705. *Phenacyl Sulphides and Related Compounds. Part I. The Action of Alkali on o-Nitrophenyl Phenacyl Sulphide.*

By K. J. Morgan.

A large number of compounds is formed by the action of alkali on *o*-nitrophenyl phenacyl sulphide. The most abundant products correspond to the displacement of the *o*-nitrothiophenoxy-group and to reductive cyclisation to benzothiazole derivatives. Smaller amounts of material obtained by fission on either side of the carbonyl group are detected.

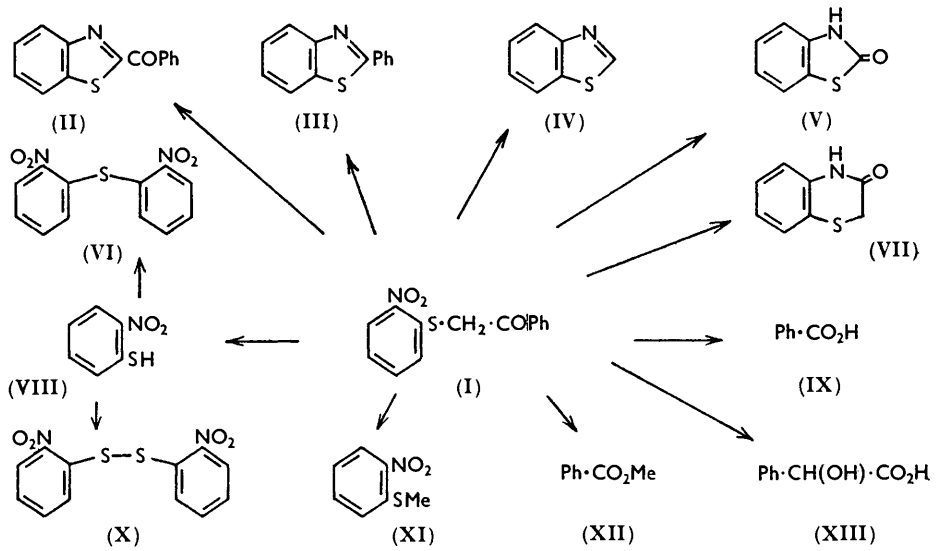
Although simple sulphides are stable to alkali [1] the presence of a carbonyl group adjacent to the sulphide bond renders it labile. Nucleophilic attack then displaces the sulphur grouping from the carbonyl moiety in such molecules to give thiols, sulphides, or elemental sulphur.[2] Also susceptible to nucleophilic attack are nitro-substituted aryl sulphides which decompose in alkaline methanol with the formation of nitroanisoles.[3] It seemed of interest to examine the behaviour under alkaline conditions of *o*-nitrophenyl phenacyl sulphide (I) since it appeared possible that fission of the two sulphur–carbon bonds would proceed competitively.

o-Nitrophenyl phenacyl sulphide was prepared from the corresponding sulphenyl chloride and acetophenone.[4] Preliminary experiments indicated that the action of alkali on this gave products more complex than the simple displacement reactions had suggested. Eventually some dozen products (II—XIII) were isolated and identified; the variation in yield of the more abundant of these with the reaction conditions is shown in the Table. A careful examination of the products failed to detect any *o*-nitroanisole or ω-mercaptoacetophenone and from the structure of those compounds that were found it is apparent that there was no displacement of sulphur from the aromatic ring. The two main reactions involve fission of the sulphur–methylene bond and reductive cyclisation of the whole molecule severally. In addition, smaller amounts of products derived from fission on

[1] See, *e.g.*, Bilheimer and Reid, *J. Amer. Chem. Soc.*, 1930, **52**, 4338.
[2] See, *e.g.*, Schönberg and Iskander, *J.*, 1942, 90; Vinkler and Autheried, *Acta Univ. Szeged Chem. et Phys.*, 1948, **2**, 105; Banfield, Davies, Gamble, and Middleton, *J.*, 1956, 4791.
[3] Kharasch and Swidler, *J. Org. Chem.*, 1954, **19**, 1704.
[4] Kharasch, Wehrmeister, and Tigerman, *J. Amer. Chem. Soc.*, 1947, **69**, 1612; Barltrop and Morgan, unpublished work.

either side of the carbonyl group are found. The facility with which these reactions occur—the molecule is sensitive even to cold sodium carbonate solution—is particularly striking.

