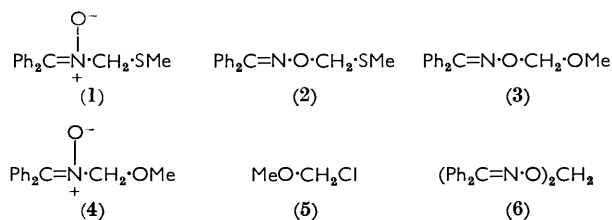


Preparation of *O*-(Methoxymethyl)benzophenone Oxime and *N*-(Diphenylmethylene)methoxymethylamine *N*-Oxide and their Reactions with Trichloroacetic Acid

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Reactions of the title compounds with trichloroacetic acid have been compared with those of the analogous methylthiomethyl compounds studied earlier. A sequence of reactions produced methoxymethyl trichloroacetate, then methanol, and finally methyl trichloroacetate from both compounds; the *N*-oxide also isomerised to the oxime *O*-ether. Added water had little effect on the first stages of the sequence. Reaction schemes are presented that account for the formation and reaction of the identified intermediates.

In a recent study of the trichloroacetic acid-catalysed reactions of the methylthiomethyl nitron (1) and the oxime ether (2), the products were interpreted as resulting from attack on the protonated substrate by water or a product hydroxylamine under moist conditions, or by the sulphur atom of a second molecule under dry conditions.¹ There was no clear evidence for the trichloroacetate ion acting as a nucleophile, and initial reaction of the oxime ether (2) was faster than that of the nitron (1). It was therefore of interest to compare the behaviour of analogous methoxymethyl compounds, having the less nucleophilic oxygen atom in place of sulphur, and also with oxygen's greater ability to stabilise a positive charge at an adjacent *sp*² centre.



Direct alkylation of benzophenone oxime and its anion under a variety of conditions gave good yields

of the *O*-methoxymethyl oxime (3), but none of the desired nitron (4). For example, reaction of the oxime with the chloro-ether (5) in chloroform, dimethylformamide, light petroleum, and chloroform containing propylene oxide (to react with the hydrogen chloride formed and minimise any acid-catalysed reaction) afforded no nitron. Alkylations of the oxime's sodium salt in benzene, of its magnesium salt in ether (from the oxime and methyl Grignard reagent), and of the oxime adsorbed onto an alumina column, similarly involved reaction solely on oxygen. We therefore turned to a method discovered earlier,² which we knew to afford the nitron in poor yield. Reaction between the oxime, methylene bromide or iodide, and sodium methoxide in methanol gave a mixture containing unchanged oxime, benzophenone, the oxime ether (3), the nitron (4), and the methylenebis-(benzophenone oxime) (6), which last compound had been the original synthetic object.¹ Variation of reaction time and temperature and reagent proportions gave, at best, about 11% yield of nitron. The low yield could in part be accounted for by reaction of the nitron with base, although it was less reactive than

¹ D. A. Kerr, I. W. Jones, and D. A. Wilson, *J. Chem. Soc. (C)*, 1971, 2591.

² I. W. Jones, M.Sc. Thesis, University of Wales, 1971.

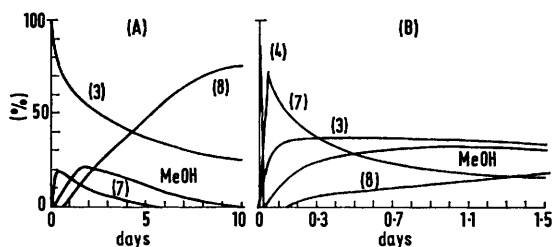
the analogous methylthiomethyl nitron (1),³ and its thermal instability. For example, 40% of the nitron (4) had isomerised to the oxime ether (3) after 6 h in refluxing benzene. Also, e.s.r. signals (as yet uninterpreted) were observed for a solution of the nitron in carbon tetrachloride at 40°. This is to be compared with the greater thermal stability of the nitron (1).⁴ Purification was effected by preparative layer chromatography, but the separated nitron had to be washed from the silica adsorbent promptly, since it isomerised appreciably to the oxime ether within an hour if left adsorbed. The spectral properties of the compounds (3) and (4) were completely analogous to those of the compounds (2) and (1).

