965. *Synthetical Studies Relating to Colchicine. Part III.*[1] *A Route to 2-Aryl-5-oxocyclohexane-β-propionic Acids*

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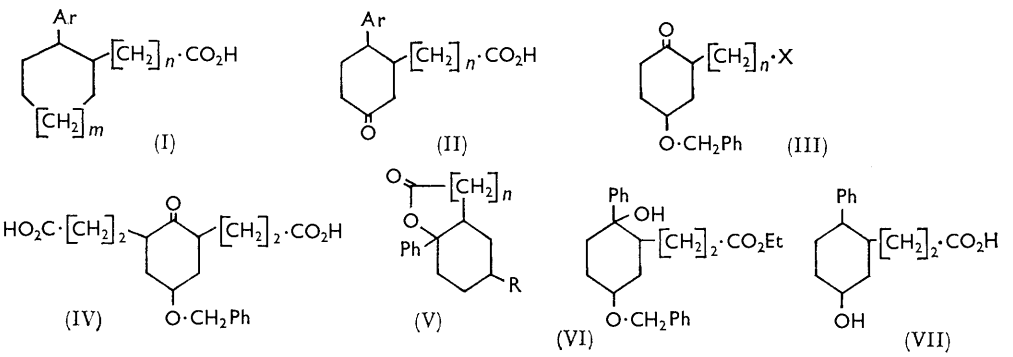
2-Phenyl-5-oxocyclohexane-β-propionic acid has been synthesised by a four-stage route from 4-benzyloxycyclohexanone, a method which promises to be applicable to a range of 2-aryl-5-oxocyclohexane-β-propionic acids.

SEVERAL workers have described the preparation of acids of the general type (I) for use in projected syntheses of colchicine by the " AC ⟶ ABC " route.[2-6] Our aim in the work to be described was to devise a simple and general route to compounds of this type, and more especially of the type (II), which would permit an approach to colchicine by ring enlargement of ring C, and which would provide a means of readily varying ring A [Ar in (II)].

Our starting material was 4-benzyloxycyclohexanone, readily available in two steps from commercial quinitol.[7] 4-Benzyloxy-1-*N*-pyrrolidinylcyclohexene was prepared from this ketone in the usual way.[8] By reaction with ethyl bromoacetate it gave the keto-ester (III; $n = 1$, X = CO_2Et). Similarly, reaction with acrylonitrile in dioxan, and hydrolysis of the product, gave the keto-nitrile (III; $n = 2$, X = CN). Alcoholysis of this nitrile gave the keto-ester (III; $n = 2$, X = CO_2Et), which was also obtained in good yield by reaction of 4-benzyloxy-1-*N*-pyrrolidinylcyclohexene with ethyl acrylate. A tar was also formed in the latter reaction, and, upon alkaline hydrolysis, this gave the di-acid (IV), a point which is further commented on below.



Reaction of (III; $n = 2$, X = CN) with phenylmagnesium bromide gave what appeared to be, from the infrared (i.r.) spectrum, a mixture of starting material and the derived carbinol-nitrile, which could not be separated. Phenyl-lithium attacked both the ketone and nitrile groups, and, since the side-chain was needed intact, use of the keto-nitrile was abandoned, and attention centred on ethyl 5-benzyloxy-2-oxocyclohexane-acetate.

[1] Part II, T. A. Crabb and K. Schofield, *J.*, 1960, 643.
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[8] G. Stork, A. Brizzolara, H. Landesman, J. Smuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, 1963, **85**, 207.

The experiments of Buchta and Ziener [9] with ethyl 2-oxocyclopentane- and 2-oxocyclohexaneacetate provided a precedent, suggesting what might be expected to happen with (III; $n = 2$, X = CO_2Et). In the first case reaction with phenylmagnesium bromide was reported to give a mixture of the expected carbinol-ester and its lactone, and in the second the lactone (V; $n = 1$, R = H) resulted. When we repeated the reaction between phenylmagnesium bromide and ethyl 2-oxocyclohexaneacetate it was apparent from the i.r. spectrum of the crude product that it contained the carbinol as well as the lactone. In the case of ethyl 5-benzyloxy-2-oxocyclohexaneacetate, reaction with phenylmagnesium bromide gave a distilled product with spectral characteristics which suggested it to be a mixture of the lactone (V; R = O·CH_2Ph) and the corresponding cyclohexene. Attempts to convert this mixture wholly into the lactone, by alkaline hydrolysis followed by heating, failed.

