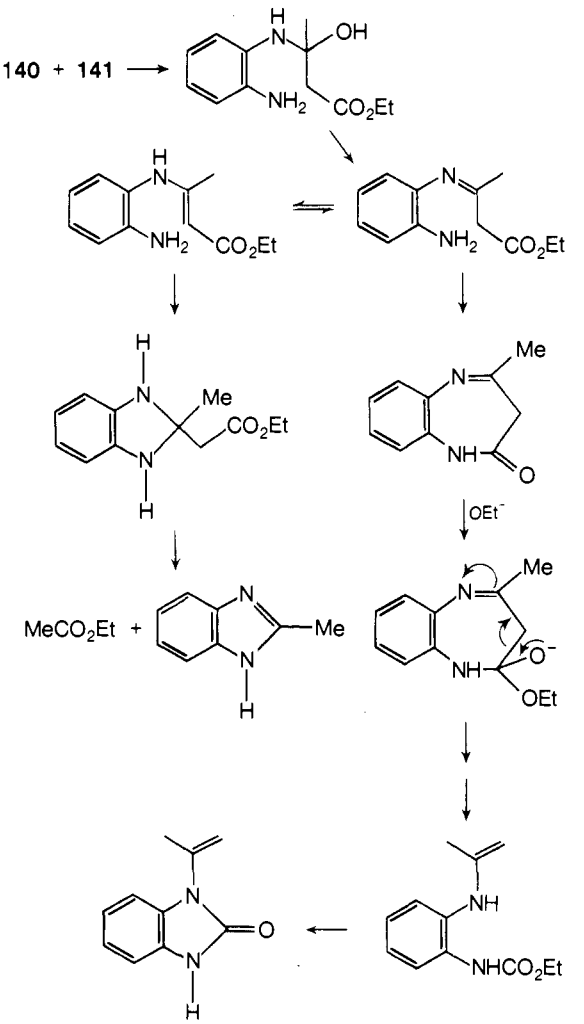
**SCHEME XVI**



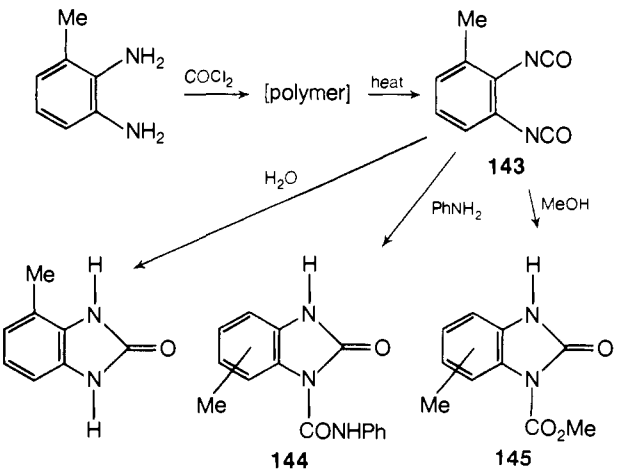
The ortho diamine route[210] to the benzimidazolone derivatives **144** and **145** involves the first recorded isolation of an ortho diisocyanate, **143**; the latter can be prepared for the tolyl derivative at least, by thermal degradation of the polymer obtained by allowing the *o*-arylene diamine to react with excess phosgene.

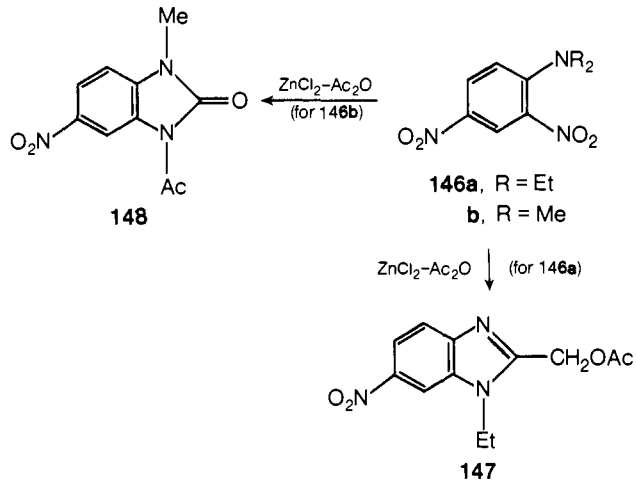
The report[211] concerning formation of the 2-acetoxymethyl derivative **147** and the benzimidazolone **148** from the reaction of *o*-nitro-*tert*-alkylanilines (**146**) with zinc

**SCHEME XVII**

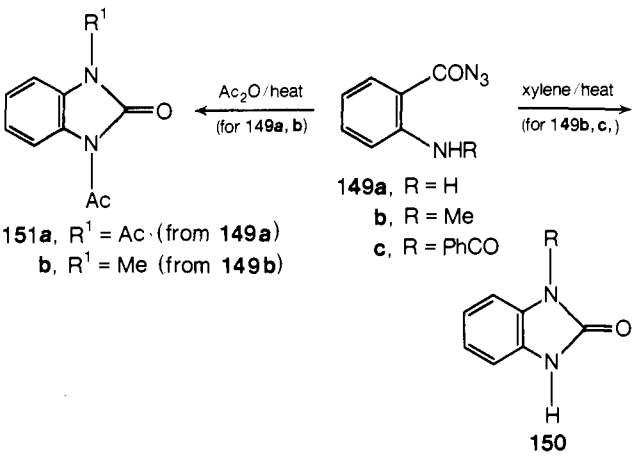


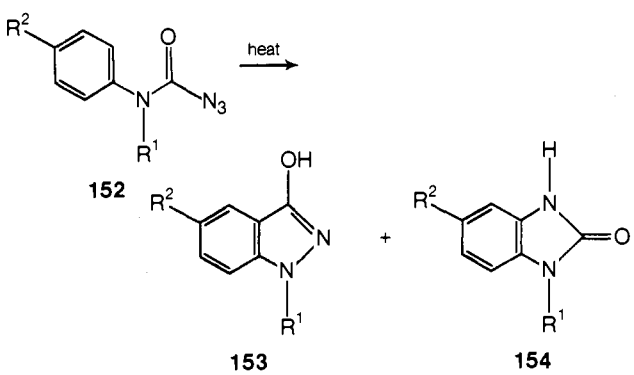
chloride and acetic anhydride is an important one since the former product **147** had been earlier erroneously formulated[212] as a quinoxaline derivative. The mechanism of formation of these products, **147** and **148**, is obscure although intermediate organometallic complexes are envisaged[211] for benzimidazole **147** formation at least. A wider investigation of the effect of a range of transition metal compounds on this and related[14] reactions could be interesting, especially in view of the known[213] ability of aromatic nitro compounds to form transition metal complexes.






Remarkably high yields (75–80%) of benzimidazolones **150** and **151** are obtained[214,215] by thermolysis of suitably substituted aroyl azides **149** in xylene or acetic anhydride, and the facility of this reaction is considered to be circumstantial evidence against the intermediacy of nitrenes which would be expected to undergo transformation into indazolones. Benzimidazolones **154** have also been isolated from the thermolysis products of carbamoyl azides **152** in either xylene[216] or tetralin,[217] but yields are much lower and indazole **153** formation is often an important competing process. The nature of intermediates in these reactions has not been established, and it would be of interest to explore their course under photolytic conditions.