The main cleavage reaction is that expected for nucleophilic displacement of the *o*-nitrothiophenoxyl ion, which is assisted by the mesomeric influence of the nitro-group.



The results indicate that the order of reactivity of the basic ions is $HO^- > MeO^- > Bu^tO^-$, and this may be ascribed partly to a steric factor and partly to the possibility of a hydrogen-bonded transition state [5] (XIV; R = S·C_6H_4·NO_2) in which case hydroxyl ion is the

Effect of reaction conditions on the products formed in the alkaline decomposition of o-nitrophenyl phenacyl sulphide.

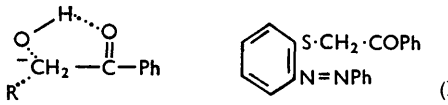
Reagent	KOH 3 equiv.	KOH 1 equiv.	KOH 1 equiv.	Na_2CO_3 [a] 1 mol.	KOMe 1 equiv.	$KOBu^t$ 1 equiv.
Solvent	MeOH	MeOH	MeOH	MeOH	MeOH	Bu^tOH
Temp.	65°	65°	20°	20°	65°	82°
Time (hr.)	2	0·5	24	24	0·5	0·5
			Yield (%)			
Product						
o-Nitrothiophenol [b]	34·5	49·7	45·1	36·5	35·0	25·3
o-Nitrophenyl sulphide	1·3	2·2	2·7	3·0	2·2	2·5
Benzoic acid	58·9	26·0	30·1	24·9	3·4	51·1
2-Benzoylbenzothiazole	19·2	30·6	23·3	12·3	27·0	6·5
2-Phenylbenzothiazole	8·6	3·0	2·0	0·4	0·7	1·8
Benzothiazole	6·2	4·7	2·7	2·6	6·7	18·9
Me benzoate	0	4·9	3·6	6·7	9·0	0
o-Nitrothioanisole	2·6	2·8	2·1	3·3	2·6	2·5

[a] 24·3% of starting material was recovered; yields are calculated on the basis of material consumed. [b] Total amounts of thiol (VIII) and disulphide (X) are listed together.

effective agent. (The low yield of disulphide when three mols. of potassium hydroxide are used is due to its decomposition; it is largely stable under the conditions used in the other experiments.) Oxidation during the analysis of the products prevented accurate estimation of the relative amounts of *o*-nitrothiophenol (VIII) and of the corresponding disulphide (X) which were formed directly in the reaction; it was noticeable that as the conditions became less vigorous the combined amount of thiophenol and disulphide isolated

[5] Cf. Baddeley, *Ann. Reports*, 1955, **52**, 150.

from the crude acidic fraction fell. Also derived from *o*-nitrothiophenol is di-*o*-nitrophenyl sulphide (VI), formed by anionic attack of the thiophenoxy-ion, a powerfully nucleophilic reagent, on the free thiophenol;[6] its uniformly low yield may be due in part to its partial decomposition under the reaction conditions.



(XIV) (XV)

Formation of *o*-nitrothiophenol should be accompanied by the production of ω-hydroxy- and ω-alkoxy-acetophenones. No such compounds were found; instead, benzoic acid (IX) was isolated in comparable yield. The instability of ω-hydroxyacetophenone under alkaline conditions is well established:[7] by a reverse benzoin reaction benzaldehyde and thence benzoic acid are formed. ω-Methoxyacetophenone with potassium hydroxide in methanol similarly gives benzoic acid, the yield of which is increased in the presence of an oxidising agent. In the absence of water ω-methoxyacetophenone is largely stable to anhydrous alcoholic alkali; ω-phenoxyacetophenone behaves similarly. The efficacy of the less nucleophilic hydroxyl ion in this reaction is best described by a transition state stabilised by hydrogen-bonding (XIV; R = OMe) which leads irreversibly to the hydroxyketone. When the decomposition of *o*-nitrophenyl phenacyl sulphide in anhydrous methanol was examined the usual large amounts of benzoic acid or ω-methoxyacetophenone were not isolated; and when ω-methoxyacetophenone was added at the start of the reaction it too was consumed. The ready condensation of ω-methoxyacetophenone with carbonyl compounds has been used synthetically[8] and it seems probable that an analogous reaction occurs here. Examination of the unresolved tarry residues revealed the presence of ketonic materials, but these could not be purified. Conversely, when dry t-butyl alcohol was used as solvent a considerable quantity of benzoic acid was formed, part of which must be derived from fission of the sulphur–methylene bond. The ability of t-butyl compounds to decompose with *O*-alkyl fission suggests that here *O*-alkyl rather than *O*-phenacyl fission of the initially formed t-butoxyacetophenone leads directly to the anion of ω-hydroxyacetophenone which can then decompose in the usual way. Accompanying the benzoic acid from the reaction in t-butyl alcohol is a smaller amount of mandelic acid (XIII). It seems probable that the lack of reducing properties of t-butyl alcohol permits the oxidation of part of the phenacyloxy-ion to phenylglyoxal which in alkaline solution tautomerises to mandelic acid.[9]