The reaction between phenylmagnesium bromide and ethyl 5-benzyloxy-2-oxocyclohexane-β-propionate gave from one experiment a distilled product which was shown by analysis and by its i.r. spectrum to be the hydroxy-ester (VI). All subsequent experiments, despite a lack of obvious difference in execution, gave only the lactone (V; $n = 2$, R = O·CH_2Ph), in good yield.

With compounds (V; $n = 2$, R = OCH_2Ph) and (VI) available, their conversion into (II; Ar = Ph, $n = 2$) could be considered

As regards the lactone, preliminary experiments were carried out on the more cheaply available (V; $n = 2$, R = H), obtained as the sole product from the reaction between phenylmagnesium bromide and ethyl 2-oxocyclohexane-β-propionate. Hydrogenation of (V; $n = 2$, R = H) over platinum in acid conditions resulted in the consumption of four molecular equivalents of hydrogen; not only was the lactone ring opened, but the phenyl group was saturated. However, hydrogenation in ethanol with palladised charcoal gave *cis*-2-phenylcyclohexane-β-propionic acid. The formation of the *cis*-acid almost certainly occurred by Walden inversion at the benzylic carbon atom during hydrogenolysis,[10] so that the Grignard reagent had attacked the keto-ester equatorially, putting the phenyl group and the side-chain in the *trans*-relationship.[11]

Hydrogenolysis of the benzyloxy-lactone (V; $n = 2$, R = O·CH_2Ph) under the same conditions gave two hydroxy-acids, stereoisomers of the structure (VII). The stereoisomerism arose from different configurations of the hydroxyl group, for oxidation of each acid gave the same ketone (II; $n = 2$, Ar = Ph). The case described above suggests this to be *cis*-2-oxo-5-phenylcyclohexane-β-propionic acid.

4-Benzyloxycyclohexanone thus provides easy access to acids of the type (II; $n = 2$), with the possibility of varying the group Ar.

We attempted, unsuccessfully, to utilise 4-benzyloxycyclohexanone in another way. With phenylmagnesium bromide and 2,3,4-trimethoxyphenyl-lithium it gave 4-benzyloxy-1-phenyl- and -1-(2,3,4-trimethoxyphenyl)-cyclohexanol, respectively. Each carbinol was dehydrated by heating with potassium hydrogen sulphate. Perbenzoic acid converted 4-benzyloxy-1-phenylcyclohexene into the epoxide. With a variety of reagents we failed to isomerise the epoxide to the ketone.

The formation of a di-ester [and thence the di-acid (IV)] in the reaction of 4-benzyloxy-1-*N*-pyrrolidinylcyclohexene with ethyl acrylate was mentioned above. The ethyl 2-oxocyclohexane-β-propionate needed (see above) was prepared in the same way from 1-*N*-pyrrolidinylcyclohexene and ethyl acrylate.[8] In this reaction, the crude enamine was boiled in dioxan with one molecular equivalent of ethyl acrylate. Hydrolysis gave 29% of ethyl 2-oxocyclohexane-β-propionate and 16% of diethyl 2-oxocyclohexane-1,3-di-β-propionate. Stork and his co-workers,[8] who used 1·5 molecular equivalents of ethyl

[9] E. Buchta and H. Ziener, *Annalen*, 1956, **601**, 155.
[10] J. H. Brewster and W. E. Braden, *Chem. and Ind.*, 1964, 1759; S. Mitsui and Y. Kudo, *ibid.*, 1965, 381.
[11] A. V. Kamernitzky and A. A. Akhrem, *Tetrahedron*, 1962, **18**, 705.

acrylate, obtained 80% of the mono-ester, but did not observe the product of di-alkylation. Di-alkylation under the present conditions has not often been observed, but occurs in good yields when the reaction is carried out in ethanol.[8] We also observed the formation of the diester from 1-*N*-pyrrolidinylcyclopentene in dioxan.

