# 1,3-Cycloadditions of 3,5-Dichloro-2,4,6-trimethylbenzonitrile Oxide to Furan, Benzofuran, Thiophen, and Benzothiophen

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The title nitrile oxide adds to furan and thiophen to give a single regioisomer, while the analogous cycloadditions to benzofuran and benzothiophen lead to both possible adducts. Side reactions occur in the case of thiophen. The orientation of the 1,3-cycloadditions was studied by a perturbational approach, using the CNDO/2 methods for computing molecular orbitals. Results are discussed in terms of the full intermolecular orbital theory as well as the frontier orbital method.

ORIENTATION rules in 1,3-dipolar cycloadditions are a major problem in organic chemistry. Over the last few years computations, with the aim of rationalizing the product distribution observed in experiments, have been performed on the basis of perturbational molecular orbital theory or the more approximate frontier orbital method.[1-5] Continuing this line of research, we were interested in comparing experimental evidence and theoretical results in the case of 1,3-cycloadditions of nitrile oxides to carbon–carbon double bonds in hetero-aromatic rings. In view of the low reactivity of such a dipolarophile, a nitrile oxide slow to dimerize seemed a suitable substrate for this purpose. Thus, the behaviour of 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide [6] (1) towards furan and thiophen was submitted to both experimental and theoretical investigation. The reactions of (1) with benzofuran and benzothiophen were


(1)
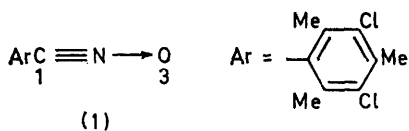
also taken into account, although the theoretical treatment adopted is questionable in these cases because of steric factors.†

RESULTS

The use of a large excess of dipolarophile was felt advisable in order to favour 1,3-cycloaddition with respect to dimerization and/or isomerization of the starting nitrile oxide as well as to minimize, in the case of furan and thiophen, further reactions of the primary monoadducts. Indeed, in all cases, a 0.2M solution of (1) in the dipolarophile as solvent was heated until the substrate disappeared, as shown by t.l.c. and i.r. analyses of the reaction mixture.

Treatment of Oxide (1) *with Furan.*—Heating compound (1) in boiling furan resulted, after 120 h, in a major product with traces of by-products (t.l.c.). Column chromatography gave adduct (2) in 78% yield, its structure being

supported by elemental analysis, the n.m.r. spectrum, and its chemical behaviour. Compound (2) gave rise to the oxime (3) in acid medium, and the dibromo-derivative (4) was readily obtained by treatment with bromine.

(2) (3) (4)
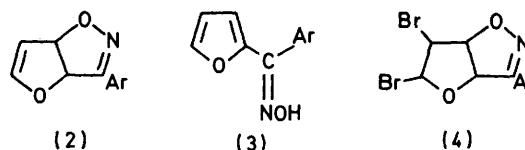
Chromatographic work-up of the mixture arising from the reaction of (1) with furan gave also a small amount of a high melting compound, identical with that obtained as the only product on treating (2) with (1) in ether. This may be a diadduct, but its insolubility precluded a detailed examination.

Treatment of Oxide (1) *with Benzofuran.*—Nitrile oxide (1) was reacted with benzofuran at 80°. The reaction was complete after 5 h and led to a mixture of two components, with negligible quantities of by-products (t.l.c.). The regioisomeric compounds (5) and (6) were isolated in 31 and 20% yield respectively by column chromatography. N.m.r. analysis before the chromatographic separation showed that compounds (5) and (6) amounted to ca. 80% of the total crude product, and are formed in the approximate ratio of 3 : 2.

The assignment of the regioisomeric formulae (5) and (6) is unequivocal in view of the n.m.r. evidence. The isoxazoline protons of (6) have similar chemical shifts (δ 6.08 and 6.38), while those of (5) resonate, as expected, at a distance from each other, giving rise to a doublet at δ 5.06 and to a downfield signal which is masked by the aromatic resonance. Also, the n.m.r. spectrum of (5) shows a singlet at δ 1.48 (3 H); this value, which is somewhat unusual for a methyl group on an aryl ring, is justified in the case of (5) since, as revealed by molecular models, one of the methyl substituents is forced close to the shielding region of the benzene ring.