The formation of small amounts of *o*-nitrothioanisole (XI) and methyl benzoate (XII) indicates that some attack must occur directly at the carbonyl group. In moist methanol, methyl benzoate is partially hydrolysed under the reaction conditions but the possibility that such an attack could produce the majority of the benzoic acid may be discounted: the small amount of *o*-nitrothioanisole cannot be reconciled with such a decomposition; neither can the comparatively small increase in yield of methyl benzoate found under anhydrous conditions. It is noteworthy that in t-butyl alcohol no t-butyl benzoate is detected although the usual small quantity of *o*-nitrothioanisole is formed. Unimolecular *O*-alkyl fission of t-butyl benzoate has been reported,[10] and it seems probable that such a decomposition occurs here. A similar bimolecular *O*–alkyl fission [11] may account for part of the small quantity of benzoic acid formed in anhydrous methanol.

[6] Cf. Cole, *Chem. and Ind.*, 1957, 1511.
[7] Zincke and Hunaeus, *Ber.*, 1877, **10**, 1486; Zincke, *Annalen*, 1883, **216**, 308; King, *J. Amer. Chem. Soc.*, 1944, **66**, 894.
[8] See, *e.g.*, Pratt and Robinson, *J.*, 1923, **123**, 748; Malkin and Robinson, *J.*, 1925, **127**, 372.
[9] Müller and von Pechmann, *Ber.*, 1889, **22**, 2556; Nef, *Annalen*, 1904, **335**, 247.
[10] Cohen and Schneider, *J. Amer. Chem. Soc.*, 1941, **63**, 3387.
[11] Bunnett, Robinson, and Pennington, *ibid.*, 1950, **72**, 2378.

A small amount of dihydro-oxobenzothiazine (VII) corresponding to fission between the phenyl and the carbonyl group was isolated, but only from the reaction in dry methanol. Reduction with zinc and acetic acid of *o*-nitrophenylthioacetic acid (which was not found among the products) leads directly to this lactam,[12] but under the conditions used here the nitro-acid is stable. Consequently, reduction of the nitro-group must precede the fission. Anionic cleavage of the carbon–carbon bond can then give the amino-ester, which through the lactam gives the water-soluble salt of the free amino-acid; the lactam is regenerated on acidification.[13] This route is preferred to cyclisation of the amino-ketone and subsequent fission of the carbon–carbon bond since no 3-phenylbenzothiazine is detected and acidic reduction of *o*-nitrophenyl phenacyl sulphide [14] gives no dihydro-oxobenzothiazine. The formation of this benzothiazine derivative must proceed competitively with the formation of the benzothiazole compounds discussed below; its occurrence only in dry methanol can be ascribed, first, to the decreased amount of carbon–sulphur fission and, secondly, to the relatively strongly reducing properties of this medium.