Experimental

Ethyl 5-Benzyloxy-2-oxocyclohexaneacetate.—4-Benzyloxycyclohexanone (10 g.), pyrrolidine (4·25 g.), and dry benzene (125 ml.) were heated together under reflux in an apparatus provided with a water separator. When no more water was formed, benzene was removed, and the residual oil, ethyl bromoacetate (16·8 g.), and dioxan (75 ml.) were heated under reflux for 48 hr. Water was added, the mixture was heated under reflux for 1 hr., and extracted with ether. The extract was washed with dilute hydrochloric acid and water. Distillation gave the *keto-ester* (5·3 g.), b. p. 200—210°/0·1 mm., n_D^{20} 1·5195 (Found: C, 69·1; H, 7·4. $C_{17}H_{22}O_4$ requires C, 70·3; H, 7·6%). The i.r. spectrum (liquid film) showed peaks at 1735 and 1714 cm.$^{-1}$.

4-Benzyloxy-2-2′-cyanoethylcyclohexanone.—The enamine (2 g.), prepared as above from 4-benzyloxycyclohexanone, acrylonitrile (1·1 g.), and dioxan (15 ml.) were heated together under reflux for 12 hr. Working up in the usual way, and distillation, gave the keto-nitrile (0·52 g.), b. p. 190—194°/0·1 mm., n_D^{18} 1·5300 (Found: C, 74·9; H, 7·6. $C_{16}H_{19}NO_2$ requires C, 74·7; H, 7·4%). The i.r. spectrum (liquid film) showed peaks at 2227 and 1708 cm.$^{-1}$.

Ethyl 5-Benzyloxy-2-oxocyclohexane-β-propionate.—(*a*) The keto-nitrile (4 g.), ethanol (20 ml.), and conc. sulphuric acid (2 ml.) were heated together under reflux for 8 hr. Treatment with water and extraction with ether gave the *ethyl ester* (3·8 g.), b. p. 174—178°/0·1 mm., n_D^{15} 1·5185 (Found: C, 70·8; H, 7·7. $C_{18}H_{24}O_4$ requires C, 71·0; H, 7·95%). The i.r. spectrum (liquid film) showed peaks at 1728 and 1712 cm.$^{-1}$.

(*b*) 4-Benzyloxycyclohexanone (65 g.) was converted into the enamine, which was heated under reflux with ethyl acrylate (48 g.) and dioxan (200 ml.) for 11 hr. Water was added and the mixture was boiled for 1 hr. before extraction with ether. The extract was washed with dilute hydrochloric acid until the washings were colourless. Distillation gave the keto-ester (69 g.), b. p. 176—180°/0·1 mm., n_D^{18} 1·5142. The residue from the distillation was a brown tar. It was heated under reflux with 20% aqueous sodium hydroxide (40 ml.) for 2 hr. Acidification gave an oil (4·8 g.) which solidified. Recrystallisation from water gave *5-benzyloxy-2-oxocyclohexane-1,3-di-β-propionic acid* as colourless crystals, m. p. 152—153° (Found: C, 65·6; H, 6·9. $C_{19}H_{24}O_6$ requires C, 65·5; H, 6·9%).

Reaction of Ethyl 2-Oxocyclohexaneacetate with Phenylmagnesium Bromide.—The reaction was carried out as described by Buchta and Ziener.[9] The reaction product gave several fractions when distilled. One fraction, b. p. 98—100°/0·25 mm., n_D^{19} 1·5069, showed main i.r. peaks at 3410 (OH) and 1724 cm.$^{-1}$ (ester), whilst another fraction, b. p. 172—182°/0·25 mm., n_D^{19} 1·4945 showed peaks at 1772 (γ-lactone) and 1721 cm.$^{-1}$ (ester).

Ethyl 2-Oxocyclohexane-β-propionate.—1-*N-Pyrrolidinylcyclohexene* (from 320 g. of cyclohexanone) in dioxan (320 ml.) was cooled and treated with ethyl acrylate (294 g.). The mixture was boiled under reflux for 7 hr., then treated with water (300 ml.) and boiled for 1 hr. more. The benzene layer was washed with dilute hydrochloric acid and with water, and dried ($MgSO_4$). Distillation gave the keto-ester (220 g.), b. p. 110—125°/0·1 mm., $n_D^{19.5}$ 1·4610, and diethyl 2-oxocyclohexane-1,3-di-β-propionate (51 g.), b. p. 150—170°/0·1 mm. From ether–light petroleum (b. p. 40—60°) the di-ester gave crystals, m. p. 60—62° (Found: C, 64·5; H, 8·6. Calc. for $C_{16}H_{26}O_5$: C, 64·4; H, 8·7%).