Compound (5) underwent a base-promoted rearrangement to isoxazole (7), while (6) was stable under the same

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† 1,3-Cycloadditions of benzonitrile and mesitonitrile oxides to furan, benzofuran, and thiophen have been reported (P. Caramella, G. Cellerino, and F. Marinoni Albini, Fifth International Congress of Heterocyclic Chemistry, Ljubljana, 1975).

[1] G. Klopman, 'Chemical Reactivity and Reaction Paths,' Wiley, New York, 1974 and references cited therein.

[2] R. Sustmann, *Pure Appl. Chem.*, 1974, **40**, 569.

[3] K. N. Houk, *Accounts Chem. Res.*, 1975, **8**, 361.

[4] J. Bastide, N. El Ghandour, and O. Henri-Rousseau, *Bull. Soc. chim. France*, 1973, 2290; J. Bastide and O. Henri-Rousseau, *ibid.*, p. 2294; 1974, 1037.

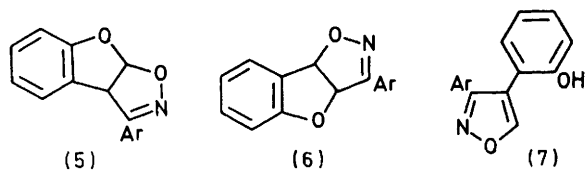[5] R. Grée, F. Tonnard, and R. Carrié, *Tetrahedron Letters*, 1974, 135; *Tetrahedron*, 1976, **32**, 675.

[6] P. Beltrame, C. Veglio, and M. Simonetta, *J. Chem. Soc.* (B), 1967, 867.

conditions. The formation of (7) is comparable with the formation of isoxazoles through elimination from 2-isoxazolines bearing a potential leaving group in the 5-position.[7]

(5)   (6)   (7)

Treatment of Oxide (1) *with Thiophen.*—The reaction of nitrile oxide (1) in boiling thiophen resulted, after 48 h, in a very complex mixture (t.l.c.). First, some material undissolved in the reaction medium was found to be a high melting compound, whose elemental analysis and i.r. absorptions (3 270 and 1 620 cm⁻¹) support formula (8).* Chromatographic work-up of the remaining mixture afforded, in addition to small amounts of unchanged (1) and of uncharacterized by-products, the following compounds (yields in parentheses): monoadduct (9) (25%), diadduct (10) (8%), furazan N-oxide (11) (6%), and a still

ArNHCONHAr
(8)

(9)   (10)   (11)

(12)   (13)   (14)
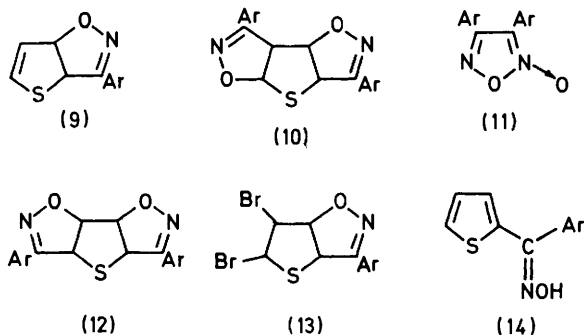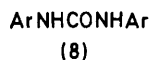
unidentified substance [15% based on (1)]. Structure (9) was assigned to the isolated monoadduct on the basis of elemental analysis and its n.m.r. spectrum. Furthermore, addition of bromine to (9) gave compound (13), and acid-catalysed hydrolysis caused cleavage of the isoxazoline ring leading to the oxime (14).

The monoadduct (9) undergoes cycloaddition of a further molecule of nitrile oxide (1) [unchanged (9), however, was still present after 48 h refluxing in benzene]. By column chromatography of the complex reaction mixture, diadduct (10) and its regioisomer (12) were obtained in 21 and 2% yield respectively. The n.m.r. spectrum of (12) showed two doublets centred at δ 5.14 and 5.83 for the isoxazoline protons whereas a more complex set of signals appeared in the n.m.r. spectrum of (10). In particular, a doublet is present at δ 6.77, indicating a deshielded proton; this is

* N.m.r. data are not available because this compound is not soluble in common solvents.
† Treatment of (1) with aniline, without preliminary heating, gives 3,5-dichloro-2,4,6-trimethyl-N-phenylbenzamidoxime.
[7] C. Grundmann, *Synthesis*, 1970, 344 and references cited therein.
[8] A. Selva and U. Vettori, *Gazzetta*, 1973, **103**, 223.

anticipated for structure (10), which possess a hydrogen atom α to both oxygen and sulphur.