$R^1$ = $PhCH_2$ or *p* $MeC_6H_4$; $R^2$ = H, Cl, $NO_2$, Me, alkoxy

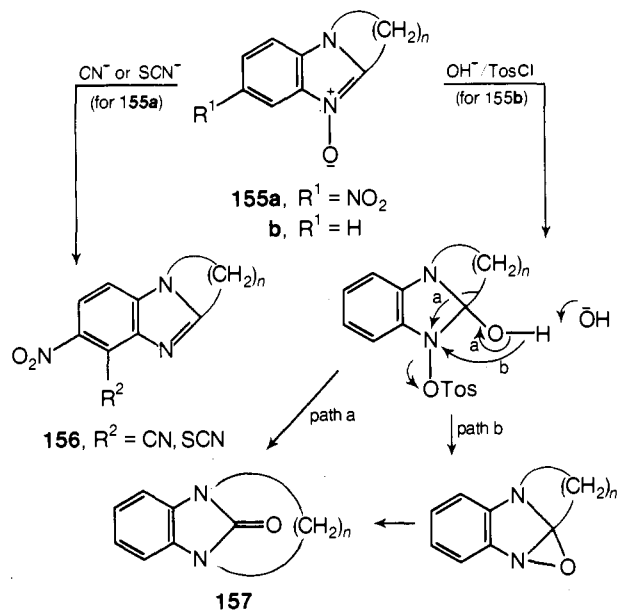
## 2. *From Heterocycles*

### a. From Benzimidazoles

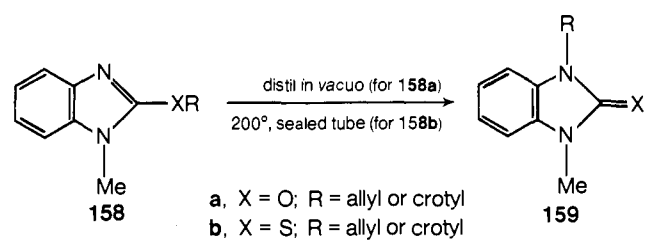
Benzimidazolone is formed[218,219] when benzimidazole *N*-oxide is heated with water in a sealed tube at 180°. More recently the hydrolytic rearrangement of 1-methylbenzimidazole 3-oxide to 1-methylbenzimidazolone has been shown[220] to be very facile and can be effected in acetone or chloroform under reflux or by allowing solutions to stand at room temperature for a few weeks. Benzimidazole *N*-oxides are probably also intermediates during the formation[66] of benzimidazolones from thermolysis of *o*-nitroaryl derivatives of $\alpha$-amino acids.

A rather interesting case of benzimidazolone formation emerged from an investigation[221] on the reactivity of polymethylenebenzimidazole *N*-oxides (**155**) with nucleophiles. In contrast to their behavior with, for example, $CN^-$ or $SCN^-$ which produces benzimidazoles **156**, they react with sodium hydroxide in the presence of *p*-toluenesulfonyl chloride to give polymethylenebenzimidazolones **157** in variable yields (13–85%). It is interesting also that the benzimidazolones **157** can be obtained[221] from the *N*-oxides **155** photochemically, which might suggest that the route involving an intermediate oxaziridine (path b) is the most likely of the two envisaged[221] mechanisms (paths a and b) for their formation (see Scheme XVIII) (*cf.* the isolation[222] of 1,3-dialkylbenzimidazolones from the photolysis of 1,2-dialkylbenzimidazole 3-oxides and also the significance of oxaziridine intermediates in the photolysis of aromatic amine *N*-oxides[223]).

**SCHEME XVIII**



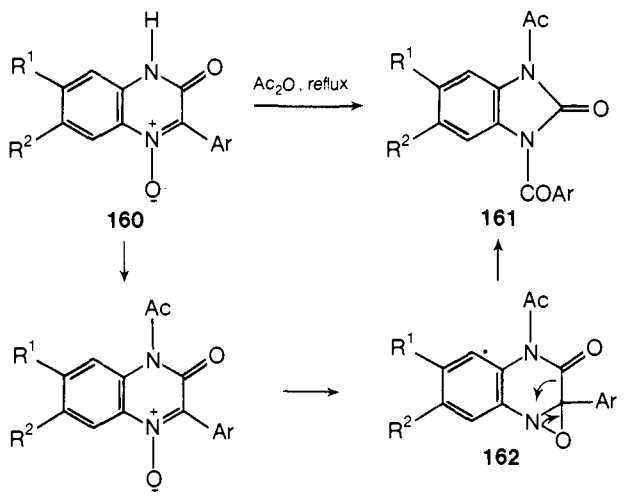

1-Methyl-3-allyl- (and crotyl-) benzimidazolones **159a** are obtained,[224] often in good yields (*e.g.*, 76% for **159a**) from Claisen-type rearrangement of the 2-allyl (or crotyl) ether derivatives **158a**; the reaction can also be used to prepare benzimidazoline-2-thiones (**159b**), but reaction conditions are rather more forcing.



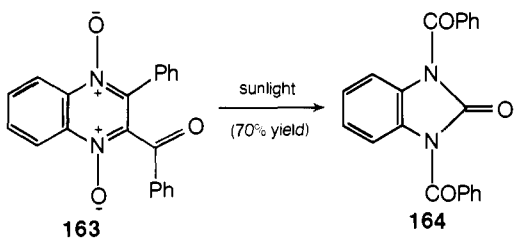

1,3-Disubstituted benzimidazolones have also been synthesized[225] by heating 1-alkyl- (or aralkyl-) 2-aminobenzimidazoles with excess of an organic halide.

### b. From Other Heterocycles

Certain quinoxaline *N*-oxides **160** are converted[226] into 1-aroyl-3-acetylbenzimidazolones (**161**) on treatment with acetic anhydride in contrast to their behavior[227] with acetyl chloride which transforms them into 6-chloro derivatives; in the first type of reaction, **160** → **161**, the aroyl derivatives **161** are often converted by transacylation into 1,3-diacetylbenzimidazolones. The essential requirements for the rearrangement **160** → **161** to occur are an *N*-oxide function at N-1, a substituent at C-2, a carbonyl group at C-3, and a free NH at N-4. A mechanism involving thermally induced rearrangement of an intermediate oxaziridine **162** has been suggested for the formation of **161** although there is no experimental evidence to




suggest this as yet. Oxaziridine intermediates have also been invoked[228] to rationalize the formation[228] of 1,3-dibenzoylbenzimidazolone (**164**) from irradiation of the quinoxaline di-*N*-oxide **163** with sunlight (but see ref 229 and 230). Disappointingly, an attempt[230] to extend this type of reaction to 2,3-diphenylquinoxaline di-*N*-oxide gave a complex product from which no pure compounds have been isolated.

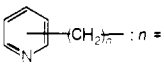



## B. Reactions

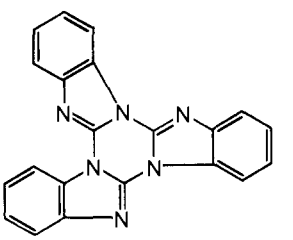
A number of routine procedures that have been reported include electrophilic aromatic substitution reactions (nitration,[231] acylation,[231,232] and carboxyalkylation[233]), nitro group reduction,[234] Wittig reactions of 5-formyl derivatives,[235] O-acetylation,[236] and carboxyamidation with aryl isocyanates.[237]

The product obtained by allowing 2-chlorobenzimidazole[238] or benzimidazolone[239] to react with phosphorus oxychloride has been shown[239] to be the *s*-triazine derivative **165**. The same product **165** can be obtained[239] by treatment of benzimidazoline-2-thione with phosphorus oxychloride and also by heating 2-chlorobenzimidazole either neat[239] or in nitrobenzene solution,[239] or with urethane in toluene at 180–200°.[240]

**TABLE XXII. S-Alkylation of Benzimidazoline-2-thiones**[a]

| Type of organic halide used (R in RX) | Ref |
|---|---|
| Alkyl, substituted alkyl, aralkyl, aryl | *a* |
| $R^1COCHR^2$: $R^1$, $R^2$ = alkyl, aryl | *b* |
|  : *n* = 1, 2 | *c* |
| Cyclohex-2-enyl | *d* |
| Alkyl, aralkyl, crotyl, $CH_2CO_2H$, $(CH_2)_2CO_2H$ | *e* |
| $CH_2CO_2H$ | *f* |
| $CH_2CO_2H$ | |
| $(CH_2)_2CO_2H$ | *g* |
| $CH_3CHCO_2H$ | |
| PhCO | *h* |
| $PhCOCH_2CH_2$ | *i* |