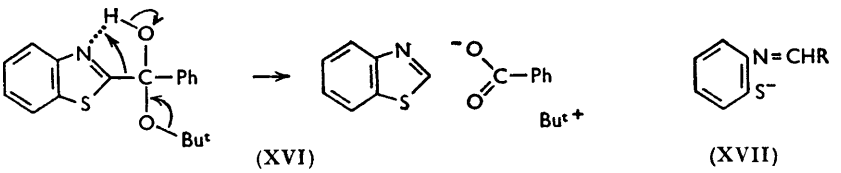
The second group of products is formed in reductive cyclisations and all contain a benzothiazole ring. The most abundant of these is 2-benzoylbenzothiazole (II) formed in good yield by reductive condensation of the nitro-group and the α-methylene group. The ready reduction of nitro-compounds under alkaline conditions [15] and the ease with which nitroso-compounds condense with active methylene groups [16] indicate the mechanism of this reaction; the considerable amounts of benzothiazole derivatives found when t-butyl alcohol is used as solvent are of additional interest in showing that much of the necessary reduction is effected by the sulphide group rather than the alcoholic substrate. A close analogy is provided by the cyclisation under alkaline conditions of *o*-nitrophenylacetaldehyde to give indole.[17] 2-Benzoylbenzothiazole is also formed by cyclisation under acidic conditions of phenacyl 2-phenylazophenyl sulphide (XV).[18] The two reactions are closely related: in each case an electron-deficient nitrogen group condenses with the reactive methylene group.

2-Benzoylbenzothiazole is largely stable in alkaline methanol but a small amount of decomposition to benzothiazole (IV) and benzoic acid does occur. The results suggest that this carbonyl fission is of similar importance to that producing *o*-nitrothioanisole. In t-butyl alcohol this reaction occurs more readily and consumes practically all the ketone. A similar fission of benzophenone with potassium t-butoxide has been reported [19] although benzophenone is completely resistant to attack by alkaline methanol. The efficacy of t-butoxide ions in promoting this reaction is best accommodated in a cyclic mechanism (XVI): separation of the t-butyl ion is supposed to occur simultaneously with fission of the carbon–carbon bond and so initiates the complete reaction sequence. Hydrogen-bonding of the hydroxyl group to the heterocyclic nitrogen atom must help by localising the hydrogen ion and also accounts for the conversion into benzoic acid rather than into a mixture with benzothiazole-2-carboxylic acid.

The isolation of small amounts of 2-phenylbenzothiazole (III) implies a rather different cyclisation. The product contains one less carbon atom than the starting material, and this suggests that fission precedes cyclisation. The formation of benzothiazoles by the condensation of *o*-aminothiophenol and carbonyl compounds represents a conventional synthetic route.[20] Treatment of *o*-nitrothiophenol with benzaldehyde in alkaline methanol gives small amounts of 2-phenylbenzothiazole and so indicates that this can provide the

[12] Friedländer and Chwala, *Monatsh.*, 1907, **28**, 247.
[13] Culvenor, Davies, and Heath, *J.*, 1949, 278.
[14] Zincke and Baeumer, *Annalen*, 1918, **416**, 86.
[15] See, *e.g.*, Simons and Ratner, *J.*, 1944, 421.
[16] See, *e.g.*, Ehrlich and Sachs, *Ber.*, 1899, **32**, 2341; Walker, *J.*, 1924, **125**, 1622.
[17] Weerman, *Annalen*, 1913, **401**, 10.
[18] Burawoy and Chaudhuri, *J.*, 1956, 648.
[19] Swan, *J.*, 1948, 1408.
[20] Hofmann, *Ber.*, 1880, **13**, 1236; Lankelma and Sharnoff, *J. Amer. Chem. Soc.*, 1931, **53**, 2654; 1932, **54**, 379.

effective route. Further support for this mechanism is given by the occurrence of 2-phenylbenzothiazole only in the alkali-soluble fraction. Bogert and Naiman [21] have shown that the anil (XVII) is formed in alkaline solution and rearranges to the thiazolidine only when the free thiol is liberated; aromatisation to the thiazole is completed by autoxidation.



(XVI) (XVII)

Benzothiazolin-2-one (V), found in small yield in the reaction in sodium carbonate solution, may well be formed in a similar reaction with carbonate ion or carbon dioxide.

Apart from the compounds isolated and identified, two orange solids, m. p. 151° and 243° respectively, were isolated; these have not been identified. There remained unresolved a considerable quantity of tar which is receiving further investigation.

Experimental

Methanol and ethanol were dried with magnesium; t-butyl alcohol was dried with lithium aluminium hydride.

Action of Alkali on o-*Nitrophenyl Phenacyl Sulphide.*—A solution of sulphide [4] (9·1 g.), m. p. 145° (from acetonitrile), in dry methanol (250 c.c.) containing potassium methoxide (from potassium, 1·3 g., 1 equiv.) was boiled under reflux for 30 min. The solution was chilled and the solvent removed *in vacuo*. The residue was partitioned between water (100 c.c.) and ether (3 × 100 c.c.); the aqueous phase was washed with ether (4 × 50 c.c.) and the ethereal extracts were combined.