The mass spectra of (10) and (12) revealed some common features, for instance a peak of low intensity at *m/e* 313 and an intense peak at *m/e* 229, which were attributed to the ions (M — ArCNO)⁺ and (ArCNO)⁺ arising from a retro-cycloaddition-type fragmentation. Peaks at *m/e* 329 [(M — ArCN)⁺] and 213 [(ArCN)⁺] were also present, to a major extent in the case of (10). Both these fragmentation patterns have been reported for 3-aryl-2-isoxazolines.[8,9]

The mass spectrum of the furazan N-oxide (11) presented an intense peak at *m/e* 442 [(M — 16)⁺], which is in line with the known behaviour of N-oxide derivatives.[10]

The structure of the fifth product obtained from the treatment of (1) with thiophen has not been established. The unstable nature of this compound, particularly in the presence of moisture, made it impossible to obtain an analytically pure sample. However, the following data are available. Significant bands are present in the i.r. spectrum at 3 210 and 1 725 cm⁻¹, while the n.m.r. spectrum shows, in addition to a broad singlet attributable to OH or NH, only a set of signals in the region δ 2.1—2.7. The latter finding indicates that the compound under study does not contain the thiophen skeleton, its formation probably occurring from (1) through a process other than 1,3-cycloaddition. On this basis, a full structural elucidation was felt to be unnecessary.

While the formation of (11) is in line with the general dimerization pattern of nitrile oxides, the formation of urea (8) could be interpreted in terms of a preliminary isomerization of (1) to isocyanate (15), which should then produce (8) owing to the presence of moisture in the reaction medium. That such an isomerization is possible, was shown by heating (1) in boiling benzene and submitting the crude product to hydrolysis, which led to amine (16). Furthermore, heating (1) in boiling benzene and subsequent treatment with aniline afforded the urea (17).† Hindered aromatic nitrile oxides have been previously reported to isomerize to isocyanates.[11]

Treatment of Oxide (1) *with Benzothiophen.*—The reaction of (1) with benzothiophen (80°; 10 h) led to a mixture of two major components (18) and (19), in the ratio 70 : 30,

ArNCO   ArNH₂   ArNHCONHPh
(15)   (16)   (17)

(18)   (19)
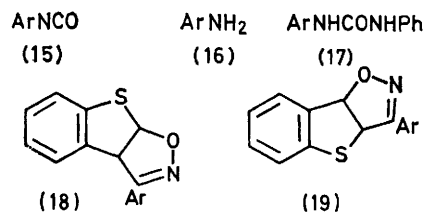
with minor quantities of other compounds. Interestingly, as observed for the related cycloadduct (5), one of the methyl groups of (18) appears to be unduly shielded, giving rise to a singlet at δ 1.53.

Computations.—According to second-order perturbation theory, for a complete intermolecular orbital treatment,[12]

[9] C. DeMicheli, R. Gandolfi, and P. Grünanger, *Tetrahedron*, 1974, **30**, 3765.
[10] A. R. Katritzky and J. M. Lagowski, ' Chemistry of Heterocyclic N-Oxides,' Academic Press, London, 1971, p. 17.
[11] C. Grundmann, H. D. Frommeld, K. Flory, and S. K. Datta, *J. Org. Chem.*, 1968, **33**, 1464.
[12] L. Salem, *J. Amer. Chem. Soc.*, 1968, **90**, 543, 553; A. Devaquet and L. Salem, *ibid.*, 1969, **91**, 3793.

the interaction energy between two conjugated systems involves, as components, a repulsive term, E_{rep}, an attractive term, E_{mix}, both depending on the overlap between interacting orbitals, and a polar term, E_{pol}, representing electrostatic interactions between net charges on the atoms. Here, as previously,[13] these three terms were considered in the evaluation of the interaction energy (E_{total} = E_{rep} + E_{mix} + E_{pol}). Resonance integrals were evaluated by the following equations:[14] $\eta_{CC} = -21S_{CC}$; $\eta_{CO} = -26S_{CO}$ (η in eV). We assumed that the two molecules remained planar when approaching each other. Energies were calculated for reactions giving the two regioisomers for several configurations of approach; in every case the centre (A) of the $C_1 \cdots O_3$ dipole on the y-axis of (I) and the centre (B) of the $C_\alpha C_\beta$ double bond * on the y'-axis of the dipolarophile were on a z-axis perpendicular to the molecular plane of (I). The four interacting centres were on a vertical plane perpendicular to both molecular planes. In symmetric configurations the molecular planes were parallel and the lengths of both incipient bonds were equal; in unsymmetric configurations the bond lengths were different. The distances between interacting atoms were independently varied from 5 to 8 a.u. Computations were made taking into account, by use of the cosine correction, the deviations from alignment of the two overlapping orbitals[15] and, when the approach is unsymmetric, the deviations due to the angle between the two molecular planes.