[a] S. Nakajima, I. Tanaka, T. Aka, and T. Yasumo, Japanese Patent 10,978 (1961); *Chem. Abstr.*, **58**, 13964i (1963). [b] A. N. Krasovskii and P. M. Kochergin, *Khim. Geterotsikl. Soedin.*, 316 (1969); *Chem. Abstr.*, 71, 22064s (1969). [c] H. O. Hankovszky and K. Hideg, *Acta Chim. (Budapest)*, 61, 69 (1969); *Chem. Abstr.*, 71, 112863l (1969); K. Hideg, O. Hideg, F. Ordogh, L. Vaczy, and G. Mehes, British Patent 1,234,058 (1971); *Chem. Abstr.*, **75**, 98570g (1971). [d] J. J. D'Amico, U. S. Patent 2,976,293 (1961); *Chem. Abstr.*, **55**, 17654i (1961). [e] W. Knobloch, G. Winkelmann, and L. Rintelen, *Arch. Pharm. (Weinheim)*, **291** 113 (1958); *Chem. Abstr.*, **52**, 17242d (1958). [f] J. A. Van Allan, *J. Org. Chem.*, **21**, 24 (1956). [g] T. L. Rebstock, C. D. Ball, C. L. Hamner, and H. M. Sell, *J. Amer. Chem. Soc.*, 78, 5831 (1956). [h] Laboratoires Cassenne, British Patent, 1,152,814 (1969); *Chem. Abstr.*, **72**, 12729u (1970). [i] H. O. Hankovsky and K. Hideg, *Acta Chim. (Budapest)*, **63**, 447 (1970); *Chem. Abstr.*, **72**, 100597e (1970). [j] Substituents on the nitrogen atoms and/or in the aryl ring are not specified. Reaction conditions are usually thione, organic halide, aq NaOH, reflux.


165

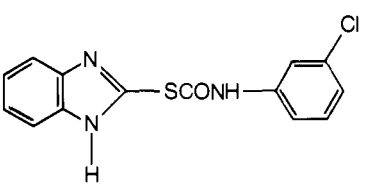
## V. Synthesis and Reactions of Benzimidazoline-2-thiones

### A. Synthesis

A number of benzimidazoline-2-thiones have been synthesized by the general method described by Van Allan and Deacon,[241] but routine methods of this type are not included here. Uncommon approaches to 2-thiones include their formation from 4,5,6,7-tetrahydrobenzimidazole by thermal reactions in the presence of sulfur[242] and from 2-chlorobenzimidazoles by reaction with thiourea.[243]

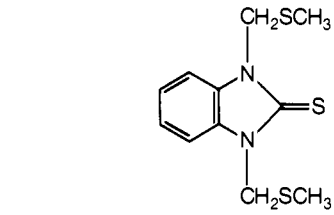
### B. Reactions

The majority of data on reactions of benzimidazoline-2-thiones relates to S-alkylation and such procedures are summarized in Table XXII; closely related processes are the synthesis of 2-thiocyanatobenzimidazoles from the reaction of benzimidazoline-2-thione with cyanogen chloride or bromide[244] and of 2-benzimidazolyl thiolcarbamates (*e.g.*, **166**) from addition of the 2-thione to aryl isocyanates.[245] Other routine procedures are the oxidation

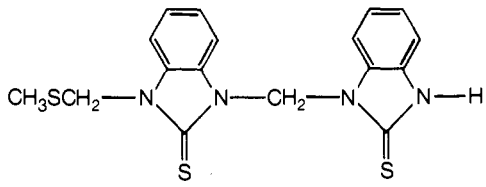

166

of 2-thiones to bisbenzimidazolyl disulfides[246,247] and benzimidazole-2-sulfonic acids[247] by hydrogen peroxide, and the formation[248] of 5-nitrobenzimidazoline-2-thione derivatives under normal aromatic nitration conditions.

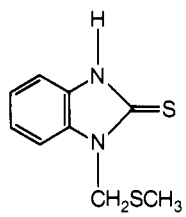
A variety of compounds, **167–170**, are obtained[249] when benzimidazoline-2-thione is allowed to react with a



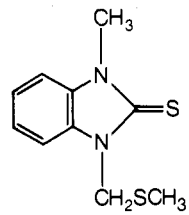
**167**



**168**

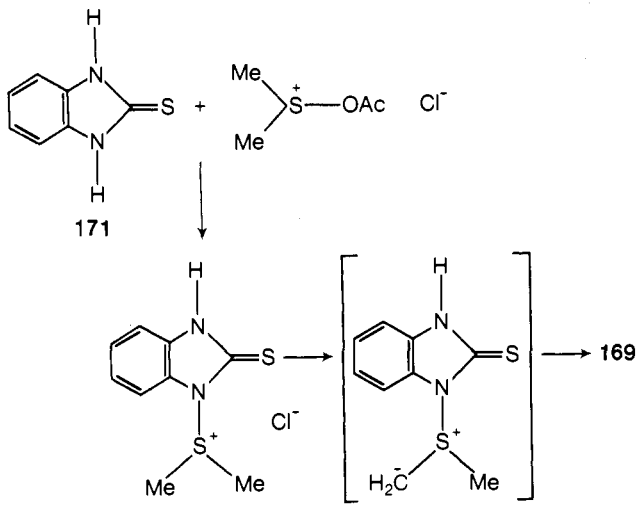


**169**



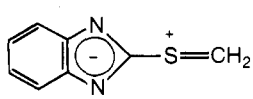
**170**

mixture of dimethyl sulfoxide and acetyl chloride at 50–60°; the formation of these products can be satisfactorily rationalized[249] in terms of displacement reactions by the thione **171** on an intermediate sulfonium acetate (*cf.* **171** → **169**). Interestingly, if the reaction is carried out below



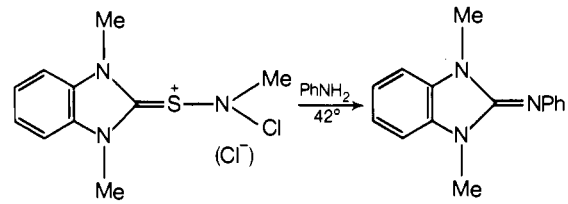
**171**

30°, the reaction product includes compounds **167–169** and also the novel 2-(methylenesulfonium)benzimidazolide (**172**) in 20% yield. The reactivity of the last type of compound, **172**, has not yet been evaluated; of particular interest in this respect would be an investigation of 1,3-dipolar cycloaddition reactions (*cf.* also the formation[83] of a 2-(pyridinium)benzimidazolide (**51**) described in section III.A.2).

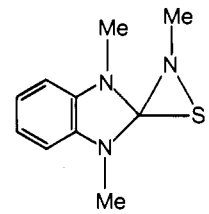


**172**

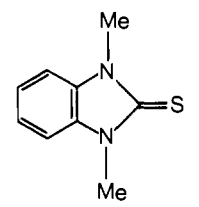
A sulfonium salt, **173**, has also been isolated[250] from the reaction of benzimidazoline-2-thione with *N,N*-dichloromethylamine, and its chemistry has been briefly investigated. Certain modes of reactivity of this salt are nicely demonstrated by its behavior with aniline in which nucleophilic attack at the benzimidazole 2-carbon atom (*cf.* **173** → **174**) or the exocyclic nitrogen atom (*cf.* **173** → **175**) can occur; formation of 1,3-dimethyl-2-methyliminobenzimidazoline (**176**), however, is probably best rationalized[250] in terms of an intermediate thiaziridine derivative (*cf.* **173** → **177** → **176**).



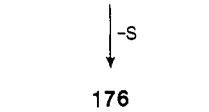
**173** **174**



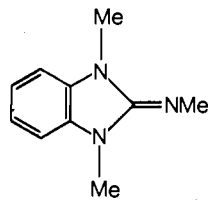
**177**



**175**



**176**



**176**

Preliminary reports have appeared concerning the photochemically induced decomposition[251] of benzimidazoline-2-thiones (*cf.* **178** → **179**; **180** → **181**) and also the base-catalyzed reaction[252] of benzimidazoline-2-thione and its *S*-methyl derivative (*cf.* **182a** → **183**; **182b** → **184**) with amines; the mechanism and scope of these processes have not been established.

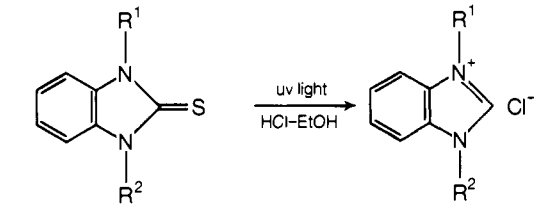
Formation of the benzimidazole trimer **165** by allowing benzimidazoline-2-thione to react with phosphorus oxychloride has been referred[240] to in section IV.B.