2-Hydroxy-2-phenylcyclohexane-β-propionic Acid Lactone.—Phenylmagnesium bromide [from magnesium (1·1 g.)] in ether (50 ml.) was added to a cooled solution of the keto-ester (7·8 g.) in ether (35 ml.). The mixture was stirred for 2 hr., and boiled under reflux for 2 hr. The cooled solution was added to 2N-sulphuric acid, and the mixture was extracted with ether. Distillation gave the *lactone* (2·82 g.), b. p. 150—160°/0·1 mm., n_D^{18} 1·5501 (Found: C, 78·6; H, 7·8. $C_{15}H_{18}O_2$ requires C, 78·2; H, 7·9%). The i.r. spectrum (liquid film) showed a peak at 1727 cm.$^{-1}$ (δ-lactone). The oil solidified when kept, and, recrystallisation from light petroleum (b. p. 40—60°), gave colourless platelets, m. p. 75—76° (Found: C, 78·2; H, 8·0%) with an i.r. spectrum identical with that of the oil. The ultraviolet (u.v.) spectrum (ethanol) showed $\lambda_{max.}$ 254, 259, and 265 mμ (log ε 3·24, 3·20, and 3·20).

Reaction of Ethyl 5-Benzyloxy-2-oxocyclohexane-β-propionate with Phenylmagnesium Bromide.—(*a*) A Grignard solution prepared from bromobenzene (5·9 g.), magnesium (0·91 g.), and ether (30 ml.) was added dropwise with stirring to an ice-cooled solution of ethyl 5-benzyloxy-2-oxocyclohexane-β-propionate (7·4 g.) in ether (12 ml.) during 1 hr. The mixture was stirred at 0° for 2 hr. and at room temperature for 15 hr., and then heated on the water-bath for 1½ hr. N-Sulphuric acid (100 ml.) was added to the cooled mixture, and the product was isolated by ether extraction. Distillation gave the *hydroxy-ester* (4·6 g.), b. p. 160—180°/0·1 mm., $n_D^{19.5}$ 1·5390 (Found: C, 75·6; H, 7·9. $C_{24}H_{30}O_4$ requires C, 75·4; H, 7·9%). The i.r. spectrum (liquid film) showed peaks at 3406 (OH) and 1720 cm.$^{-1}$ (ester).

(*b*) A similar reaction was carried out using 30·8 g. of the ester. The reaction solution was stirred at 0° for 3 hr., heated on the water-bath for 1½ hr., then kept at room temperature overnight. It was cooled and added slowly to 10% aqueous hydrochloric acid. Distillation of the ether extracts gave the *lactone* (21·5 g.) and the hydroxy-ester (1·8 g.). The lactone (initial b. p. 210—240°/0·35 mm.) gave on redistillation an oil, b. p. 200—202°/0·15 mm., $n_D^{16.5}$ 1·5699 (Found: C, 78·1; H, 7·1. $C_{22}H_{24}O_3$ requires C, 78·5; H, 7·2%). The i.r. spectrum (liquid film) showed main peaks at 3019, 2924, 2858, 1717, 1594, 1442, 1353, 1250, 1202, 1085, 1062, 1000, 733, and 688 cm.$^{-1}$.

cis-2-*Phenylcyclohexane-β-propionic Acid.*—2-Hydroxy-2-phenylcyclohexane-β-propionic acid lactone (4·5 g.), in ethanol (40 ml.) with 1 drop of water, was shaken with hydrogen in the presence of 10% palladised charcoal (0·66 g.) for 24 hr. Filtration and removal of the solvent gave a viscous oil (4 g.). The solution of the oil in ether was shaken with 2N-sodium hydroxide solution. Acidification of the aqueous layer, and ether extraction, gave *cis*-2-phenylcyclohexane-β-propionic acid (2·1 g.), m. p. 93—95° (alone, or mixed with an authentic specimen, m. p. 93—94°, kindly supplied by Professor C. D. Gutsche) (Found: C, 77·5; H, 8·7. Calc. for $C_{15}H_{20}O_2$: C, 77·6; H, 8·7%).