Orbital energies, coefficients, and net charges were calculated by the CNDO/2 method.[16] Geometries determined by Bak et al. for thiophen[17] and furan[18] were used. For thiophen the highest occupied molecular orbital (HOMO) was essentially centred on the sulphur atom; in this case, the next highest occupied molecular orbital was considered to be the HOMO.

The Table reports some results for the two possible symmetrical approaches giving the regioisomers, named

Calculated energies (E/meV) as a function of distance R (a.u.) for symmetrical approach

R	E_{main}	E_{front}	E_{mix}	E_{rep}	E_{pol}	E_{total}
Thiophen (i) formation of CC_α						
8	−0.08	−0.10	−0.51	1.08	−17.5	−17.0
7	−0.78	−1.01	−5.01	10.0	−23.9	−18.8
6	−6.93	−8.83	−42.3	80.9	−33.3	5.30
(ii) formation of CC_β						
8	−0.07	−0.08	−0.51	1.06	17.3	17.9
7	−0.70	−0.84	−4.99	9.86	23.5	28.4
6	−6.46	−7.73	−42.1	79.5	32.5	70.0
Furan (i) formation of CC_α						
8	−0.09	−0.12	−0.52	1.10	−3.76	−3.18
7	−0.90	−1.17	−5.02	10.3	−4.40	0.84
6	−7.82	−10.0	−42.2	82.7	−4.59	35.9
(ii) formation of CC_β						
8	−0.06	−0.08	−0.50	1.10	3.68	4.28
7	−0.70	−0.88	−4.90	10.3	4.59	9.95
6	−6.73	−8.26	−41.4	82.7	5.60	46.9

C_1C_α and C_1C_β, at various distances ($R = R_{C_1C} = R_{O_3C}$). Similar total energy gaps were obtained for unsymmetric approaches.

* α and β relate to the heteroatom.

[13] P. Beltrame, P. L. Beltrame, and M. G. Cattania, *Gazzetta*, 1975, **105**, 59.

[14] K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, *J. Amer. Chem. Soc.*, 1973, **95**, 7301.

Some computations were also made for the reactions of (1) with benzothiophen and benzofuran. The geometrical parameters were considered to be those of a benzene ring and the corresponding five-membered heterocyclic ring in which the appropriate C–C bond was taken as 1.397 Å. For benzothiophen the HOMO has been defined as above for thiophen. The results were similar to those obtained for thiophen and furan.

DISCUSSION

All the substrates tested were found to behave as dipolarophiles towards the nitrile oxide (1), in spite of the moderately unsaturated character of their carbon–carbon double bonds, particularly in the case of thiophen and benzothiophen. Thus, the present work may well be of interest in heterocyclic synthesis. The product distribution represents the most striking feature of the 1,3-cycloadditions. While benzofuran and benzothiophen gave both possible orientational isomers, a single cycloadduct was obtained in the case of furan and thiophen, although regiospecificity cannot be claimed since a small amount of the missing isomer could have escaped detection.

The observed regioselectivities will now be considered in the light of the perturbational treatment. Thiophen and furan are particularly suitable substrates for such a study since they are planar and the two possible directions of attack are very similar from a steric point of view. For these substrates results indicate (Table) that at different levels of approximation (E_{main}, E_{front}, E_{total}) the formation of isomers in which the carbon atom of dipole (1) is linked to C_α of the dipolarophile is correctly predicted at all distances considered. The significant role of the polar term at large distances should be noted.

The results for benzothiophen and benzofuran, which are essentially the same as those for thiophen and furan, are in disagreement with the experimental orientations. However, as molecular models indicate, for these compounds approaches involve steric interactions which perturbation theory does not take into account.