## VI. Synthesis and Reactions of Benzimidazole N-Oxides

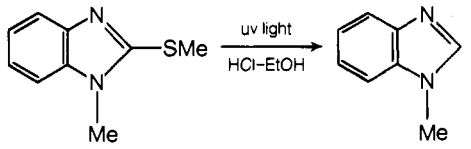
The chemistry of benzimidazole *N*-oxides has been described in detail in the texts of Ochiai,[10] and Katritzky and Lagowski[11] and also in a review by Lettau;[12] synthetic methods involving thermal, photochemical, and acid- and base-catalyzed reactions of ortho-substituted nitrobenzene derivatives have also been recently summarized.[13,14]

Subsequently a process relating to the synthesis of benzimidazole *N*-oxides by sodium borohydride reduction of 2-nitroformanilides has been patented[253] and 2-phenylbenzimidazole *N*-oxide has been isolated[66] in moderate yield from the thermolysis of *N*-(o-nitrophenyl)-α-aminophenylacetic acid.

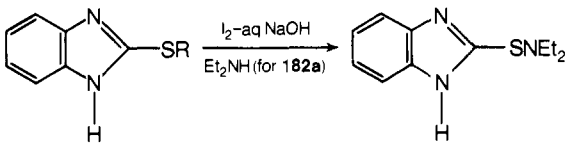
The base-catalyzed reactions of benzofuroxan with primary and secondary nitroalkanes[254-256] to give 1-hydroxybenzimidazole 3-oxides (**185**) and 2,2-dialkylisobenzimidazole 1,3-dioxides (**186**), respectively, are valuable



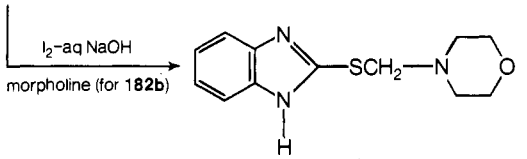
**178a**, $R^1 = R^2 = CH_3$
**b**, $R^1 = CH_3$; $R^2 = H$



**180** **181**



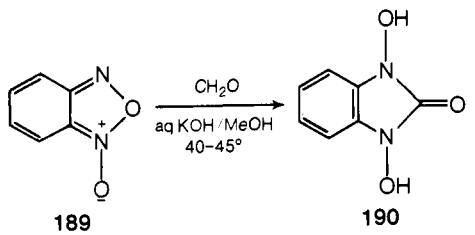
**182**
**182a**, R = H
**b**, R = $CH_3$



**184**

synthetic procedures since yields in both cases are high (>60%)[255] and the reactions can be effected below room temperature. This type of synthesis has also been used[257] to prepare 1-hydroxy-2-carboxylamidobenzimidazoles [**185**: $R^1$ = $CONHR^2$($R^2$ = alkyl, aryl, hetaryl)] using N-substituted cyanoacetamides. A possible[255] route to the mono-*N*-oxides **185** *via* the nitroalkanes[254-256] is shown in Scheme XIX. Very little is known about the chemistry of the di-*N*-oxides **186** except that they can be reduced[255] by sodium borohydride in a stepwise fashion to mono-*N*-oxides **187** and isobenzimidazoles **188**; a detailed investigation of the reactivity of the di-*N*-oxides **186** would be valuable.

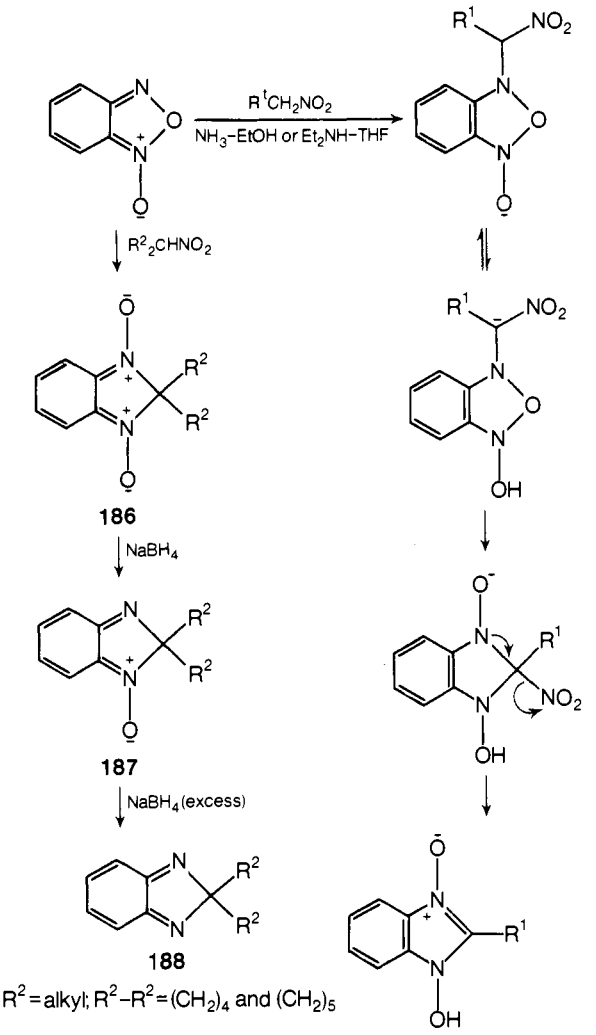
Compounds (*e.g.*, **190**) closely related to the *N*-oxides **185** are formed[258] when benzofuroxans **189** are allowed to react with formaldehyde under basic conditions; oxidation of these hydroxy compounds **190** with silver oxide provides nitroxide radicals as evidenced by esr spectra (*cf.* related compounds[259] described in section VIII.B and analogous radicals in the chemistry of imidazolines[260]).



**189** **190**

1-Benzyl-2-ethylbenzimidazole 3-oxide (**191**) decomposes photochemically[222] to give the benzimidazolone **192** or the anil **193** as major products in methanol and dioxane, respectively. This difference in behavior is explained[222] in terms of an intermediate oxaziridine **194**

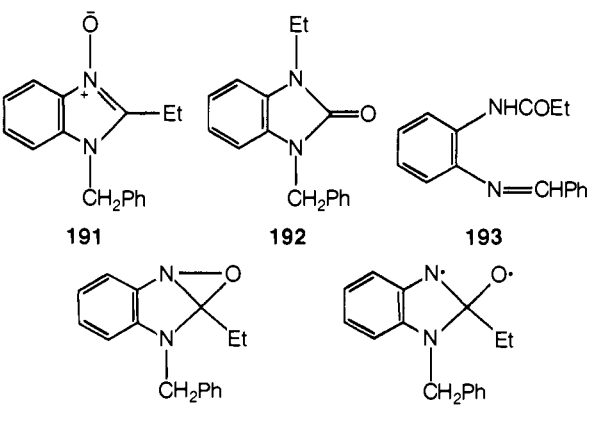
**SCHEME XIX**[254-256]



**185**

$R^1$ = H, alkyl, $(CH_2)_3CONH_2$, $CH_2CO_2Et$, Ph

which in protic solvent at room temperature is thought to undergo ionic rearrangement to give the benzimidazolone **192**; in an aprotic solvent or even in a protic solvent at low temperature (−58°) this intermediate **194** is thought[222] to decompose *via* a diradical **195** into the anil **193**.