TABLE 1
Reaction of the oxime ether (3) with trichloroacetic acid in [²H]chloroform at 33°

| Time | (3) | (7) | MeOH (8) | lost CH ₂ | Unknowns | | | Ph ₂ C=O |
|---------|-----|-------|----------|----------------------|----------|--------|--------|---------------------|
| | | | | | τ 5.25 | τ 4.48 | τ 4.06 | |
| 0 | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 40 min | 94 | 6 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1.50 h | 89 | 11 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2.25 | 87 | 13 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5.13 | 79 | 18 | 3 | 0 | 2 | 1 | 0 | 0 |
| 1.0 day | 63 | 15 | 16 | 6 | 21 | 5 | 0 | Trace |
| 1.2 | 61 | 13 | 19 | 9 | 20 | 8 | 0 | Trace |
| 4.0 | 44 | 4 | 17 | 38 | 38 | 8 | 5 | 36 |
| 5.0 | 37 | Trace | 14 | 49 | 43 | 8 | 6 | 43 |
| 7.2 | 33 | 0 | 5 | 62 | 56 | 3 | 8 | 45 |
| 12.2 | 22 | 0 | Trace | 78 | 70 | 0 | 8 | 58 |
| 18.0 | 19 | 0 | 0 | 81 | 75 | 0 | 8 | 64 |

^a ±2%, except Ph₂C=O, ±5%.

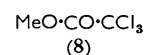
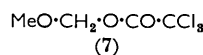
Reaction of the Oxime Ether (3) with Trichloroacetic Acid.—The ether and the acid in deuteriochloroform were kept in sealed n.m.r. tubes at 33° and examined by n.m.r. spectroscopy at intervals. Peak heights



Reactions with trichloroacetic acid of (A) the oxime ether (3) and (B) the nitron (4)

and electronic integration were both used to estimate proportions of products as before.¹ The n.m.r. signals of the *O*-ether decayed, to be replaced first by those of methoxymethyl trichloroacetate (7) [τ 6.45 (Me) and 4.51 (CH₂)]. This reached a maximum concentration and was then replaced by methanol (τ 6.52), which

was then followed by methyl trichloroacetate (8) (τ 6.00), the final product. It was soon apparent that benzophenone was being formed (low-field *ortho* proton signals and t.l.c.), and that some CH₂ signal had moved to the aryl proton region (the 'lost CH₂'). There were also a number of minor unidentified intermediates evident, one of which (τ 4.84) could have been polymerised formaldehyde. These results are given in Table 1, and the earlier stages are shown in the Figure. Methanol and the two esters were compared with authentic samples by g.l.c. on two columns as well as by n.m.r.

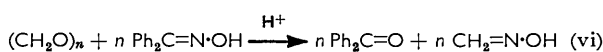
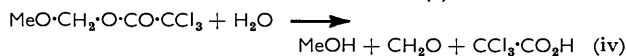
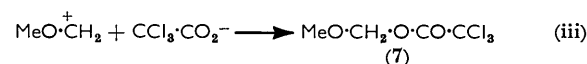
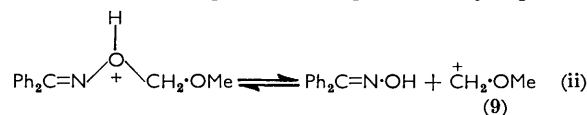
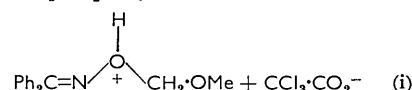
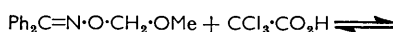


Addition of a limited amount of water had little effect in the early stages, the main difference eventually showing up in the faster formation of methanol and, correspondingly, methyl trichloroacetate. Table 2 gives these results.