Approximate perturbation MO methods are not able to rationalize the four experimental orientations at the same time. If one considers the reactions as dipole LUMO controlled, C_1C_α regioisomers are predicted in all cases; C_1C_β products are predicted for dipole HOMO control. If one uses the CNDO/2 energy gaps as the criterion for the choice of dipole LUMO or HOMO control, C_1C_β regioisomers for sulphur compounds and C_1C_α regioisomers for oxygen compounds are preferred. Moreover, computations based only on the frontier orbitals, but taking into account both interactions, fail at distances higher than 5 a.u. (four C_1C_α regioisomers)

[15] T. Inukai, H. Sato, and T. Kojima, *Bull. Chem. Soc. Japan*, 1972, **45**, 891.

[16] J. A. Pople and G. A. Segal, *J. Chem. Phys.*, 1966, **44**, 3289; D. P. Santry and G. A. Segal, *ibid.*, 1967, **45**, 158.

[17] B. Bak, D. Christensen, L. Hansen-Nygaard, and F. R. Andersen, *J. Mol. Spectroscopy*, 1961, **7**, 58.

[18] B. Bak, D. Christensen, W. B. Dixon, L. Hansen-Nygaard, J. R. Andersen, and M. Schottlander, *J. Mol. Spectroscopy*, 1962, **9**, 124.

as well as at short distances (1.75 Å) [14] (four C_1C_β regio-isomers).

EXPERIMENTAL

I.r. spectra were taken on a Perkin-Elmer model 377 spectrophotometer. N.m.r. spectra were usually recorded on a Varian A-60A instrument with tetramethylsilane as internal standard; a Varian HA-100 instrument was used for compound (2). Mass spectra were measured on an LKB 9000 apparatus. All m.p.s are uncorrected.

Reaction of Oxide (1) *with Furan.*—Compound (1) (1.3 g) was refluxed in furan (28 ml) for 120 h. The solvent was removed and the residue was chromatographed on silica gel (130 g) with benzene as eluant. After a small amount of uncharacterized material, 3-(3,5-*dichloro-2,4,6-trimethyl-phenyl*)-3a,6a-*dihydrofuro*[2,3-d]*isoxazole* (2) (1.3 g) was obtained, m.p. 154° (from n-pentane–chloroform) (Found: C, 56.0; H, 4.4; N, 4.9. $C_{14}H_{13}Cl_2NO_2$ requires C, 56.3; H, 4.4; N, 4.7%); δ (CDCl$_3$) 2.25 (6 H, s, Me), 2.57 (3 H, s, Me), 5.37—5.47 (1 H, m, 6-H), 5.90 (1 H, d, *J* 8.5 Hz, 3a-H), 6.00 (1 H, m, 6a-H), and 6.55—6.65 (1 H, m, 5-H). Further elution gave unidentified crystals (0.10 g).

Reaction of Adduct (2) *with Hydrochloric Acid.*—Adduct (2) (0.25 g) was refluxed in a mixture of concentrated HCl (2 ml), water (3 ml), and dioxan (12 ml) during 2 h. After addition of water, the mixture was extracted with ether and the organic solution was dried and evaporated. The residue was recrystallized from chloroform to afford 3,5-*dichloro-2,4,6-trimethylphenyl 2-furyl ketone oxime* (3) (0.18 g), m.p. 187—188° (Found: C, 56.3; H, 4.2; N, 4.9. $C_{14}H_{13}Cl_2NO_2$ requires C, 56.4; H, 4.4; N, 4.7%); $\nu_{max.}$ (Nujol) 3 210 (OH) cm^{-1}; δ (CD$_3$COCD$_3$) 2.18 (6 H, s, Me), 2.55 (3 H, s, Me), 6.63 (1 H, dd, *J ca.* 2 and 3.5 Hz, 4-H), 7.47 (1 H, dd, *J ca.* 2 and 1 Hz, 5-H), 7.59 (1 H, dd, *J ca.* 3.5 and 1 Hz, 3-H), and 11.2br (1 H, s, OH).

Reaction of Adduct (2) *with Bromine.*—A solution of (2) (0.20 g) in chloroform (20 ml) was treated with 2M-bromine in chloroform (0.7 ml). After a few minutes, the solvent was removed and the residue was taken up with di-iso-propyl ether. Filtration gave *dibromide* (4) (0.22 g), m.p. 177—179° (decomp.) (Found: C, 36.6; H, 2.8; N, 3.0. $C_{14}H_{13}Br_2Cl_2NO_2$ requires C, 36.7; H, 2.9; N, 3.0%); δ (CD$_3$SOCD$_3$) 2.37 (6 H, s, Me), 2.53 (3 H, s, Me), and 5.3—6.0 (4 H, complex, furan protons).