**191** **192** **193**

**194** **195**

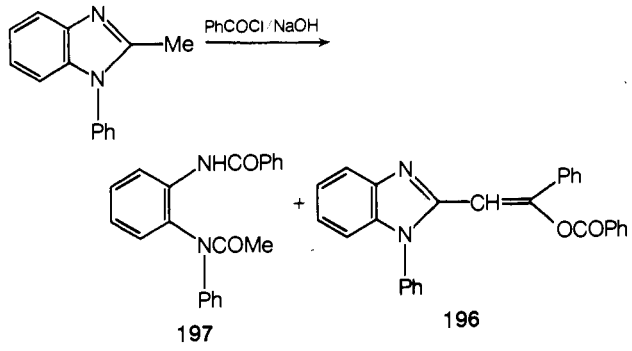
## *VII. Reactions of Benzimidazolium Compounds*

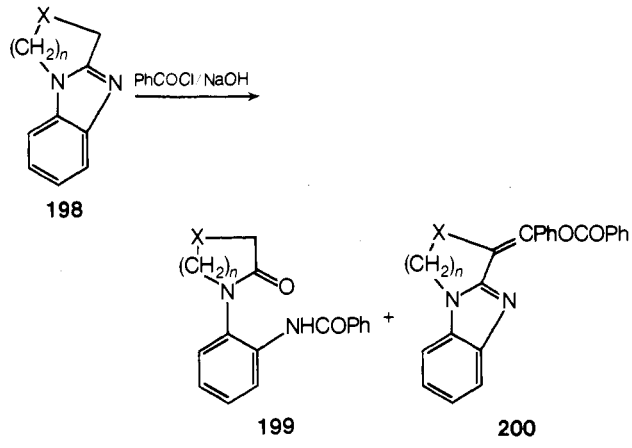
A plethora of new benzimidazolium compounds has been synthesized over the last few years, and a number of patents have been granted, for example,[261] in connec-

tion with their use in color photography; no attempt has been made in this review to survey the variety of compounds characterized.

## A. Reactions with Nucleophiles

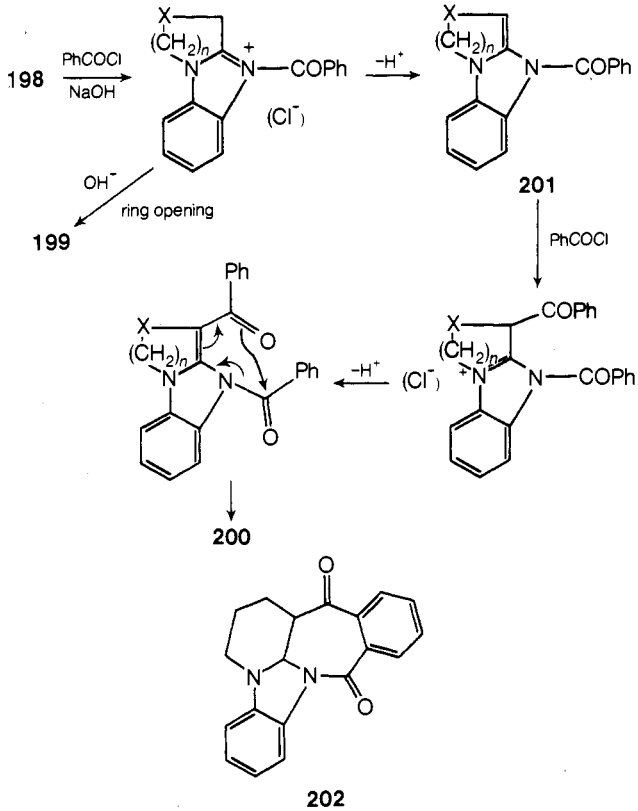
A number of studies concerning the behavior of benzimidazolium compounds with nucleophiles has been reported: ring opening is particularly facile when a nitrogen atom bears a 2,4-dinitroaryl moiety, and this type of reaction can be effected by weak bases such as aniline and pyridine.[262,263] A rather more involved reaction accompanies the ring opening[264] of 1,2-disubstituted benzimida-