5-*Hydroxy-2-phenylcyclohexane-β-propionic Acid.*—The lactone (4·4 g.), ethanol (100 ml.), and 2 drops of water were shaken with hydrogen in the presence of 10% palladised charcoal (1·6 g.). One molecular equivalent was consumed within an hour, the second in 23 hr. Working up as above gave the product (1·13 g.), a mixture of two acids. The pure isomeric 5-*hydroxy-2-phenylcyclohexane-β-propionic acids* were separated by recrystallisation from ether, and each formed crystals; (i) (0·66 g.) m. p. 104—107° (Found: C, 72·6; H, 8·1. $C_{15}H_{20}O_3$ requires C, 72·6; H, 8·1%), and (ii) (0·30 g.) m. p. 165—167° (Found: C, 72·5; H, 8·1%). The i.r. spectrum of the first (KBr disc) showed main peaks at 3378, 2928, 2873, 2575, 1701, 1292, 1269, and 1057 cm.$^{-1}$, and of the second, at 3439, 2934, 2858, 2660, 1713, 1311, 1269, and 1056 cm.$^{-1}$. The neutral product of the reaction, which may have been 2,5-dihydroxy-2-phenylcyclohexane-β-propionic acid lactone, was an oil (0·8 g.), b. p. 172—176°/0·3 mm., n_D^{25} 1·5925 (Found: C, 73·5; H, 8·4. $C_{15}H_{18}O_3$ requires C, 73·1; H, 7·4%). The i.r. spectrum (liquid film) showed main peaks at 3415, 2923, 2868, 1712, 1594, 1448, 1376, 1264, 1165, 1014, 750, and 698 cm.$^{-1}$.

(cis?)-5-*Oxo-2-phenylcylohexane-β-propionic Acid.*—To an ice-cooled solution of the alcohol (2·8 g.), m. p. 165—167°, in acetic acid (40 ml.) was added during ½ hr. a solution of chromium trioxide (1 g.) in acetic acid (15 ml.) and water (1 ml.). The solution was stirred at room temperature for 12 hr., water was added, and the product was extracted with ether. Removal of the ether gave the *ketone* (2·2 g.), which separated from benzene as needles, m. p. 144—146° (Found: C, 73·0; H, 7·4. $C_{15}H_{18}O_3$ requires C, 73·1; H, 7·4%). The i.r. spectrum (KBr disc) showed main peaks at 3056, 2944, 1726, 1674, 1442, 1241, 1127, and 760 cm.$^{-1}$. The u.v. spectrum (95% ethanol) showed $\lambda_{max.}$ 255, 260, and 265 mμ (log ε 2·20, 2·29, and 2·15). The *semicarbazone* separated from methanol as needles, m. p. 210—212° (Found: C, 64·0; H, 6·9. $C_{16}H_{21}N_3O_3$ requires C, 63·4; H, 7·0%).

Oxidation of the isomeric alcohol, m. p. 104—107°, gave the same ketone.

4-*Benzyloxy-1-phenylcyclohexanol.*—To a stirred solution of phenylmagnesium bromide [from magnesium (0·26 g.), bromobenzene (1·7 g.), and ether (10 ml.)] was added 4-benzyloxycyclohexanone (2 g.) in ether (10 ml.). The mixture was boiled under reflux for 1 hr., cooled to 0°, and decomposed with ice-cold 10% aqueous ammonium chloride solution. Evaporation of the washed and dried ($MgSO_4$) ethereal layer gave the *product* (1·29 g.) which separated from light petroleum (b. p. 40—60°) as platelets, m. p. 81—82° (Found: C, 81·2; H, 7·9. $C_{19}H_{22}O_2$ requires C, 81·1; H, 7·5%). The i.r. spectrum (Nujol) showed a strong band at 3419 cm.$^{-1}$.

4-*Benzyloxy-1-phenylcyclohexene.*—The alcohol (12·2 g.) was heated with potassium hydrogen sulphate (24·4 g.) at 160—180°/0·1 mm. for ½ hr. Extraction with ether gave the *product*

(10·1 g.) which from ether–light petroleum (b. p. 40—60°) gave colourless crystals, m. p. 44—45° (Found: C, 86·4; H, 7·6. $C_{17}H_{20}O$ requires C, 86·3; H, 7·6%). The u.v. spectrum (95% ethanol) showed $\lambda_{max.}$ 247 mμ (log ε 4·3).