TABLE 2
Reaction of the oxime ether (3) with trichloroacetic acid and water in [²H]chloroform at 33°

| Time | (3) | (7) | MeOH | (8) |
|---------|--|-----|------|-----|
| | (mole fraction as % initial concn., ±2%) | | | |
| 0 | 100 | 0 | 0 | 0 |
| 1.25 h | 92 | 8 | 0 | 0 |
| 2.42 | 86 | 14 | 0 | 0 |
| 4.0 | 82 | 18 | 0 | 0 |
| 6.0 | 76 | 16 | 6 | 2 |
| 8.0 | 71 | 16 | 10 | 3 |
| 12.0 | 66 | 15 | 14 | 5 |
| 1.0 day | 56 | 12 | 20 | 12 |
| 1.5 | 48 | 11 | 21 | 20 |
| 2.0 | 43 | 8 | 21 | 28 |

These observations can be explained by the reactions shown in Scheme 1. Initial protonation on oxygen



SCHEME 1

[step (i)] gave a species that could form benzophenone oxime and the methoxymethyl cation (9) [step (ii)]. Evidence for the reversibility of this step is provided by the results for the nitron discussed later. Trichloroacetate ion (or the acid) then would form [step (iii)]

³ D. A. Kerr and D. A. Wilson, *J. Chem. Soc. (C)*, 1970, 1718.

⁴ D. A. Kerr, I. W. Jones, and D. A. Wilson, *J. Chem. Soc. (C)*, 1971, 2595.

the first observed product, the ester (7). With a trace of water, the ester could be hydrolysed [step (iv)] and the methanol formed would then react with trichloroacetic acid to give the methyl ester (8) [step (v)] and water, which thus need only be present in catalytic amount. The formaldehyde formed in step (iv), which would reversibly polymerise (see later) and the benzophenone oxime from step (ii) together would exchange the oxime function to give benzophenone, as observed, and formaldehyde oxime, whose CH₂ protons absorb in the aryl proton region of the n.m.r. spectrum [step (vi)]. We have separately demonstrated steps (v) and (vi).

Methanol and trichloroacetic acid, in deuteriochloroform, did react to form methyl trichloroacetate, a reaction followed by n.m.r. spectroscopy as recorded in Table 3.

TABLE 3

Reaction of methanol and trichloroacetic acid ^a in [2H]chloroform at 33°

| Time (h) | 0 | 0.5 | 1 | 2 | 3 | 4 | 8 | 12 | 24 | 30 |
|----------|-----|-----|----|----|----|----|----|----|----|----|
| MeOH (%) | 100 | 95 | 93 | 88 | 84 | 82 | 76 | 73 | 65 | 63 |

^a Initial mole ratio 2.5 : 1.

When formaldehyde was bubbled into deuteriochloroform, an n.m.r. spectrum of the solution showed the aldehyde protons clearly (τ 0.3). Addition of benzophenone oxime, however, caused polymerisation of the aldehyde [τ 4.8 (trioxan ?)]. Addition of trichloroacetic acid then initiated a reaction in which benzophenone was formed (four low-field *ortho* protons) and the CH₂ signal was lost to the aryl proton region. This reaction, which was complete in about 12 h, must also have accounted for the benzophenone seen in our previous work.¹

An alternative to step (iv) would allow the ester (7) to react with trichloroacetic acid to give methanol, formaldehyde, and trichloroacetic anhydride, thus not involving water. However, the anhydride was shown to react rapidly with methanol, so that the build-up and slow loss of methanol would not have been seen had the anhydride been involved, and this alternative can be rejected.

Reaction of the Nitron (4) with Trichloroacetic Acid.— Under the same conditions, the nitron reacted more than 100 times faster than the oxime ether (3). The main initial product was the methoxymethyl ester (7), which was then more slowly lost, giving methanol and methyl trichloroacetate. The second initial product was the oxime ether (3) which built up to a maximum concentration and was slowly lost. Table 4 details the results, and the early stages of the reaction are shown in the Figure. These observations are explained by the reactions given in Scheme 2.