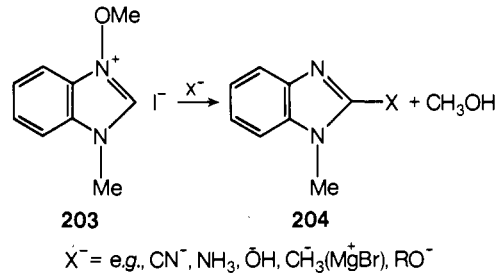


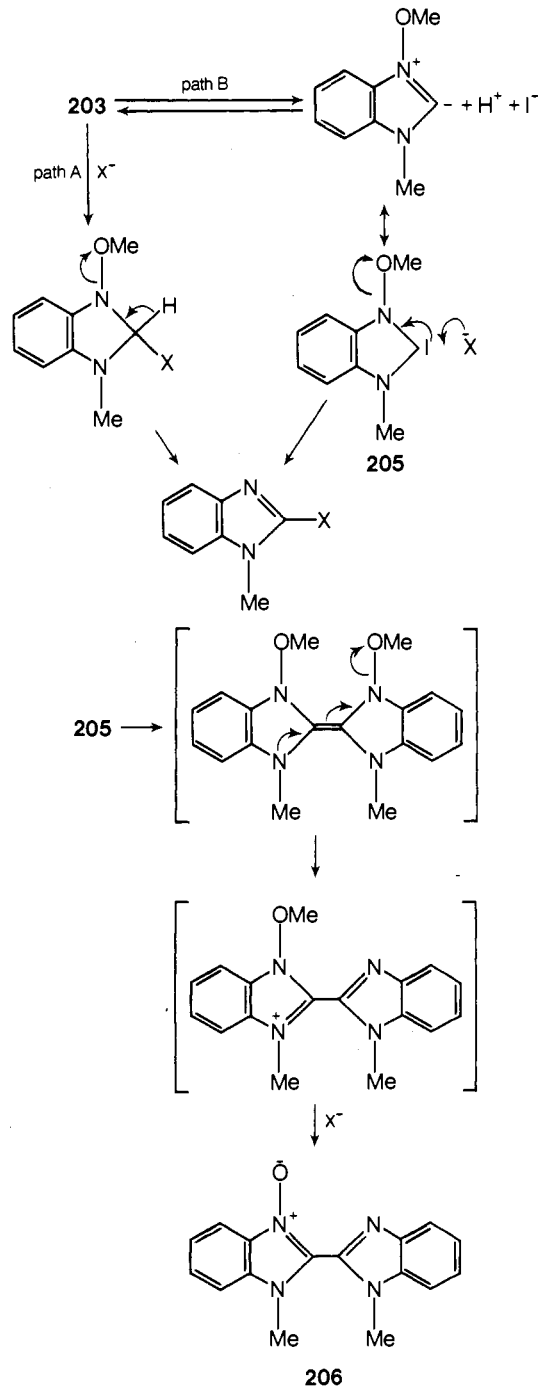

**a**, $n = 1$, X = $CH_2$; **b**, $n = 2$, X = $CH_2$; **c**, $n = 2$, X = O

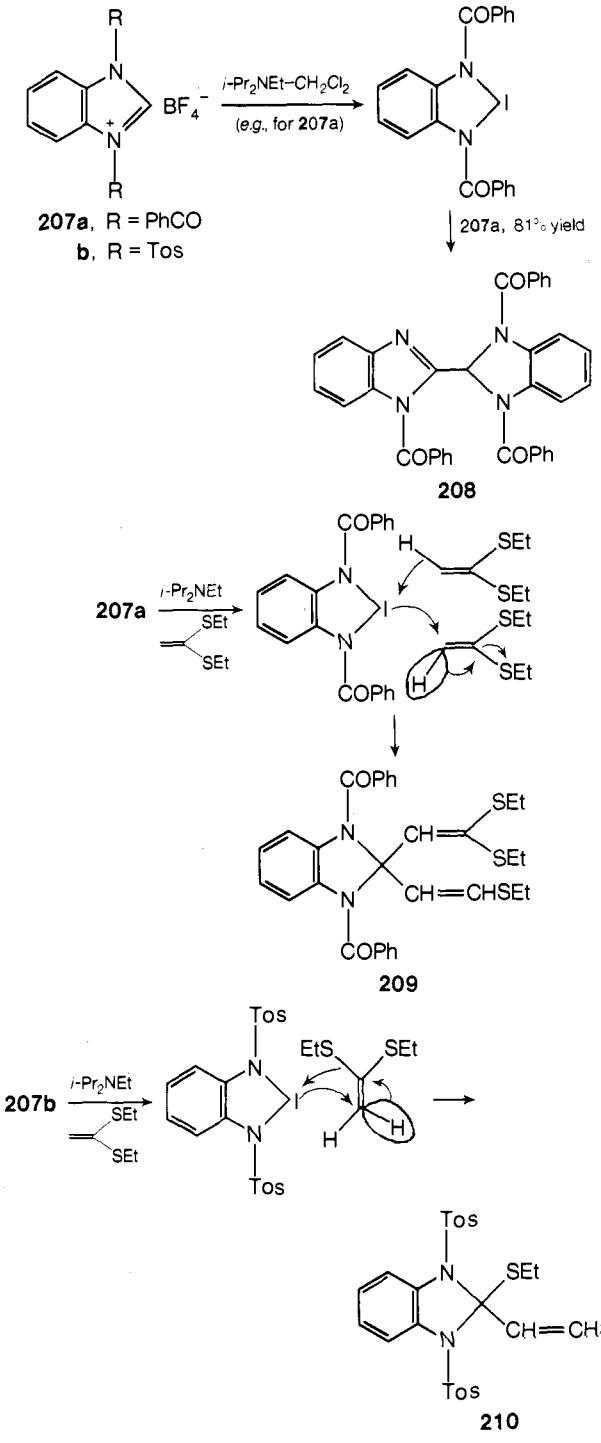
**SCHEME XX**



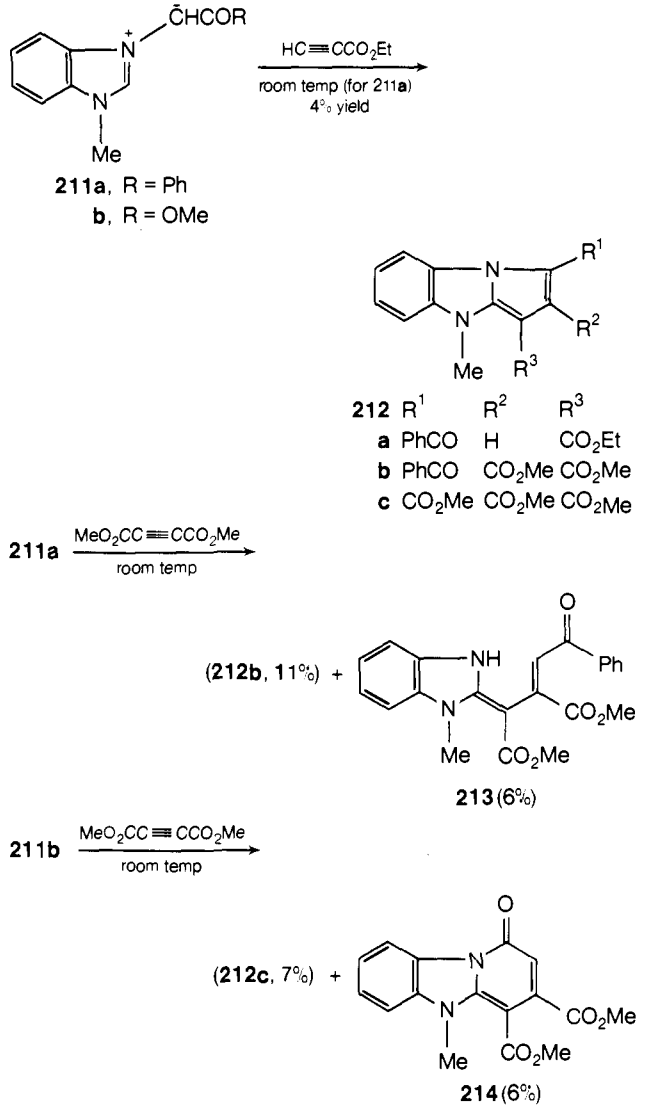

**SCHEME XXI**






zoles under the influence of benzoyl chloride in aqueous alkali. Apparently enol esters (*e.g.*, **196**) are formed in addition to o-phenylenediamine derivatives (*e.g.*, **197**) providing a methylene or methyl group is present in the 2 position. Circumstantial evidence in relation to the mechanism of this type of reaction has subsequently been adduced by Meth-Cohn[265] who demonstrated that analogous products, **199** and **200**, are obtained from the tricyclic derivatives **198a–c** under comparable conditions; furthermore, reaction of the pyridine derivative **198b** with phthaloyl chloride in pyridine gave a product believed to be the dione **202**, the formation of which can be rationalized on the basis of diversion of an intermediate enamine (*cf.* **201** in Scheme XX)

The scope of the reaction of 3-methoxy-1-methylbenzimidazolium iodide with nucleophiles has been assessed[266] (*cf.* **203** → **204**). In general, yields are very



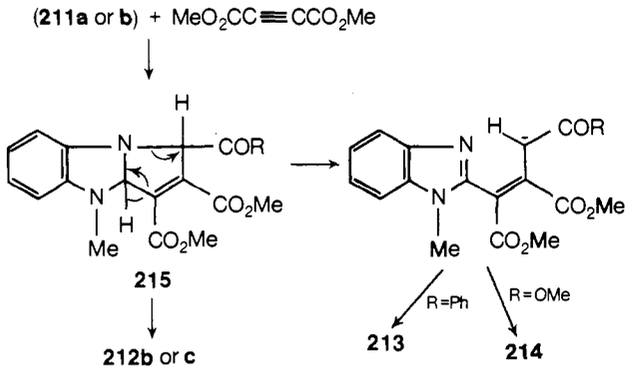

high for this type of reaction and, in contrast to the case for pyridine analogs, they can be used to synthesize 2-hydroxy and 2-alkylamino derivatives. The mechanism of these processes is probably different from the simple addition–elimination reactions (*cf.* path A in Scheme XXI) responsible[267] for reactions in the pyridine series. Thus treatment of the salt **203** with triethylamine in acetonitrile under reflux gives the bibenzimidazole 3-oxide **206** in 64% yield, and this result is considered[266] to afford evidence in favor of carbene intermediates (*cf.* **205**) in these nucleophilic reactions (*cf.* path B in Scheme XXI and also related reactions in the chemistry of imidazoles[268] and thiazoles[269]). Formation[270] of the dimer **208** from the benzimidazolium tetrafluoroborate **207a** in basic media is probably a closely related process, and indeed the intermediacy of carbenes in this type of reaction is convincingly demonstrated[270] by their interception in reactions with ketene diethyl thioketal (*cf.* **207a** → **209** and **207b** → **210**).

## B. 1,3-Dipolar Cycloaddition Reactions

The recent investigation[195] of 1,3-dipolar cycloaddition reactions of benzimidazolium ylides (*cf.* **211a** → **212a**) demonstrates that a variety of tricyclic derivatives should be accessible by careful selection of the 1,3-dipolarophile. An additional feature of such reactions, for acetylenic dipolarophiles at least, is that rearrangements can occur within intermediate dihydro adducts (*e.g.*, **215**,

Scheme XXII); although yields are generally very low in all these reactions (Scheme XXII), they are single step and proceed at room temperature.