4-Benzyloxy-1,2-epoxy-1-phenylcyclohexane.—To an ice-cooled solution of the above product (2·45 g.) in ether (20 ml.) was added, with stirring, a solution of perbenzoic acid (1·41 g.) in ether (26 ml.), at such a rate that the temperature did not rise above 5°. The solution was stirred at 0° for 4 hr., and kept overnight at 5°. It was washed with N-sodium hydroxide solution, and with water, and dried ($MgSO_4$). Distillation gave the *epoxide* (2·0 g.), b. p. 170—174°/0·1 mm., n_D^{20} 1·5729 (Found: C, 81·5; H, 7·2. $C_{19}H_{20}O_2$ requires C, 81·3; H, 7·2%). The i.r. spectrum (liquid film) showed main peaks at 3054, 2948, 2884, 1609w, 1500, 1458, 1373, 1215w, 1099, 1087, 1035, and 855w cm.$^{-1}$.

Old specimens of the epoxide developed peaks at 3523 and 1707 cm.$^{-1}$, perhaps from formation of diol and ketone, but, despite the use of a variety of conditions, we could not convert the epoxide into the isomeric ketone. Use of freshly prepared magnesium bromide etherate gave an oil from which crystals, m. p. 62—63°, were isolated (i.v. peak at 1712 cm.$^{-1}$), but the elemental composition of this material was not that of the required ketone.

4-Benzyloxy-1-(2,3,4-trimethoxyphenyl)cyclohexanol.—To a stirred solution of phenyl-lithium [from lithium (0·61 g.), bromobenzene (6·8 g.), and ether (50 ml.)] was added, at 0°, 4-bromo-1,2,3-trimethoxybenzene (10·5 g.) in ether (20 ml.), followed by 4-benzyloxycyclohexanone (4·7 g.) in ether (20 ml.). The solution was stirred at 0° for ½ hr., and overnight at room temperature. The cooled mixture was added slowly to ice-cold ammonium chloride solution. The ether layer was washed with 5% aqueous sodium hydroxide, and with water. Removal of the ether and crystallisation from ether–light petroleum (b. p. 40—60°) gave the *product* as needles (2·81 g.), m. p. 114—115° (Found: C, 70·5; H, 7·4. $C_{22}H_{28}O_5$ requires C, 70·9; H, 7·5%); i.r. maximum: 3547 cm.$^{-1}$.

4-Benzyloxy-1-(2,3,4-trimethoxyphenyl)cyclohexene.—The alcohol (0·2 g.) and potassium hydrogen sulphate (0·4 g.) were heated at 180°/0·1 mm. Extraction with ether and recrystallisation of the product (0·15 g.) from methanol gave platelets of the *cyclohexene*, m. p. 66—67° (Found: C, 74·2; H, 7·1. $C_{22}H_{26}O_4$ requires C, 74·5; H, 7·4%). The u.v. spectrum (95% ethanol) showed $\lambda_{max.}$ 240 mμ (log ε 5·0).

Ethyl 2-Oxocyclopentane-β-propionate.—1-*N*-pyrrolidinylcyclopentene (from 205 g. of cyclopentanone), ethyl acrylate (244 g.), and dioxan (530 ml.) were heated under reflux for 24 hr. Working up in the usual way gave the keto-ester (204 g.), b. p. 110—120°/0·1 mm., n_D^{20} 1·4575, and diethyl 2-oxocyclopentane-1,3-di-β-propionate (64 g.), b. p. 147—148°/0·2 mm., n_D^{19} 1·4652 (Found: C, 63·8; H, 8·4. Calc. for $C_{15}H_{24}O_5$: C, 63·4; H, 8·5%). Hydrolysis of the di-ester with methanolic potash gave 2-oxocyclopentanone-1,3-di-β-propionic acid, m. p. 120—122° (lit.,[12] m. p. 122°).

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[12] N. J. Leonard and W. J. Middleton, *J. Amer. Chem. Soc.*, 1952, **74**, 5114.