Protonation of the nitron on oxygen was indicated by a downfield shift of the CH₂ signal (τ 4.95 to 4.70) and an upfield shift of the signal for the two *ortho*-protons of the phenyl ring *cis* to the nitron oxygen atom (τ 2.0 to *ca.* 2.3), as noted previously for the

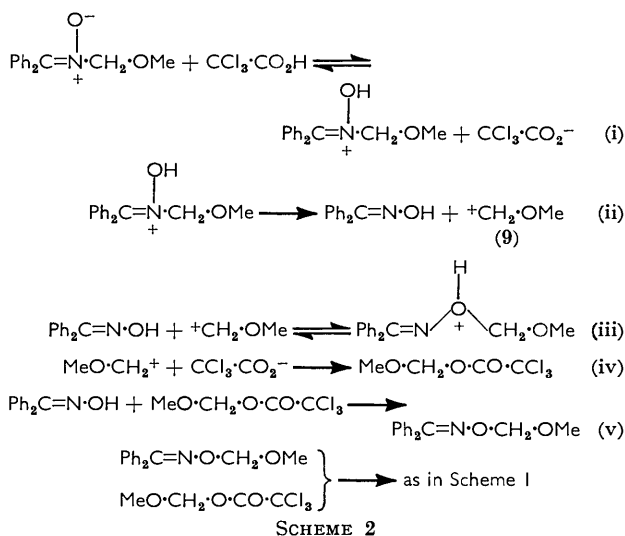
nitron (1).¹ The equilibrium in step (i) would lie much more to the right-hand side than the equilibrium in step (i) of Scheme 1; many nitrones form salts with acids. Dissociation of the protonated nitron into oxime and the stabilised carbonium ion (9) is in accord

TABLE 4
Reaction of nitron (4) and trichloroacetic acid in [2H]chloroform at 33°

| Time | (4) | (7) | (3) | MeOH | (8) | Un-known τ 5.3 | Ph ₂ C=O |
|----------|--|-------|-------|------|-------|------------------------|---------------------|
| | (mole fraction as % initial concn.) ^a | | | | | | |
| 0 | 100 | 0 | 0 | 0 | 0 | 0 | 0 |
| 10 min | 65 | 25 | 10 | 0 | 0 | 0 | 0 |
| 40 | Trace | 73 | 27 | 0 | 0 | 0 | 0 |
| 1.25 h | 0 | 65 | 28 | 7 | Trace | 0 | 0 |
| 2.42 | 0 | 56 | 34 | 10 | Trace | 0 | Trace |
| 4.50 | 0 | 43 | 35 | 18 | 3 | 5 | Trace |
| 1.06 day | 0 | 20 | 37 | 34 | 10 | 20 | Yes ^b |
| 1.12 | 0 | 19 | 39 | 32 | 10 | 17 | Yes ^b |
| 1.90 | 0 | 17 | 32 | 29 | 22 | 20 | 24 |
| 2.21 | 0 | 13 | 31 | 29 | 28 | 20 | 28 |
| 5.0 | 0 | 8 | 16 | 13 | 63 | 8 | 51 |
| 7.0 | 0 | 5 | 15 | 5 | 74 | 0 | 59 |
| 12.0 | 0 | Trace | Trace | 4 | 95 | 0 | 60 |

^a $\pm 2\%$, except Ph₂C=O, $\pm 5\%$.

^b Observable but not measurable



SCHEME 2

with the known behaviour of, for example, methoxymethyl halides.⁵ Recombination could give the oxime ether (3), but alternatively the carbonium ion and trichloroacetate ion could give the ester (7). At the point where the nitron had just disappeared, the ratio ester (7) to oxime ether (3) was *ca.* 2.7 and this represents a measure of the competition for the carbonium ion. A repeat experiment with nearly an equimolar amount of benzophenone oxime present at the start gave the results listed in Table 5. The pattern was the same, except that methanol began to appear before all the nitron had reacted, a consequence of the slightly

⁵ C. K. Ingold, 'Structure and Mechanism in Organic Chemistry,' 2nd edn., Bell, London, 1969, p. 444.

slower initial reaction. At the point where nitron had just disappeared, the ratio of esters (7) and (8) and methanol to oxime ether (3) was again *ca.* 2.7.*

TABLE 5

Reaction of nitron (4), benzophenone oxime, and trichloroacetic acid in [²H]chloroform at 33°

| Time | (4) | (7) | (3) | MeOH | (8) | Unknown τ 5.3 |
|----------|---|-----|-----|------|-----|-----------------------|
| | (mole fraction as % initial concn., $\pm 2\%$) | | | | | |
| 0 | 100 | 0 | 0 | 0 | 0 | 0 |
| 35 min | 50 | 39 | 10 | 0 | 0 | 0 |
| 65 | 27 | 51 | 13 | 4 | 0 | 0 |
| 4.50 h | 0 | 39 | 27 | 23 | 10 | 12 |
| 5.35 | 0 | 37 | 28 | 24 | 11 | 10 |
| 1.21 day | 0 | 0 | 28 | 34 | 38 | 22 |
| 3.46 | 0 | 0 | 25 | 27 | 48 | 17 |