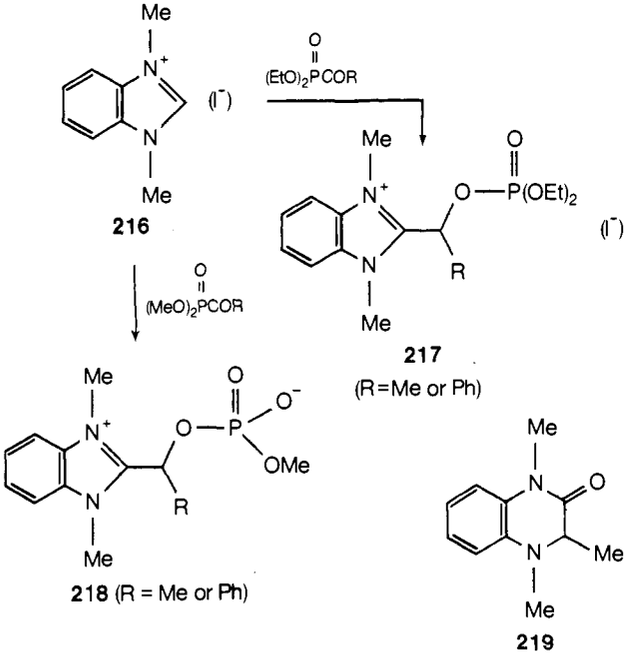
**SCHEME XXII**



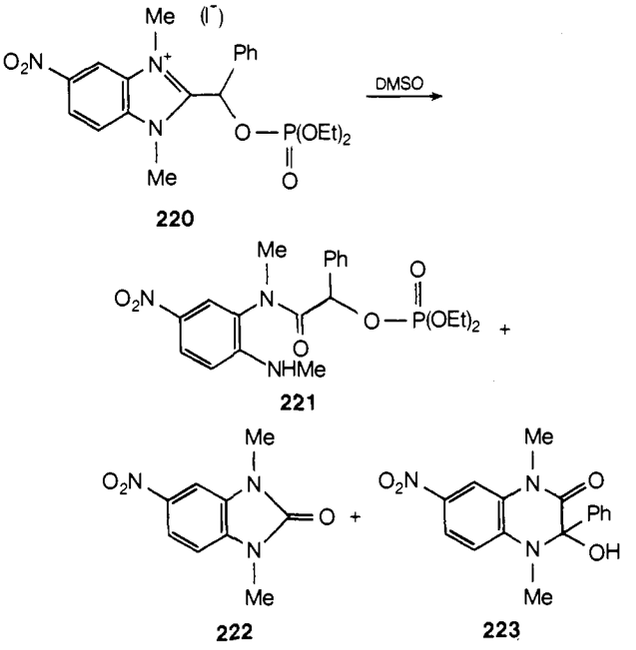

## C. Miscellaneous Reactions

The conversion[271] of thiazolium salts by dialkyl acylphosphonates into 1,4-thiazine derivatives encouraged an investigation[272] of the behavior of analogous benzimidazolium compounds.

Either the benzimidazolium salt **217** or the betaine **218** is formed from the benzimidazolium iodide **216** depending on the structure of the reactant phosphonate; unfortunately, unlike related reactions[271] in the thiazolium series, these adducts (**217** and **218**) cannot be converted into quinoxaline derivatives (*e.g.*, **219** from **217**, R = Me)




under basic conditions. On the other hand, the benzimidazolium phosphonate adduct **220** provides the quinoxaline derivative **223** in moderate yield together with other products (**221** and **222**) on treatment with dimethyl sulfoxide at room temperature. The mechanisms of adduct (**217** and **218**) formation and of DMSO-induced transformation (*cf.* **220** → **223**) have not been established.




## *VIII. Spectroscopic Properties of Benzimidazoles*

General aspects of the spectroscopy of benzimidazoles have been reviewed,[8] and no attempt has been made in this review to compile an exhaustive list of data in this area. Accordingly, the content of this section is restricted to material dealing specifically, rather than incidentally, with spectroscopic data.

## A. Infrared and Ultraviolet Spectra

An excellent summary of trends in the ir and uv spectra of benzimidazole derivatives has been compiled by Rabiger and Joullié.[273,274] Subsequently, the difficulty in making definitive ir carbonyl assignments in acetyl and benzoyl derivatives of benzimidazolin-2-one has been commented upon,[275] and the vapor absorption spectrum of benzimidazole near 2850 Å has been analyzed;[276] the latter investigation indicates that the strongest band is the origin at 36023 $cm^{-1}$. By comparison of this spectrum with those of closely related heterocycles and with aromatic compounds, it has been concluded[276] that the 2850-Å transitions in benzimidazole are localized within the aryl ring.

## B. Magnetic Resonance Spectra

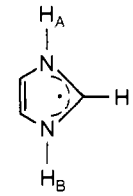
An interpretation of the $A_2B_2$ part of the proton magnetic resonance spectrum of benzimidazole has been reported,[277] but a detailed analysis of the aromatic part of unsymmetrically substituted benzimidazole derivatives has not been attempted. Rapid 1,3-proton exchange occurs[277,278] in neutral solutions of benzimidazole; in dilute alcoholic sulfuric acid solutions a rapid proton exchange with solvent occurs,[278] but this process is considerably decelerated in concentrated sulfuric acid, and in the latter medium H-2 appears as a triplet with $J_{12} = J_{23} = 2.5$ Hz. Apparently[278] protonation takes place on the tertiary rather than the secondary nitrogen atom.

A detailed interpretation of the $^{13}C$ nmr spectra of benzimidazole and its protonated and deprotonated species has been presented.[279] An important feature of this work is that the protonation parameters derived from simple five- and six-membered heterocycles can be used to predict chemical shift changes resulting from nitrogen protonation and deprotonation in more complex molecules.

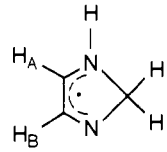
The application of nmr spectroscopy in benzimidazole chemistry appears to be restricted to $^1H$ and $^{13}C$ studies, and in this respect it would be of interest to utilize $^{14}N$,

$^{15}N$, and $^{19}F$ nmr experiments on benzimidazoles, $^{15}N$-enriched compounds, and perfluorinated derivatives, respectively.

Electron spin resonance spectroscopy has been used recently[280] to identify the structure of free radicals produced at room temperature by X-irradiation of crystalline imidazole and benzimidazole and their 2-methyl homologs. Significantly the radicals produced from imidazole and benzimidazole are almost identical and consist of a 1:2:1 triplet ($a$ = 45 G) with each line showing further poorly resolved hyperfine splitting. Accordingly the radical produced from imidazole is assigned structure **224** in which coupling occurs with two equivalent protons ($H_A$, $H_B$). On this basis, structure **225** which was earlier assigned[281] to the same free radical produced from imidazole by $\gamma$-irradiation is unacceptable.

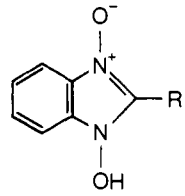


**224**

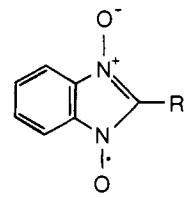


**225**

Oxidation of the 1-hydroxybenzimidazole 3-oxides (**226a,b**) with silver oxide or lead tetraacetate proceeds[282] in conventional[283] fashion to give symmetrical nitroxide radicals **227.** A well-resolved 41 line spectrum



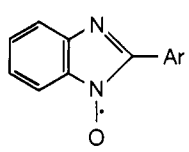
**226**



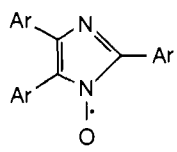
**227**

**a**, R = Me; **b**, R = Ph

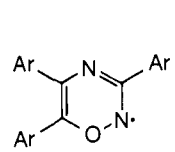
is obtained from **226a** with $a_{N-1} = a_{N-3}$ = 4.20 G: $a_{Me}$ = 2.80 G; and $a_{H-5} = a_{H-6} = a_{H-7} = a_{H-8}$ = 0.70 G in benzene solution. The spectrum of the phenyl derivative **226b** is less well resolved, but a five-line pattern with $a_{N-1} = a_{N-3}$ = 4.30 G is apparent. It would be of interest to synthesize benzimidazoles containing the nitroxide function in the side chain in both the benzo and imidazole rings; such free radicals should be accessible from either hydroxylamine[283] or nitro derivatives.[284] Investigations of deoxygenated analogs (*e.g.*, **228**) of the nitroxides **227** would also be of interest in relation to esr spectra of potential benzo-1,2,4-oxadiazine radicals (*cf.* the rearrangement[285] of the imidazole nitroxide, **229** → **230**).



**228**

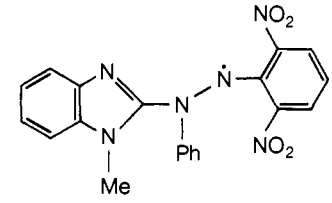


**229**



**230**

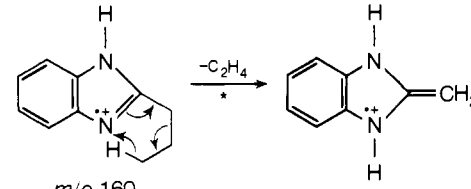
The other reported example of a benzimidazole-containing free radical concerns the hydrazyl derivative **231**,[286] although no structural information has been adduced from the esr spectrum. The use of esr should also be encouraged for investigations of benzimidazole radical anions and cations as well as on metal-containing complexes (*cf.* the work of Kasai and McLeod[287] on the imidazole radical anion and also the investigations of Nikitaev, *et al.*,[288] on imidazole complexes of $Cu^{II}$.