Reaction of Oxide (1) *with Benzofuran.*—A solution of (1) (1.0 g) in benzofuran (22 ml) was heated at 80° for 5 h. The solvent was removed under reduced pressure and the residue was adsorbed on silica gel column (150 g). Elution with chloroform–benzene (4 : 1 v/v) afforded 3-(3,5-*dichloro-2,4,6-trimethylphenyl*)-3a,8a-*dihydrobenzofuro*[3,2-d]*isoxazole* (5) (0.47 g), m.p. 197° (from n-pentane–benzene) (Found: C, 61.9; H, 4.3; N, 3.9. $C_{18}H_{15}Cl_2NO_2$ requires C, 62.1; H, 4.3; N, 4.0%); δ (CDCl$_3$) 1.48 (3 H, s, Me), 2.39 (3 H, s, Me), 2.55 (3 H, s, Me), 5.06 (1 H, d, *J* 7 Hz, 3a-H), and 6.5—7.4 (5 H, m, aromatic and 8a-H).

Further elution gave 3-(3,5-*dichloro-2,4,6-trimethylphenyl*)-3a,8b-*dihydrobenzofuro*[2,3-d]*isoxazole* (6) (0.30 g), m.p. 203° (from n-pentane–benzene) (Found: C, 61.8; H, 4.0; N, 3.9%); δ (CDCl$_3$) 2.21 (6 H, s, Me), 2.55 (3 H, s, Me), 6.08 and 6.38 (2 H, AB, *J* 8 Hz, OCH–CHO), and 6.8—7.6 (4 H, m, aromatic).

Reaction of Adduct (5) *with Sodium Hydroxide.*—Adduct (5) (0.10 g) was refluxed in ethanolic 0.01M-NaOH (5 ml) for

2 h. After addition of water, the mixture was neutralized and extracted with ether. The organic solution was dried and evaporated, giving 3-(3,5-*dichloro-2,4,6-trimethylphenyl*)-4-(2-*hydroxyphenyl*)*isoxazole* (7) (0.090 g), m.p. 235—236° (from di-isopropyl ether–chloroform) (Found: C, 62.4; H, 4.3; N, 3.9%); $\nu_{max.}$ (Nujol) 3 330 (OH) cm^{-1}; δ (CDCl$_3$) 2.10 (6 H, s, Me), 2.54 (3 H, s, Me), 6.5—7.1 (4 H, m, aromatic), 8.9br (1 H, s, OH), and 9.18 (1 H, s, CH=).

Reaction of Oxide (1) *with Thiophen.*—Compound (1) (6.0 g) was refluxed in freshly distilled thiophen (130 ml) for 48 h. The solid material was collected by filtration and washed with benzene to yield NN'-*bis*-(3,5-*dichloro-2,4,6-trimethylphenyl*)*urea* (8) (0.35 g), m.p. 355—360° (decomp.) (Found: C, 52.4; H, 4.5; N, 6.4. $C_{19}H_{20}Cl_4N_2O$ requires C, 52.6; H, 4.6; N, 6.4%); $\nu_{max.}$ (Nujol) 3 270 (NH) and 1 620 (CO) cm^{-1}. The filtered solution was evaporated and the residue was chromatographed on silica gel (700 g), eluting with benzene. The first fractions afforded 3,4-*bis*-(3,5-*dichloro-2,4,6-trimethylphenyl*)-1,2,5-*oxadiazole* 2-*oxide* (11) (0.36 g), m.p. 247—248° (from n-pentane–benzene) (Found: C, 52.4; H, 3.8; N, 6.0. $C_{20}H_{18}Cl_4N_2O_2$ requires C, 52.2; H, 3.9; N, 6.1%); $\nu_{max.}$ (Nujol) 1 580 (C=N) cm^{-1}; $\lambda_{max.}$ (ethanol) 265 nm (ε 4 600) [3,4-diphenyl-1,2,5-oxa-diazole 2-oxide [19] shows $\nu_{max.}$ 1 595 cm^{-1}, $\lambda_{max.}$ 283 nm (ε 5 700)]; δ (CDCl$_3$) 2.0—2.7 (set of s). Further elution gave a small amount of (1) (0.3 g) followed by 3,7-*bis*-(3,5-*dichloro-2,4,6-trimethylphenyl*)-3a,4a,7a,7b-*tetrahydrothieno*-[2,3-d:4,5-d']*di-isoxazole* (10) (0.57 g), m.p. 256° (from chloroform) (Found: C, 52.9; H, 3.9; N, 4.9. $C_{24}H_{22}Cl_4$-N_2O_2S requires C, 53.0; H, 4.1; N, 5.1%); δ (CDCl$_3$) 2.37, 2.54, and 2.58 (18 H, set of s, Me), 4.8—5.25 (3 H, m, 3a-, 7a-, and 7b-H), and 6.77 (1 H, d, *J* 7.5 Hz, 4a-H); *m/e* 546 (5%), 544 (10), 542 (7), 329 (4), 313 (4), 258 (42), 229 (64), 213 (62), and 178 (100).