The same competition ratio in the presence of added oxime indicates that reaction between oxime and methoxymethyl cation occurred without prior complete separation, *i.e.* a molecule-ion pair of some kind was involved. Reaction of the carbonium ion (9), when freed from the oxime, was then mostly with trichloroacetate ion [step (iv)].

The oxime ether continued to form after the nitron had all reacted, but the maximum concentration of the ester (7) coincided with the final disappearance of nitron. This points to a reaction between benzophenone oxime and the ester (7) in which the ether (3) was formed [step (v)]. This has been demonstrated separately. The oxime and the ester in the presence of a little trichloroacetic acid in deuteriochloroform did form the oxime ether (n.m.r. and t.l.c.), and methanol, and subsequently the trichloroacetate (8) and benzophenone. Subsequent reactions of the ether (3) and the ester (7) were those detailed in Scheme 1.

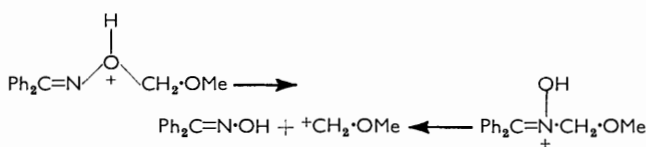
Addition of water to the nitron reaction had little effect on the early stages, but, as with the oxime ether reaction, methanol and methyl trichloroacetate were both formed a little more quickly. The results are not tabulated, but the conclusion is that water played no part as a reactant until it reacted with methoxymethyl trichloroacetate. It may have had a solvent effect, since at the point of nitron disappearance, the ratio of ester (7) and methanol to oxime ether (3) was *ca.* 4.0, suggesting more ready separation of the molecule-ion pair formed in step (ii).

The differences in reactivity and products formed between the pair of methylthiomethyl derivatives (1) and (2) and the methoxymethyl pair (3) and (4) can best be attributed to the readiness of compounds (3) and (4) to form, after protonation, the methoxymethyl cation (9), allowing reaction with the trichloroacetate ion. On the other hand, direct attack on the protonated compounds (1) and (2) by the alternative nucleophiles

* This calculation is justified since the methanol comes from the ester, and little ester or methanol would have been derived from the oxime ether in the short time involved. Similarly, very little oxime ether would have been formed from the ester (7).

water, a hydroxylamine, or the sulphur atom of a second molecule, was preferred to dissociation into oxime and the methylthiomethyl cation, a species often postulated, but not fully accepted.⁶

These reactions present an interesting situation in which two different species dissociate to give the same products, one by fission of a C-O⁺ bond, and the other of a C-N⁺ bond:



This, with the greater basicity of the nitron, leads to the much faster reaction of the nitron (4) than that of the oxime ether (3).

EXPERIMENTAL

N.m.r. spectra were measured on a Perkin-Elmer R14 100 MHz instrument. G.l.c. experiments used a Perkin-Elmer 457 instrument with helium as carrier gas, and columns of polypropylene glycol (15%) on Chromosorb W, and silicone grease (20%) on Chromosorb P.

O-(Methoxymethyl)benzophenone Oxime (3).—A mixture of benzophenone oxime (12.5 g), chloromethyl methyl ether (30 g), and chloroform (50 ml) was heated under reflux for 30 min. The residue left on evaporation was triturated with light petroleum (b.p. 60–80°), which dissolved the product. Two crystallisations from the same solvent gave the *oxime ether* (7.5 g), m.p. 41–43°, λ_{max} (EtOH) 234 (ϵ 10,800) and 253 nm (9800), ν_{max} (Nujol) 1160, 1022, and 958 cm^{-1} , τ (CDCl_3) 2.5 (m, 10 aromatic H), 4.80 (s, CH_2), and 6.55 (s, OMe), *m/e* 241 (M^+ , 11%), 240(7), 195(6), 194(35), 165(18), 77(24), 51(13), and 45(100, $\text{CH}_3\cdot\text{O}\cdot\text{CH}_2^+$) (Found: C, 74.5; H, 6.7; N, 5.7. $\text{C}_{15}\text{H}_{15}\text{NO}_2$ requires C, 74.7; H, 6.3; N, 5.8%).