**231**

## C. Mass Spectra

A number of investigations on the mass spectra of benzimidazoles have been carried out including benzimidazolium barbiturates[289] and alkyl,[290] 1-skatyl,[291] 2-phenoxy,[292] and *N*-oxide[293] derivatives. The most systematic study has been reported by Bowie, *et al.*,[294] from which it appears that the fragmentation pathways of simple benzimidazoles are similar to those of imidazoles.[295] The spectrum[294] of benzimidazole indicates a sequential loss of two molecules of hydrogen cyanide from the molecular ion, the first of which is nonspecific as evidenced by deuterium-labeling procedures. A characteristic feature[294] in the fragmentation of 2-*n*-propylbenzimidazole is the elimination of ethylene from the molecular ion; a cyclic mechanism has been invoked[294] for this type of process **232** → **233** (*cf.* the spectra of analogous alkylpyridines[296]). Like 2-acylthiophenes,[297] 2-acyl- and 2-benzoylbenzimidazoles are characterized[294] by loss of carbon monoxide from the molecular ion, and, since this fragmentation mode is not apparent[298] in the spectra of acylbenzenes, it is a diagnostic transition for acyl substituents in the imidazole ring.



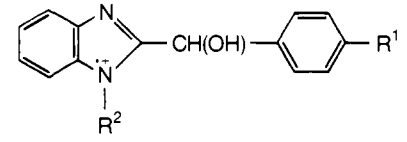
*m/e* 160

**232**

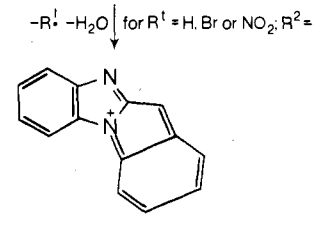
*m/e* 132

**233**

Two important features emerge[294] from the spectra of the series of secondary alcohols **234.** Combined loss of the para substituent and water from the molecular ion gives rise to an ion at *m/e* 205 (represented as **235**) for **234a** but not for the methyl homolog **234b.** Similarly loss of water from the molecular ion occurs only for the 1-H and not the 1-Me derivatives. Clearly further research is warranted on the mass spectra of a wider series of derivatives containing various functional groups in 1- and 2-



**234a**, $R^2$ = H; **b**, $R^2$ = Me



*m/e* 205

**235**

**TABLE XXIII. Commercially Available Pharmaceuticals and Veterinary Anthelmintics**

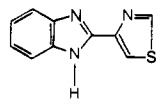
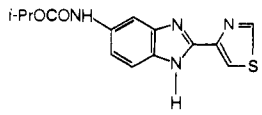
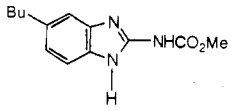
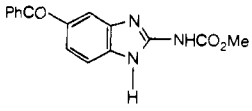
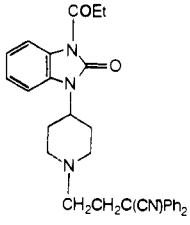
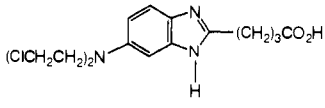
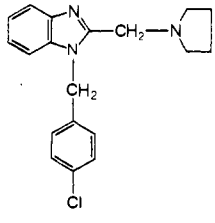
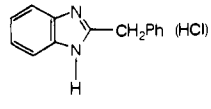
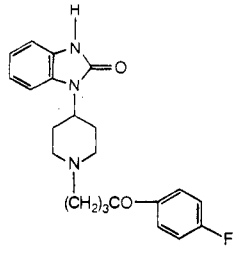
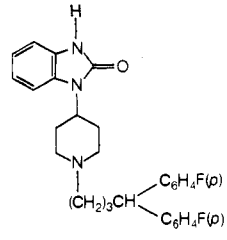
| Approved name | Proprietary name | By whom marketed | Where marketed | Use | Structure |
|---|---|---|---|---|---|
| Thiabendazole | Mintezol | Merck Sharpe and Dohme | | Human anthelmintic |  |
| | Thibenzole | Merck Sharpe and Dohme | | Veterinary anthelmintic | |
| Cambendazole | | Merck Sharpe and Dohme | | Veterinary anthelmintic |  |
| Parbendazole | Helmatac | Smith Kline and French | | Veterinary anthelmintic |  |
| Mebendazole | Telmin | Crown Chemicals | U. K. Ireland | Veterinary anthelmintic |  |
| | Equiverm Plus | Crown Chemicals | U. K. | | |
| | Vermox | Janssen | Belgium | | |
| Bezitramide | Burgodin | Janssen | | Analgesic |  |
| Imet 3393 | Cytostasan | | Germany | Anticancer |  |
| Clemizole Penicillin | Bellocillin | Laboratoires Roger Bellon | France | Bactericide | Combination of benzylpenicillin and  |
| | Megacillin | Grünenthal | Germany | | |
| Clemizole | Allercur<br>Hérol<br>Histacur<br>Histacuran<br>Reactrol | Schering Chemicals | | Antihistamine | Structure as above |
| Diabazole<br>Diabazol | Tromasédan | Laboratoires Millot | France | Vasodilator spasmolytic hypotensive |  |
| Benperidol | Frénactil | Laboratoires Clin-Comar-Byla | France | Psychopharmacological agent |  |
| | Glianimon | Troponwerke Dinklage | Germany | | |
| Pimozide | Orap | Janssen | U. K. | Psychopharmacological agent |  |
| | Opiran | Laboratoires Cassenne | France | | |

**TABLE XXIII** (continued)

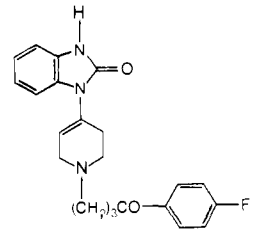
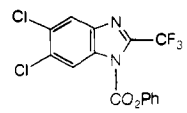
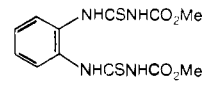
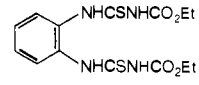
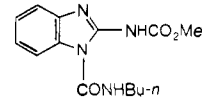
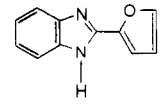
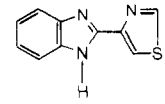
| Approved name | Proprietary name | By whom marketed | Where marketed | Use | Structure |
|---|---|---|---|---|---|
| Droperidol | Droleptan | Janssen | | Psychopharmacological agent |  |
| | Inapsine | McNeil | U. S. | | |

**TABLE XXIV. Commercially Available Fungicides**

| Approved name | Proprietary name | By whom marketed | Use | Structure |
|---|---|---|---|---|
| Fenzaflor | Lovozal | Fisons | Acaricide |  |
| Thiophanate-methyl[a] | Cercobin-methyl or Topsin-methyl | Nippon Soda | Fungicide |  |
| Thiophanate[a] | Cercobin or Topsin | Nippon Soda | Fungicide |  |
| Benomyl[a] | Benlate | Dupont | Fungicide |  |
| Fuberidazole | Voronit | Bayer | Fungicide |  |
| Thiabendazole | Mertect (TBZ) | Merck Sharpe and Dohme | Fungicide |  |

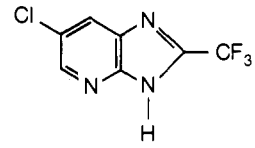
[a] These compounds are converted *in vivo* (and also under some *in vitro* conditions) to benzimidazole-2-carbamates.

side chains with a view to extending diagnostic behavior of this type.

## IX. Benzimidazoles of Commercial Importance as Pharmaceuticals, Veterinary Anthelmintics, and Fungicides

Definite information on commercial uses of benzimidazoles is rather difficult to accumulate, and this section is restricted to applications in the fields described above. It contains a compilation (Tables XXIII and XXIV) of benzimidazole derivatives that have been marketed in the past decade. The most successful drugs have been "thiabendazole" and "cambendazole" which have found wide use as anthelmintic agents for both human and veterinary purposes.

One obvious research area of interest is the synthesis of analogs of the known benzimidazole drugs in which the benzo ring is replaced by other heterocyclic rings (*cf.* the herbicide, Nortran, **236**[299]); however, analogs of this type (**236**) are generally more expensive and so far have made little real impact in the pesticide field. Further research is also warranted within the field of synthetic antiviral agents. Moderate success in this area has been achieved by the use of 2-($\alpha$-hydroxybenzyl)benzimidazoles[300,301] and bisbenzimidazoles.[302]



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