(a) *Aqueous extract.* Acidification and extraction with chloroform gave a black tar (3·5 g.) from which hot water extracted *o*-nitrothiophenol (20 mg.), m. p. 54° [from carbon tetrachloride–light petroleum (b. p. 40—60°)], benzoic acid (90 mg.), m. p. 121° (from water), and 3,4-dihydro-3-oxo-2*H*-benzothiazine (160 mg.), m. p. 177—178° (after sublimation). The water-insoluble residue (3·2 g.) was extracted into ether; *o*-nitrophenyl disulphide (350 mg.), m. p. 199° (from benzene), remained as an insoluble residue. Washing the ethereal extract with alkali gave further quantities of *o*-nitrothiophenol (900 mg.), benzoic acid (50 mg.), and dihydro-oxobenzothiazine (150 mg.). Chromatography of the residual ethereal extract on alumina gave the following fractions: (i) 2-phenylbenzothiazole (50 mg.), m. p. 114° (from methanol), eluted with light petroleum; (ii) 2-benzoylbenzothiazole (120 mg.), m. p. 105° (from methanol), eluted with light petroleum–benzene; (iii) *o*-nitrophenyl disulphide (200 mg.), eluted with light petroleum–benzene; and an unidentified tarry residue.

(b) *Ethereal extract.* Evaporation of the ether left an oil (5·4 g.) whcih was steam-distilled. The distillate (1·2 g.) gave methyl benzoate (400 mg.), b. p. 79°/10 mm., and benzothiazole (230 mg.), b. p. 110°/10 mm., as readily distillable fractions which left a mixture of 2-benzoylbenzothiazole (80 mg.), and *o*-nitrothioanisole (150 mg.), m. p. 63° (from methanol), separated by chromatography on alumina. The steam non-volatile residue (4·2 g.) was chromatographed on alumina to give the following fractions: (i) benzoylbenzothiazole (1·95 g.); (ii) *o*-nitrophenyl disulphide (125 mg.); (iii) *o*-nitrophenyl sulphide (100 mg.), m. p. 123° (from ethanol); (iv) an orange solid (50 mg.), m. p. 151° (from methanol), $\lambda_{max.}$ 253 (log ε 4·40), 330 mμ (log ε 3·85) in methanol (Found: C, 74·1; H, 4·2; S, 10·4. Calc. for $C_{18}H_{13}ONS$: C, 74·2; H, 4·5; S, 11·0%); this was not identical with azo-*o*-anisole or azo-*o*-thioanisole; (v) an orange solid (60 mg.), m. p. 243° (from methanol), $\lambda_{max.}$ 266 (log ε 4·33), 310 mμ (log ε 3·68) in methanol (Found: C, 71·0; H, 4·7; S, 12·6. Calc. for $C_{15}H_{13}ONS$: C, 70·6; H, 5·1; S, 12·6%); (vi) tarry fractions showing carbonyl bands in their infrared spectra.

In each case the identity of the product was confirmed by comparison of infrared spectra.

[21] Bogert and Naiman, *J. Amer. Chem. Soc.*, 1935, **57**, 1529.

With appropriate modifications this analysis was applied to each set of reaction conditions. Dihydro-oxobenzothiazine was found in no other experiment; mandelic acid (400 mg., 7·4%), m. p. 120° (from benzene), was obtained from the reaction in t-butyl alcohol; benzothiazolin-2-one (150 mg., 5%), m. p. 136° (from aqueous ethanol), was found only in the reaction with sodium carbonate. No reaction occurred with sodium acetate or with sodium formate in methanol at 20° for 24 hr.

Action of Alkali on 2-Benzoylbenzothiazole.—The ketone, colourless needles, m. p. 107° (from methanol) (lit.,[22] m. p. 102·5°) (Found: C, 69·9; H, 3·7; N, 6·0; S, 13·5. Calc. for $C_{14}H_9ONS$: C, 70·3; H, 3·8; N, 5·9; S, 13·4%), gave an *oxime*, m. p. 168° (from methanol) (Found: C, 66·1; H, 3·9. $C_{14}H_{10}ON_2S$ requires C, 66·1; H, 4·0%), and a *2,4-dinitrophenylhydrazone*, m. p. 248° (from benzene) (Found: C, 57·5; H, 3·2. $C_{20}H_{13}O_4N_5S$ requires C, 57·3; H, 3·1%).