Following fractions contained 3-(3,5-*dichloro-2,4,6-tri-methylphenyl*)-3a,6a-*dihydrothieno*[2,3-d]*isoxazole* (9) (2.05 g), m.p. 170° (from n-hexane–benzene) (Found: C, 53.7; H, 4.0; N, 4.3. $C_{14}H_{13}Cl_2NOS$ requires C, 53.5; H, 4.2; N, 4.4%); δ (CDCl$_3$) 2.28 (6 H, s, Me), 2.54 (3 H, s, Me), 5.34 (1 H, d, *J* 10.5 Hz, 3a-H), 5.84 (1 H, dd, *J* 6 and 2.5 Hz, 6-H), 6.22 (1 H, m, 6a-H), and 6.45 (1 H, dd, *J* 6 and 1.5 Hz, 5-H). Further elution gave crystals (0.90 g), m.p. 132—137°; $\nu_{max.}$ (Nujol) 3 210 and 1 725 cm^{-1}; δ (CDCl$_3$) 2.1—2.7 (18 H, set of s) and 7.5br (1 H, s).

Reaction of Isoxazole (9) *with Hydrochloric Acid.*—Adduct (9) (0.30 g) was refluxed in a mixture of concentrated HCl (2.5 ml), water (3.5 ml), and dioxan (14 ml) during 90 min. The mixture was then poured in water and extracted with ether. The organic solution was dried and evaporated, giving 3,5-*dichloro-2,4,6-trimethylphenyl 2-thienyl ketone oxime* (14) (0.28 g), m.p. 189—190° (from chloroform) (Found: C, 53.4; H, 4.2; N, 4.4. $C_{14}H_{13}Cl_2NOS$ requires C, 53.5; H, 4.2; N, 4.4%); $\nu_{max.}$ (Nujol) 3 220 (OH) cm^{-1}; δ (CD$_3$COCD$_3$) 2.20 (6 H, s, Me), 2.53 (3 H, s, Me), 6.75—7.10 (2 H, m, 3- and 4-H), 7.69 (1 H, dd, *J* 5 and 1.5 Hz, 5-H), and 11.0br (1 H, s, OH).

Reaction of Isoxazole (9) *with Bromine.*—Adduct (9) (0.10 g) was treated with bromine as described for compound (2). The product was *dibromide* (13) (0.12 g), m.p. 173° (decomp.) (from chloroform) (Found: C, 35.8; H, 2.7; N, 2.7. $C_{14}H_{13}Br_2Cl_2NOS$ requires C, 35.5; H, 2.8; N, 2.9%); δ (CDCl$_3$) 2.47 (6 H, s, Me), 2.54 (3 H, s, Me), and 5.0—5.6 (4 H, complex, ring H).

[19] J. H. Boyer, U. Toggweiler, and G. A. Stoner, *J. Amer. Chem. Soc.*, 1957, **79**, 1748.

Reaction of Oxide (1) *with Isoxazole* (9).—A solution of (1) (0.30 g) and (9) (0.30 g) in benzene (10 ml) was refluxed for 48 h. The solvent was removed and the residue was chromatographed on silica gel (60 g) with benzene–n-hexane (70 : 30 v/v) as eluant. After some uncharacterized material and substrates, diadduct (10) was obtained (0.12 g), followed by 3,5-*bis*-(3,5-*dichloro*-2,4,6-*trimethylphenyl*)-3a,4a,7a,7b-*tetrahydrothieno*[2,3-d:5,4-d']*di-isoxazole* (12) (0.012 g), m.p. 284° (decomp.) (from di-isopropyl ether–chloroform) (Found: C, 53.1; H, 4.1; N, 5.0. $C_{24}H_{22}Cl_4$-N_2O_2S requires C, 53.0; H, 4.1; N, 5.1%); δ (CDCl₃) 2.2—2.7 (18 H, set of s, Me), and 5.14 and 5.83 (4 H, A_2B_2, J 7 Hz, ring H); m/e 546 (7%), 544 (15), 542 (11), 329 (2), 313 (4), 258 (100), 229 (89), 213 (47), and 178 (72).