N-(Diphenylmethylene)methoxymethylamine *N*-Oxide (4).—Benzophenone oxime (16.0 g) was dissolved in methanol (160 ml) containing dissolved sodium (1.9 g). Methylene iodide (12.0 g) was added and the solution was heated under reflux for 7 h. After extraction into ether and washing the ethereal solution with water, a gum (18.9 g) was obtained that contained (by n.m.r.) unchanged oxime (49%), benzophenone (4%), the oxime *O*-methoxymethyl ether (6%), *OO'*-methylenebis(benzophenone oxime) (30%), and the nitron (11%). Trituration with chloroform–light petroleum (b.p. 40–60°) (1:9) gave a solution that contained 31% nitron. Separation was effected on preparative layer plates (20 × 40 cm; Woelm silica gel HF254; 150 mg of mixture giving 25–30 mg of product per plate) developed with ethyl acetate; compounds were detected by u.v. illumination. The product was immediately washed from the silica with chloroform and crystallised from light petroleum (b.p. 60–80°) to give the *N*-oxide, m.p. 85°, λ_{max} (EtOH) 239 (ϵ 11,700) and 301 nm (10,700), ν_{max} (Nujol) 1238, 1120, and 965 cm^{-1} , τ (CDCl_3) 2.0 (m, 2 aromatic H), *ca.* 2.6 (m, 8 aromatic H), 4.95 (s, CH_2), and 6.28 (s, OMe) (Found: C, 74.8; H, 6.2. $\text{C}_{15}\text{H}_{15}\text{NO}_2$ requires C, 74.7; H, 6.3%).

⁶ R. L. Autry and P. W. Scullard, *J. Amer. Chem. Soc.*, 1968, **90**, 4924.

Reactions Followed by N.m.r.—The following solutions were kept at 33° and examined by n.m.r. spectroscopy after the time intervals shown in the Tables. (a) Benzophenone oxime *O*-methoxymethyl ether (44 mg) and trichloroacetic acid (60 mg) in [²H]chloroform (0.4 ml) (Table 1). (b) As in (a) but with water (5 μl) added (Table 2). (c) Methanol (29 mg) and trichloroacetic acid (57 mg) in [²H]chloroform (0.4 ml) (Table 3). (d) Benzophenone oxime (109 mg), formaldehyde (13 mg), and trichloroacetic acid (36 mg) in [²H]chloroform (1.0 ml). (e) *N*-(Diphenylmethylene)methoxymethylamine *N*-oxide (27 mg) and trichloroacetic acid (36 mg) in [²H]chloroform (0.4 ml) (Table 4). (f) The *N*-oxide (46 mg), benzophenone oxime (29 mg), and trichloroacetic acid (68 mg) in [²H]chloroform (0.4 ml) (Table 5). (g) Benzophenone oxime (50 mg), methoxymethyl trichloroacetate (200 mg), and trichloro-

acetic acid (5 mg) in [²H]chloroform (0.5 ml) gave the ether (3) (15%) in 3 h. (h) The *N*-oxide (39 mg), trichloroacetic acid (60 mg), and water (5 μl) in [²H]chloroform (0.4 ml). Results were similar to those for solution (e).

Products methanol, methoxymethyl trichloroacetate, and methyl trichloroacetate were compared with authentic samples by n.m.r. spectroscopy (solutions in [²H]chloroform and benzene), and by g.l.c. on two different columns. Methoxymethyl trichloroacetate⁷ was prepared from the acid, sodium hydride, and chloromethyl methyl ether in benzene.

We thank Dr. J. C. Evans for the e.s.r. observation.

[2/1195 Received, 25th May, 1972]

⁷ P. Salomaa, *Acta Chem. Scand.*, 1965, **19**, 1263.