(i) *Action of alkaline methanol.* 2-Benzoylbenzothiazole (190 mg., 90%) was recovered after being boiled with methanol (25 c.c.) and potassium hydroxide (1·0 g.) for 2 hr. Benzoic acid (5 mg.) was obtained.

(ii) *Action of alkaline t-butyl alcohol.* 2-Benzoylbenzothiazole (750 mg.) was boiled under reflux with potassium t-butoxide (from potassium, 650 mg.) in t-butyl alcohol (150 c.c.) for 30 min., giving benzoic acid (350 mg., 81%) and benzothiazole.

2-Phenylbenzothiazole.—A solution of *o*-nitrothiophenol (2 g.), benzaldehyde (4 g.), and potassium hydroxide (5 g.) in methanol (250 c.c.) was boiled for 2 hr., to give 2-phenylbenzothiazole (100 mg.), m. p. 114° (from methanol) (Found: C, 73·9, 73·8; H, 4·2, 4·3. Calc. for $C_{13}H_9NS$: C, 73·9; H, 4·3%); benzoic acid is formed in large amounts. A higher yield (230 mg.) was obtained by adding zinc (1·0 g.) to the reaction mixture.

Action of Alkali on ω-Methoxyacetophenone.—The ketone,[8] b. p. 115°/12 mm., gave a 2,4-dinitrophenylhydrazone, m. p. 198° (from methanol–methyl acetate) (lit.,[23] m. p. 192—194°). (i) A solution of ketone (1·35 g.) in methanol (125 c.c.) containing potassium hydroxide (2·8 g.) was boiled under reflux for 30 min., giving benzoic acid (300 mg.). (ii) A similar mixture containing additionally *o*-nitroanisole (1·2 g.) gave benzoic acid (800 mg.). (iii) Ketone (1·2 g., 96%) was recovered after being boiled in dry methanol (120 c.c.) containing potassium methoxide (from potassium, 0·5 g.) for 30 min. (iv) Ketone (0·9 g. 65%) was recovered after being boiled under reflux in dry ethanol (120 c.c.) containing potassium ethoxide (from potassium, 0·5 g.) for 44 hr. (v) A mixture of ketone (2 g.) and *o*-nitrophenyl phenacyl sulphide (7·0 g.) in dry methanol containing potassium methoxide (from potassium, 1·0 g.) was boiled for 30 min. Examination of the products in the usual way (omitting the steam-distillation) failed to detect any ω-methoxyacetophenone.

Action of Alkali on ω-Phenoxyacetophenone.—Ketone [24] (2·25 g., 98%), m. p. 72° (2,4-dinitrophenylhydrazone, m. p. 188—190°), was recovered after being boiled for 45 hr. with 0·1N-potassium methoxide in methanol (120 c.c., 1·25 equiv.). The ketone (2·25 g.), boiled under reflux for 2 hr. with 0·16N-potassium hydroxide in methanol (120 c.c., 2 equiv.), gave benzoic acid (25 mg.); after 40 hr., benzoic acid (0·3 g.) and phenol, characterised as tribromophenol (0·8 g.), m. p. 91—93°, were formed.

Stability of Nitro-compounds under Reaction Conditions.—*o*-Nitrothioanisole and *o*-nitrophenylthioacetic acid were stable under all reaction conditions; *o*-nitrophenyl disulphide was stable to all but 3 equiv. of potassium hydroxide, *o*-nitrophenyl sulphide was partially decomposed by boiling 0·2N-methanolic potassium hydroxide in 30 min.

Infrared spectra were measured on a Perkin–Elmer Model 21 spectrophotomer; the spectra will be deposited in the D.M.S. collection.

Part of this work was performed during the tenure of an I.C.I. Fellowship. The author thanks Dr. J. A. Barltrop and Dr. E. J. Forbes for helpful discussions.

CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15.

[*Received, May 19th,* 1959.]

[22] Gilman and Beel, *ibid.*, 1949, **71**, 2328.
[23] Yates, *J. Amer. Chem. Soc.*, 1952, **74**, 5376.
[24] Davies and Middleton, *J.*, 1958, 822.