Reaction of Oxide (1) *with Benzothiophen*.—A solution of (1) (0.50 g) in molten benzothiophen (11 ml) was heated at 80° for 10 h. Benzothiophen was removed *in vacuo* and the residue was adsorbed on silica gel column (100 g). Elution with benzene afforded uncharacterized material followed by 3-(3,5-*dichloro*-2,4,6-*trimethylphenyl*)-3a,8a-*dihydrobenzo-thieno*[3,2-d]*isoxazole* (18) (0.12 g), m.p. 184—185° (from cyclohexane) (Found: C, 59.2; H, 4.4; N, 3.8. $C_{18}H_{15}$-Cl_2NOS requires C, 59.3; H, 4.2; N, 3.9%); δ (CDCl₃) 1.53 (3 H, s, Me), 2.39 (3 H, s, Me), 2.53 (3 H, s, Me), 5.27 (1 H, d, J 9 Hz, 3a-H), and 6.3—7.3 (5 H, complex, aromatic and 8a-H).

Further elution gave 3-(3,5-*dichloro*-2,4,6-*trimethylphenyl*)-3a,8b-*dihydrobenzothieno*[2,3-d]*isoxazole* (19) (0.080 g), m.p. 209—210° (from cyclohexane) (Found: C, 59.5; H, 4.1; N, 3.9%); δ (CDCl₃) 2.23 (6 H, s, Me), 2.53 (3 H, s, Me), 5.38, 6.48 (2 H, AB, J 10 Hz, OCH–CHS), and 7.0—7.7 (4 H, m, aromatic).

N-(3,5-*Dichloro*-2,4,6-*trimethylphenyl*)-N'-*phenylurea* (17). —A solution of (1) (0.50 g) in benzene (15 ml) was refluxed for 48 h. Aniline (0.33 g) was added and the resulting mixture was allowed to cool. Filtration gave *urea* (17) (0.23 g), m.p. 350—355° (decomp.) (Found: C, 59.5; H, 5.1; N, 8.6. $C_{16}H_{16}Cl_2N_2O$ requires C, 59.3; H, 5.0; N, 8.6%); $v_{max.}$ (Nujol) 3 250 (NH) and 1 630 (CO) cm⁻¹.

3,5-*Dichloro*-2,4,6-*trimethylaniline* (16).—A solution of (1) (0.50 g) in benzene (15 ml) was refluxed for 48 h. After removal of the solvent, the residue was taken up with 50% aqueous ethanol (15 ml) and refluxed for 7 h. The mixture was then extracted with CH_2Cl_2 and the organic layer was dried and evaporated. The residue was chromatographed on silica gel (50 g) with benzene as eluant to give the *amine* (16) (0.13 g), m.p. 166—167° (from ethanol) (Found: C, 53.0; H, 5.7; N, 6.7. $C_9H_{11}Cl_2N$ requires C, 53.0; H, 5.4; N, 6.9%); $v_{max.}$ (Nujol) 3 380—3 550 (NH₂) cm⁻¹; δ (CDCl₃) 2.28 (6 H, s, Me), 2.56 (3 H, s, Me), and 3.7br (2 H, s, NH₂).

3,5-*Dichloro*-2,4,6-*trimethyl*-N-*phenylbenzamidoxime*.— A solution of (1) (0.15 g) and aniline (0.30 g) in methanol (8 ml) was refluxed for 0.5 h. After addition of water (1 ml), the mixture was treated with charcoal and filtered. By cooling, the title *amidoxime* separated as crystals (0.18 g), m.p. 162° (Found: C, 59.5; H, 4.8; N, 8.7. $C_{16}H_{16}Cl_2N_2O$ requires C, 59.3; H, 5.0; N, 8.6%); $v_{max.}$ (Nujol) 3 000—3 300 (NH and OH) cm⁻¹; δ (CDCl₃) 2.28 (6 H, s, Me), 2.52 (3 H, s, Me), and 6.4—7.2 (5 H, m, aromatic).